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Puberty and the Evolution of Developmental Science

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Abstract

In recent decades, theoretical and methodological advances have operated synergistically to advance understanding of puberty well beyond simplistic “Storm and Stress” views to increasingly comprehensive models that engage with the temporal, psychosocial, and biological dimensions of this maturational milepost. This paper discusses these theoretical and methodological advances and their implications for research and intervention to promote human development in the context of changing maturational schedules and massive ongoing social transformations.

Keywords

pubertal onset; globalization; secular trends

Introduction: Why Puberty Matters

Young people aged 10 –19 today number over 1.2 billion, or 17 % of humanity (United Nations, Department of Economic and Social Affairs, & Population Division, 2015), and have grown up with healthier childhoods and mass education but obdurate inequalities (Ortiz & Cummins, 2011). Their emerging capabilities and health are cornerstones for future economic and social flourishing, particularly in an era of demographic aging (Sheehan et al., 2017). Global policy has begun to absorb the lesson that, following successes in child survival and health, hard-won developmental gains in the first decade must be secured with support for critical maturational milestones in the second decade (Sawyer et al., 2012). Goals and attitudes of parents, communities, and agencies are evolving under the weight of massive ongoing social transformations and the challenge to allocate limited resources (Patton et al., 2016).

Here developmental science can play a particularly timely role by offering comprehensive models and new information that illuminate the temporal, psychosocial, and biological dimensions of this maturational phase. In recent decades, theoretical and methodological

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advances have operated synergistically to advance understanding of puberty well beyond simplistic “storm and stress” views (Casey et al., 2010). Indeed, the concept of puberty itself is undergoing revision (Herbison, 2016; Le Tissier et al., 2017). Emerging models and novel insights have moved from treating puberty as a largely physical process driven by a switch-initiated hierarchical neuroendocrine- and gonadal-steroid driven cascade (Sisk & Foster, 2004), to regarding it as a multidimensional interacting suite of maturational processes in body and brain as well as socioemotional capacities (Blakemore & Mills, 2014; Byrge, Sporns, & Smith, 2014; Dahl, 2016). The stakes are high: maturational trajectories of the body-brain-psychosocial nexus in puberty/adolescence leverage long-term outcomes for function and health (Zeanah, Gunnar, McCall, Kreppner, & Fox, 2011). These dynamics also conduce to a “social embedding” of rearing environment and reproduction of disparities whereby differential exposure to developmental advantages or risks and their biobehavioral impact both influence likelihood of realizing full potential during this stage, and capacity to capitalize on developmental gains (Holz et al., 2015; Noble et al., 2015; Theall, Drury, & Shirtcliff, 2012).

In the following review, we survey recent conceptual and methodological advances in the study of puberty and their implications for research and intervention to promote human development in the context of tectonic shifts in maturational schedules and massive ongoing social transformations

Theoretical and Conceptual Advances

Current views of puberty reflect three interlocking streams of inquiry at the level of physiology, individual, and population. These literatures concern the mechanisms regulating onset and pace of puberty, context sensitivity in developmental processes, and secular trends and population differences, respectively. As such, the work reflects the multi-dimensional nature of puberty as a biological, psychobehavioral, and social phenomenon.

Physiology: Onset and Pace of Puberty

Control of timing and onset of puberty remains an enduring biological mystery. The hypothalamo-pituitary-gonadal (HPG) system is suppressed a few months after birth to open an extended window of immaturity in childhood, and must be derepressed for puberty to occur (Livadas & Chrousos, 2016). Reactivation of the HPG system requires both re-initiation of hypothalamic secretion of gonadotropin releasing hormone (GnRH) and of the pulse generator regulating its pattern of release (Plant, 2015). Both genetic and environmental factors play substantial roles in pubertal onset (Ge, Natsuaki, Neiderhiser, & Reiss, 2007), but the precise pathways by which these influences work are topics of intense inquiry. Recent research has begun to unravel the mystery, starting with discovery of kisspeptin and going on to understand the GnRH neuronal network as a suite of interrelated functional modules (Kwon, Kim, & Kim, 2016). Kisspeptin initially was recognized as essential for hypothalamic GnRH release and, hence, a key link in GnRH pulse generation and regulation of gonadal function (Livadas & Chrousos, 2016). Opposing or permissive signaling of two other peptides, neurokinin B and dynorphin, provide close modulation of kisspeptin (Livadas & Chrousos, 2016). Similarly, an upstream suite of opposing epigenetic

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mechanisms repress or activate promoter genes and thereby finely regulates initiation and progress of puberty itself (Lomniczi et al., 2013; McCarthy, 2013). Together, these mechanisms suggest how activation of the pulse generator is achieved through coordinated activity of gene sets organized into functional networks (Lomniczi, Wright, & Ojeda, 2015). The mystery of the mechanisms behind puberty onset is closer to being solved, thanks largely to preclinical research.

