Development and Psychopathology **30** (2018), 721–724

doi:10.1017/S095457941800069X

SPECIAL ISSUE EDITORIAL

Future directions in prenatal stress research: Challenges and opportunities related to advancing our understanding of prenatal developmental origins of risk for psychopathology

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Throughout history, scholars have explored the idea that experiences early in life have a profound and persisting influence on health and well-being (Cicchetti, 2017). Over the past century, this idea has inspired the emergence of a vigorous field of research dedicated to understanding how the prenatal environment shapes long-term developmental outcomes. The foundation of this literature can be found in vanguard studies on fetal physiology dating back to the 1930s and 1940s (Barcroft, 1946; Gottlieb 1976, 1983; Sontag & Richards, 1938). Today, the convergence of diverse disciplines continues to fuel an expansion of research that has given rise to a conceptual paradigm called the developmental origins of health and disease (DOHaD; Gluckman & Hanson, 2006; Wadhwa, Buss, Entrigner, & Swanson, 2010). Sometimes known as "Barker's hypothesis," the "thrifty phenotype hypothesis," or the "fetal programming hypothesis," the central hypothesis guiding this approach is that the in utero environment shapes fetal development and subsequently sets probabilistic parameters for both adaptive and maladaptive outcomes. Historically, the emphasis of DOHaD research has been on physical health outcomes, such as cardiovascular disease, obesity, and type 2 diabetes. More recent work examining neurobehavioral and clinical outcomes has provided compelling evidence of long-term educational, behavioral, and psychological sequelae of prenatal stress. Of note, the influence of developmental principles on the field of DOHaD research is increasingly visible, for example, in a growing interest in plasticity and the probabilistic nature of development (in contrast to "programmed" outcomes; Cicchetti & Curtis, 2006), in the recognition of the bidirectional relationship between a pregnant woman and a fetus (e.g., DiPietro, 2010), as well as in the recognition of pregnancy as a significant period of organization and development for a fetus *and* a woman, and in a mounting interest in the association between prenatal stress and adaptive outcomes and individual differences (and not only maladaptive outcomes) and what factors and processes may buffer stress effects and promote resilience.

Despite the recent maturation and rapid growth of the DOHaD field of research, precisely how prenatal stress may alter developmental trajectories is not well understood. The goal of this Special Issue is to examine the wealth of research investigating prenatal stress and its effects on offspring development. Our hope is that the research featured in this issue will increase our understanding of the putative mechanisms and pathways by which variation in the prenatal environment may have a persisting influence on developmental organization and outcomes in infancy, childhood, adolescence, and adulthood. Our aims for this Special Issue are threefold. The first two aims relate to twin themes of theory building and theory appraisal within this area of work. In this issue, investigators outline theoretical frameworks that have guided recent prenatal stress research, and examine the accumulating evidence that support, amend, or extend these frameworks. These reviews reveal an increasing emphasis on moderating and mediating processes that may influence or explain the association between prenatal factors and offspring risk for psychopathology.

The third theme of the issue is the consideration of challenges (and opportunities) related to advancing our understanding of the prenatal origins of risk for psychopathology. Among the challenges touched on by authors in this issue are three challenges we briefly review here: developing a systematic conceptual framework for defining and studying prenatal stress; parsing the heterogeneity of the construct of prenatal stress in the service of identifying latent risk phenotypes; and leveraging experimental and quasi-experimental designs and novel statistical approaches to conduct informative tests of the fetal programming hypothesis.

Our work on this Special Issue was supported by grants from the National Science Foundation Graduate Research Fellowship (to C.D.) and from the Emerald Foundation and the Klaus J. Jacobs Research Prize (to D.C.).

