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## Editorial

## Early ontogeny as a unique developmental epoch for learning, memory and consequences of alcohol exposure: A Festschrift to honor the work of Dr. Norman E. Spear



### 1. Introduction to the Special Issue

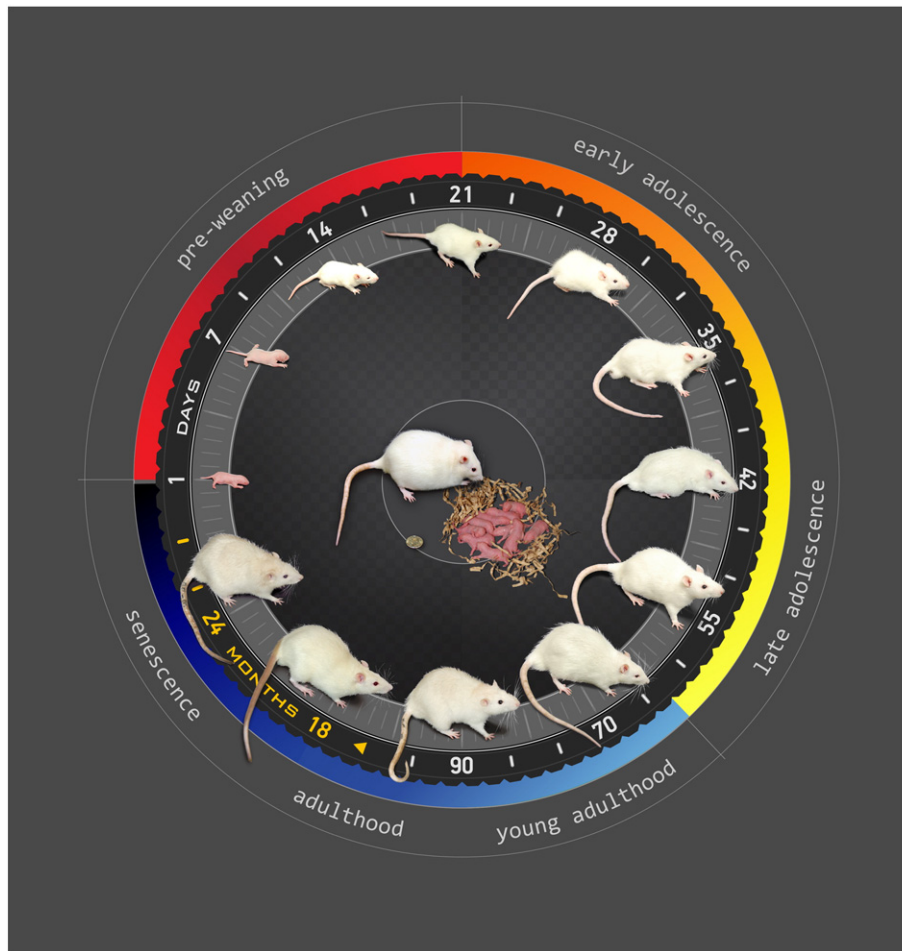
The developmental concepts of critical and sensitive periods for brain development—and the mechanisms by which early development defines both opportunities and vulnerabilities for an organism's future—have permeated the literature across all taxonomic orders. Indeed, pioneering studies that have identified early ontogeny as a unique developmental period cross a wide range of seemingly disparate fields. Though our interest in many cases lies in furthering our understanding of the human condition, substantive milestones have been accomplished through the use of preclinical (particularly rodent) models, whose brain and behavioral development can be readily aligned with that of humans (see Fig. 1). For instance, brain development during the first postnatal week in rat is considered to be the developmental equivalent of the third trimester in humans based on brain maturation processes ongoing at that time. Whereas the first week or so after weaning is often considered to be the juvenile period in rat, early manifestations of adolescence begin to emerge at around P28 and subside around P65. Rats are considered to be fully mature, young adults starting about P70–P90, and at this point investigators often switch from a focus on early developmental processes toward examination of aging and lifespan-related issues. Thus, rats aged 9–15 months probably correspond to middle-aged humans of about 40–60 years old, whereas 18 months often demarcates early stages of senescence in the laboratory rat. There are, of course, notable species and strain differences in neurobehavioral development that might cause these age boundaries to “slide” somewhat across rodent model systems. Nevertheless, the developing rodent provides a superb model through which cross-sectional and longitudinal studies can be performed readily, thereby underscoring the value of rodent models for advancing our understanding of brain–behavior relationships in a diverse range of research areas.

Regardless of the species/strain being studied, developmental models have taught us that sophisticated analyses of sensory/perceptual, cognitive, and behavioral processes require extraordinary attention to innate differences in how developing organisms transduce, perceive, and encode environmental and social experiences throughout the lifespan. Furthermore, developmental research has illustrated that the building blocks of early experience give rise to neural rubrics which guide early behavior and often persist, even if in latent form, for a lifetime. Today, advances in our understanding of molecular physiology have extended many of these “programming” effects into altered genomic function that can even endure across generations.

Several guiding principles have emerged from the study of early life experiences and form the common parlance of developmentally oriented psychologists and neurobiologists. For instance, early exposure to enriched environments appears to confer competitive advantage relative to individuals from impoverished environments. Similarly, adverse early life experiences (social or nutritional deprivation, harsh rearing conditions, or hostile environments) appear to engrain long-lasting health and disease vulnerabilities throughout life. Together, the relative balance of enrichment (opportunity) versus adversity (threat) has shaped not only the development of the organism exposed to such circumstances, but also the major questions being asked in the field of developmental psychobiology.

There have been many pioneers who have identified early ontogeny as a unique developmental epoch during which experience (or lack thereof) hard-wires behavior and brain function across the lifespan. The work presented in this Special Issue of *Physiology & Behavior* pays special tribute to one such pioneer in developmental psychobiology who has shaped the thinking of generations of scholars: our friend and colleague, Dr. Norman E. “Skip” Spear (see Fig. 2). As such, this Special Issue is organized into “epochs” that resemble areas related to Skip's work, whose contributions over nearly 50 years as an independent investigator gave birth to a wide range of basic and translational studies. This Special Issue evolved from a symposium held in May, 2014 to honor and recognize the contributions of Dr. Spear. Present at the symposium were many former students, long-term collaborators, and colleagues (Fig. 3), and we are pleased to dedicate the work presented in this Special Issue to him. Not only has Skip contributed significantly to all of the research areas contained in this collection, but he has also shaped the intellectual development and scholarly achievements for many of the authors in this issue. In this way, it seems fitting to distinguish the work of a pioneer in developmental psychobiology with a developmentally-themed Special Issue.

In the first section, you will find a series of articles examining developmental differences in basic aspects of cognitive function, and how these developmental differences are altered by early alcohol exposure. For instance, Revillo et al. (in this issue) [1] reviewed the literature on context learning as a means to better understand cognitive development in both rodents and humans. This article presented a summary of two, often competing, hypotheses regarding the acquisition of cognitive abilities across early development. Whereas some studies seem to support a gradual accumulation of cognitive abilities that corresponds with neuronal maturation (particularly in the hippocampus for context learning effects), other studies seem to support the hypothesis that



**Fig. 1.** Schematic illustration of developmental stages in the rat, from birth through senescence, which have often been the focus of early ontogenetic investigations in the field of developmental psychobiology (early postnatal/preweaning stage; early to late adolescence; young adulthood; adulthood; and senescence). The photos shown in this figure were taken by Anny Gano and Dr. Tamara Doremus-Fitzwater. We are grateful for the excellent illustration work contributed by Igor Khranov in the production of this graphic.

infants rely on distinct cues (relative to adults) and attentional processes that are optimized to their developing niche, but are not necessarily reflective of deficits in cognitive function per se (relative to adults). Robinson-Drummer and Stanton (in this issue) [2] utilized the well-established context pre-exposure facilitation effect (CPFE) in order to better understand differences in cognitive capacity as a function of early ontogeny. It was demonstrated that younger rats show weaker retention of the CPFE effect relative to older animals, with these findings extending what is already known about infantile amnesia and the gradual addition of complex cognitive abilities across early ontogeny. Chan et al. (in this issue) [3] assessed the role of glutamatergic signaling via the NMDA receptor using a fear conditioning procedure in preweaning rats. In addition to replicating previous findings showing that memories for fear conditioning erode rapidly when training occurs at an early age (training on P17, forgetting by P27), these data helped elucidate the role of NMDA-dependent and independent processes in the forgetting response.

Together, these fundamental, age-related differences offer important insight into the nature of cognitive development in preclinical models, and provide a foundation for better understanding alterations in cognitive development induced by other challenges, such as the response to early alcohol (ethanol) exposure. As a first example of this theme, Hunt and Barnett (in this issue) [4] examined the impact of early postnatal ethanol exposure (5 g/kg from P4–P9; a developmental period corresponding to the third trimester in humans) on trace conditioning deficits observed during early adolescence. Interestingly, the deficits in peri-adolescent trace conditioning produced by ethanol in

this model were effectively reversed by dietary supplementation of choline or acute physostigmine at the time of conditioning, providing promising alternatives for rescuing cognitive deficits that may be characteristic of Fetal Alcohol Spectrum Disorders (FASD). In a highly relevant translational study, Infante et al. (in this issue) [5] examined ADHD symptomatology in 7–14 year old children with an established history of Prenatal Alcohol Exposure (PAE). Their findings supported the notion that inattention represents a core deficit in children prenatally exposed to ethanol, and may explain other cognitive deficits associated with FASD.