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The first major challenge to the field is related to the current lack of a strong systematic conceptual framework, or nomological net (Cronbach & Meehl, 1955), for studying the construct of prenatal stress. This effort begins with the need for definitional and conceptual consensus and clarity, as the delineation of prenatal stress effects depends on the definition of the construct itself (e.g., see Barnett, Manly, & Cicchetti, 1993; Cicchetti & Barnett, 1991). Currently, within the literature *prenatal stress* is a complex umbrella term that encompasses many types of maternal factors that can influence the in utero environment, including physiological, psychological, and behavioral responses to perceived threat or challenge. These factors can include variables related to biological functioning (i.e., hormonal and immune), cognitive and affective states associated with "distress" or negative mood (i.e., frustration, anxiety, and depression), and characteristic ways of experiencing, managing, or responding to stressful events (i.e., personality traits, cognitive appraisal processes, coping strategies, and health behaviors). Frequently, in human studies of prenatal stress, "stress" is conceptualized as distress (Kemeny, 2003). This is problematic for several reasons. First, not all stressful states are negative; stressful events that are mild, brief, and controllable function as normative developmental experiences, and can be experienced as positive and exert a positive influence on development. Second, the perception or interpretation of whether something is stressful depends on characteristics of the individual, which investigators often do not attempt to measure or account for, such as personality traits, outlook on life, and views of the world as safe or unsafe. Of note, DiPietro, Costigan, and Sipsma (2008) have shown that correlations among self-report measures of perceived stress and symptoms of depression and anxiety are high during pregnancy and remain stable through the first 2 years after delivery. These results suggest that measures of prenatal distress may gauge important moderating factors and mediating processes such as personality traits and social support. Third, although anxiety, depression, and chronic psychological stress have been associated with the dysregulation of biological stress response systems, primarily the hypothalamus–pituitary–adrenal axis, stress hormones do not function as "emotion juice" (Gunnar, 2016; Hennessy & Levine, 1979). Instead, mood dysregulation likely has unique biological mechanisms, such as serotonergic activity, that may go overlooked within a "stress" approach (Beijers, Buitelaar, & de Weerth, 2014). Due to the lack of definitional and conceptual consensus on prenatal stress, it is unclear if studies examining the effects of the maternal biological stress response in humans, or translating prenatal stress findings from animal models, are investigating the same phenomena as studies examining psychological distress. The field's current reliance on a conceptual model of prenatal stress that "lumps" potential mediating and/or moderating processes in with stressors is conceptually unclear and empirically problematic (Grant et al., 2003). Future research that defines and measures prenatal stress factors and related moderating and mediating variables, and provides data to integrate, identify, and quantify the higher order interrelationships among and between them, has the potential to profoundly advance our knowledge of how the construct of prenatal stress operates to shape developmental outcomes.

The difficulty of defining the construct of prenatal stress is closely related to its heterogeneous nature. Due to this variability, maternal exposure risk groups are latent and unobservable, and this represents a second challenge/opportunity facing the field. Contributing to the complexity of prenatal stress is variability across the typical-to-atypical continuum of (dys)regulation in mood and stress regulation systems in the context of pregnancy, as well as heterogeneity within and across symptoms of psychiatric disorders. One approach to this challenge of characterizing the complexity of the construct of prenatal stress is the research domain criteria (RDoC) initiative (Insel et al., 2010). RDoC seeks quantitative approaches that are agnostic to traditional psychiatric nosology to improve characterization of the genotypic and phenotypic heterogeneity observed within and across DSM disorders. To this end, RDoC has formalized research strategies for parsing the heterogeneity inherent to the etiology, phenotypic presentation, and treatment response of major psychiatric disorders using data-driven subtyping. Identifying and defining different (and more homogeneous) maternal subtypes can advance a deeper understanding of prenatal stress and its effects by facilitating the discovery of maternal risk phenotypes and multiple etiological pathways whereby prenatal stress can lead to various effects on offspring development. These data are needed to enable the design of effective and timely preventative interventions for pregnant women and their children. Examples of subtyping are rapidly accumulating in different literatures (e.g., Bebko et al., 2014; Ivleva et al., 2017) with a significant body of evidence emerging from the B-SNIP study that has identified distinct neurobiological "biotypes" that cross clinical diagnostic boundaries (e.g., Karalunas et al., 2014). These studies leverage novel, data-driven statistical techniques such as machine learning or factor mixture modeling (e.g., see Lubke & Muthén, 2005; Orru, Pettersson-Yeo, Marquand, Sartori, & Mechelli, 2012) that effectively reduce data dimensions and identify meaningful phenotypes. The growing subtyping literature reinforces that greater measurement precision is required to identify more homogenous subgroups. Although most DOHaD studies to date have examined a single prenatal stress exposure, prenatal stress risk factors typically do not occur in isolation (Stroud, McCallum, & Salisbury, 2018 [this issue]), thus, to fully understand how these distinct variables relate to one another in the prediction of psychopathology, it is important to define and measure each of these variables separately. Expanding measurement to include a wider range of risk factors, moderators, and mediators will be key to identifying risk groups and understanding the complex pathways and mechanisms by which the prenatal and perinatal environment influences neurobehavioral trajectories. Finally, existing subtyping studies reveal that parsing the complexity of prenatal