The second section includes a series of articles examining the impact of early sensory experience on preferences for, and acceptance of, odors and cues experienced early in life. For instance, Kamenetzky et al. (in this issue) [6] performed an interesting set of studies designed to assess how neonatal exposure to a novel odorant (within a few hours of birth) impacted consumption of either palatable or aversive tastants. They found greater consumption of an aversive solution (quinine), but not of a palatable one (saccharin) in the presence of the familiar odor cue, suggesting that neonatal rats were more accepting of (normally aversive) substances in the presence of familiar cues. Gaztanaga et al. [7] (in this issue) tested a similar hypothesis regarding how early sensory experiences via the chemical senses (odorant and tastant) impact later chemosensory preferences. They found that prenatal exposure to either vanilla or alcohol odor led to increased neonatal crawling behavior when rat pups were re-exposed to the same cue. Additionally, they found that the enhanced crawling behavior toward either vanilla or ethanol was blocked by mu opioid receptor antagonism, whereas kappa



**Fig. 2.** Dr. Norman E. "Skip" Spear, to whom this Special issue is dedicated. Skip has touched many lives throughout his 50 years in the field. His legacy will continue through the work of his students and collaborators. We are delighted to mark his retirement with publication of this Special Issue in his honor. This photo was taken by Jonathan Cohen/Binghamton University.

opioid receptor antagonism only reversed enhanced crawling toward alcohol. Furthermore, the article by Brassler et al. (in this issue) [8] summarizes neural pathways activated by the chemosensory aspects of

ethanol and argues that these pathways are critical to understanding the post-absorptive consequences of ethanol.

Interestingly, the findings from these preclinical studies are supported by translational studies in humans. For instance, Hannigan et al. (in this issue) [9] performed an assessment of alcohol-related odor preferences in young adults for which detailed information regarding their PAE was available. For the first time, these authors reported that PAE led to an increased rating of the pleasantness of alcohol odor in young adult humans. These findings support and extend what has been established in rodent models, and suggest that the chemosensory properties of alcohol likely contribute to the initiation and maintenance of high levels of alcohol consumption in young adults with a history of PAE. These findings are also consistent with those of Faas et al. (in this issue) [10], who demonstrated that human infants exposed to alcohol via frequent maternal consumption recognized alcohol odor several weeks after parturition (i.e., 7–14 day old newborns), and responded with appetitive facial expressions. Overall, these findings illustrate how early exposure to chemosensory agents forge preferences that may persist across weeks to months (in rat) and potentially decades in humans.

The final section of this Special Issue emphasizes how sensitivity to ethanol effects varies as a function of the developmental epoch in which ethanol exposure occurs, and dives into mechanisms that may underwrite those age-related differences. For instance, in a review article by Pautassi et al. (in this issue) [11], studies examining operant self-administration of ethanol across early ontogeny are summarized. The research reviewed in that article supported several conclusions regarding early ethanol exposure, including (i) infant rats consume surprisingly large quantities of ethanol; (ii) ethanol self-administration at these early ages is potently reinforcing; and (iii) early ethanol exposure increases ethanol intake during adolescence—a key ontogenetic period during which problematic ethanol consumption is often initiated. Based on this growing body of literature, Bordner and Deak (in this issue) [12] examined the impact of PAE (0, 1, or 2 g/kg/day from G17–G20) on the expression of opioid ligands and receptors across the neonatal period (P4, P8, P12). In addition to showing signs of escalating opioid function across this early developmental epoch, these studies also reported a substantial decrease in opioid receptor expression after



**Fig. 3.** Photo from the Festschrift in honor of Dr. Norman E. Spear, which was held at Binghamton University in May 2014. The scientific symposium held at Binghamton University included more than 100 scientists from around the world, many of whom trained with, or are former/current colleagues of Dr. Spear. Support for the scientific symposium was provided by the Health Sciences Steering Committee and the Center for Development and Behavioral Neuroscience at Binghamton University. This photo was taken by Jonathan Cohen/Binghamton University.

PAE (in the high dose group) that was specific to the Nucleus Accumbens. These findings suggest that naturally occurring differences in opioid tone—and its modification by PAE—may be critical to heightened alcohol reinforcement in the neonatal rat. Interestingly, Popoola et al. (in this issue) [13] examined the impact of gestational ethanol exposure (1 g/kg/day from G17–G20) on maternal care of offspring in two commonly used strains of rat (Sprague Dawley and Long Evans) and across two generations. Although significant strain differences were observed in the expression of maternal care, surprisingly few changes in maternal care were documented as a result of prenatal alcohol exposure. Regarding this latter point, it should be noted that more severe regimens of PAE in the range that would likely produce teratogenic influences have been shown to significantly impact maternal behavior, whereas lower-dose, sub-teratogenic regimens of PAE (such as those used here) likely produced effects on offspring that were independent of ethanol's influences on maternal care.

The adolescent period is well-established as a critical period during which ethanol consumption can adversely impact brain development. An intriguing review by Dr. Linda Spear (in this issue) [14] describes differences between early initiation of alcohol consumption by young adolescents (P25–45 in rat) relative to increased binge drinking that is more characteristic of late adolescence (P45–65 in rat), and how the timing of ethanol exposure may confer unique vulnerabilities toward later substance use and abuse. Consistent with this notion, Doremus-Fitzwater et al. (in this issue) [15] examined pro-inflammatory cytokine expression in several key brain structures (hippocampus, amygdala and PVN) after either ethanol exposure (4 g/kg ip or ig) or injection of lipopolysaccharide (a component of the cell walls of gram negative bacteria that is often used to simulate infection). The findings of these studies suggested that young adolescents (P29–31) display blunted cytokine responses to both challenges (ethanol or LPS) relative to adults (P67–P69). In addition to demonstrating reduced sensitivity of adolescents to rapidly induced, acute neuroimmune responses to ethanol during adolescence, these findings suggested that adolescents differ markedly in natural aspects of the inflammatory response relative to their adult counterparts.

The adolescent period, however, is not just riddled with unique sensitivities to ethanol, but also to stressful life circumstances. These issues are reviewed by Varlinskaya and Spear (in this issue), where they suggest that stressful experiences during adolescence facilitate ethanol consumption, particularly when ethanol consumption occurs within a social context [16]. Interestingly, the findings of Lopez and Laber (in this issue) [17] demonstrated that social isolation of mice during the adolescent period (relative to group housed mice) led to enhanced voluntary intake of ethanol, and these effects were reversed by providing isolated adolescents with environmental enrichment (nesting material). Furthermore, Comeau et al. (in this issue) [18] examined how PAE (liquid ethanol diet from G1–G21) impacted sensitivity of adolescents to chronic mild stress (imposed from P31–41), and showed that PAE enhanced the sensitivity of adolescents to stress-related deficits in cognitive function in female rats. Furthermore, Wellmann and Mooney (in this issue) [19] showed that prenatal alcohol exposure (liquid ethanol diet from G6–G21) produced profound social deficits that persisted into late adolescence for both male and female offspring. Interestingly, when PAE was combined with a mild sensory challenge (unilateral whisker clipping during the first post-natal week), the effects of PAE on social deficits were potentiated through adolescence, with effects of the combined PAE/whisker clipping challenge persisting longer in males (still present at P42) relative to females (no combined effect by P42). These intriguing findings support and extend critical investigations on the importance of alcohol–stress interactions, particularly when these exposures occur within the spectrum of early ontogeny, for determining clinically relevant outcomes. Together, studies such as those described above, highlight the importance of social factors as critical determinants of developmental sensitivities to both stress and ethanol for humans, as well as in preclinical models.

In reflecting upon the 19 articles included in this Special Issue, we are struck by the consistent themes that emerged, and the extent to which these submissions support the view that early ontogeny truly represents a unique developmental epoch, consisting of numerous, naturally occurring vulnerabilities and opportunities. In this way, experiences during early ontogeny likely support successful niche adaptation and prepare developing organisms to survive within an environment comparable to its rearing environment. Our challenge for the future, therefore, must be to use theoretical and empirical works, such as those included here, to minimize the influence of adversity to the developing organism, while at the same time exploiting the opportunities afforded by early development for precise, developmentally-timed exposure to highly effective forms of enrichment that promote health, happiness and vitality. In doing so, we have the opportunity to use basic biomedical research to tip the scales of human health toward more favorable outcomes.

### Conflict of interest statement

This Special Issue includes several articles for which the Guest Editors were authors or held a conflict of interest with authors who submitted articles for consideration in the Special Issue. In all cases, the Guest Editor deemed to be in conflict was recused from the review process, and all articles received the same rigorous peer review as is customary for *Physiology & Behavior*. The Guest Editors have no financial conflicts of interest to declare.

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