https://doi.org/10.1017/S095457941800069X Published online by Cambridge University Press

stress via data-driven subtyping approaches will require the recruitment of larger samples to increase statistical power. Already, prenatal stress investigators have called for the field to leverage the benefits of a "big data" approach (de Weerth, 2018 [this issue]). Studies like the recent NIH research project, PregSource, will begin to help fill this gap (Kuehn, 2017).

A third challenge facing the field is related to strengthening causal inference. Although epidemiological and correlational research with human subjects supports the "fetal origins hypothesis," confounding variables prevent these studies from providing definitive proof (Thapar & Rutter, 2009). Strong causal evidence for prenatal stress effects on offspring development comes primarily from animal experiments; however, animal models have both benefits and limitations (Lickliter, 2018 [this issue]). Currently, prenatal stress research is increasingly moving from a long phase of documenting correlations between offspring outcomes and variables that might be putative causes, to studies that use experimental or quasi-experimental designs to conduct informative tests of causal hypotheses. In this issue, investigators draw attention to the benefits of incorporating novel and genetically informed designs and statistical approaches, as well as translational synthesis across human and animal studies, which are needed to improve causal inference and conduct a "risky test" (Popper, 1959). There is growing recognition that assessing and controlling for inherited confounders, postnatal risk, and even preconception risk is required to disaggregate the influence of unique prenatal environmental exposures from other factors. In addition, the importance of randomized controlled trial designs as an experimental test of the fetal programming hypothesis is noted (Davis, Hankin, Swales, & Hoffman, 2018 [this issue]; Goodman, Cullum, Dimidjian, River, & Kim, 2018 [this issue]).

The prenatal period is a time of rapid and dynamic development, during which the brain develops from a simple three cell-layer structure to a complex network of neurons and glia designed to support the increasingly complex behaviors that are necessary for successful navigation of the *ex utero* environment (Ciaranello et al., 1995; Stiles, 2008). This time of enhanced development, plasticity, and potential vulnerability represents an unmatched opportunity for adaptation to the environment, whether that environment involves exposure to harsh conditions or not. In recent decades, research from a wide range of disciplines has shown prenatal development provides a foundation for learning and health throughout the life span. The rapidly growing body of work examining prenatal stress and its effects and neurobehavioral outcomes indicates this topic is of increasing interest to researchers, clinicians, and policy makers (e.g., Glover, 2011; Green et al., 2005; Huizink, Mulder, & Buitelaar, 2004; O'Donnell & Meaney, 2016; Schetter & Tanner, 2012). Understanding the prenatal developmental origins of risk for psychopathology has immense preventative and therapeutic value. We believe that this Special Issue will focus much-needed attention on theoretical frameworks and evidence that increases our understanding of how prenatal stress alters the in utero environment, shapes fetal development, and influences long-term outcomes. We also believe the research featured here will direct attention to many practical concerns involved in advancing this area of work and ultimately accelerating the translation of this science to practice. It has been said that "science is built up of facts, as a house is built of stones; but an accumulation of facts is no more a science than a heap of stones is a house" (Poincaré, 1913). To begin to usher in a gestalt-like shift in our understanding of prenatal stress effects, we believe that investigators in this area must work toward elaborating a causal taxonomy of the construct of prenatal stress, parsing the complexity of prenatal stress to identify patterns of prenatal stress factors that may characterize maternal risk group profiles, and adopting novel designs and statistical approaches to test hypothesized causal pathways. We hope that the articles included in this Special Issue will stimulate innovative research initiatives directed toward an increased understanding of how prenatal stress may eventuate in psychopathology, and the exportation of this knowledge to inform strategic prevention efforts that may support optimal outcomes for women and their children.

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https://doi.org/10.1017/S095457941800069X Published online by Cambridge University Press

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