The Individual: Development and Context

As understanding of physiological mechanisms that operate within individuals to control the timing and pace of puberty has advanced, so also has knowledge of pathways linking context with individual development. Evidence associating quality of postnatal environment with physical development in general, and puberty in particular, is firmly established at the population level and briefly reviewed in a later section. By contrast, the effects of gestational as well as ancestral conditions only recently have been recognized (Barker, 2012; Gluckman & Hanson, 2006b). Insights into processes operating across time—preconceptional, gestational, and postnatal-have important implications for understanding variation at puberty and thereafter. Systematic research in rodents by Michael Meaney and colleagues probed the role of early rearing environment on cognitive, behavioral, and maturational patterns, documenting effects of early maternal behavior on environmental reactivity, stress vulnerability, timing of puberty, and adult behavior of offspring (Francis, Diorio, Liu, & Meaney, 1999; Meaney et al., 2013). They have gone on to elucidate pathways behind these effects, including epigenetic mechanisms that modify gene expression (Meaney, Szyf, & Seckl, 2007; Weaver et al., 2004). Similar physiologic signatures of early adversity have been identified in humans (McGowan et al., 2009; Zhang, Labonte, Wen, Turecki, & Meaney, 2013). These revolutionizing lines of investigation not only have indicated how conditions of children's lives "get under the skin" through biological embedding (Hertzman, 2012), but also have stimulated related research identifying relationships of early rearing conditions with long term health (McDade et al., 2017; G. E. Miller et al., 2009) as well as revealing factors that buffer such relationships (Chen, Miller, Kobor, & Cole, 2011). For instance, the association of early harsh conditions with earlier menarche is attenuated by secure attachment in infancy (Sung et al., 2016). Ongoing inquiry also points beyond stress response systems to neuroimmune interactions that mediate pathways from early adversity to inflammation and health (Hostinar, Nusslock, & Miller, 2017). A longitudinal study of adolescent Canadian girls, for example, found an association of proinflammatory phenotype with early life adversity but not with current social stress (Ehrlich, Ross, Chen, & Miller, 2016).

The contexts informing individual development also may be distal: transgenerational sex-specific effects of parental as well as grandparental circumstances on descendants' maturation, health, and survivorship increasingly have been documented (Pembrey et al., 2006). Maternal hardship in early life increases likelihood of poor outcomes of pregnancy including low birth weight (Miller et al., 2017), which is known to be associated with offspring age at menarche and long-term health outcomes (Adair, 2001). In addition, evidence has been accumulating for age-specific (pre- vs. late puberty) effects of paternal nutrition on offspring health across one or two generations (Isganaitis, Suehiro, & Cardona,

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2017; Rando, 2012). Preconceptional effects of parental stress on offspring stress reactivity, behavior and mental health furthermore have been reported (Dias, Maddox, Klengel, & Ressler, 2015; Provencal & Binder, 2015). An expanding array of extra-genomic maternal and paternal mechanisms mediating transgenerational inheritance have been identified, including epigenetic markers, micro- and mRNA, and gamete constituents (Isganaitis et al., 2017; Klengel, Dias, & Ressler, 2016).

The aforementioned independent lines of research that identify important roles for epigenesis in both normative development (onset of puberty) and developmental variation (timing of puberty, vulnerability to stressors) converge with an avalanche of theoretical and empirical findings that are reshaping foundational models of heritability and thus, of development (Edelman & Tononi, 1997), evolution (Jablonka & Raz, 2009), and the relationship of the two (Bateson & Gluckman, 2011; D. Noble, 2013; West-Eberhard, 2003). Successful mapping of genomes spurred appreciation that genetic information is limited; therefore, mechanisms capturing information from internal and external environments to guide development and function are integral features of biological design (Grigorenko & Dozier, 2013). Mounting evidence for neo-Lamarckian intergenerational transmission of acquired characteristics appears to support this view (Davey Smith, 2012), famously illustrated by the demonstration that intergenerational transmission of psychobehavioral phenotypes is mediated by maternal caregiving style via epigenetic mechanisms (Cameron et al., 2008). Mounting recognition of the significant roles of context led to proposal of the exposome (Wild, 2012). Encompassing as it does the entirety of human environmental exposures, the concept has been critiqued as too broad for utility, though some have focused on biological impact or chemical and other pollutants (Miller & Jones, 2014; Ogino et al., 2013).

Rather than attempt to engage “the environment” entirely and returning the focus to puberty, we can build on the evidence for context sensitivity to identify the maturational moments where context affects the course of development when it is particularly open to, expectant of, or reliant on incoming information. Such sensitive periods open windows of opportunity as well as vulnerability that are important sites for variation and disparities in outcomes, and for constructive intervention as well (Dorn et al., 2019). Thanks to a new generation of research, puberty is coming into focus as such a moment during which unique maturational milestones in brain, body, and behavior are attained (Crone & Dahl, 2012). Although much of the pathbreaking work on sensitive periods, intergenerational transmission, and developmental origins of disease has focused on early life, particularly the “first thousand days” from gestation through infancy, many lines of evidence draw attention to puberty as a sensitive period of similar albeit distinctive importance (Scherf, Behrmann, & Dahl, 2012; Worthman, Tomlinson, & Rotheram-Borus, 2016). Indeed, adoption of a multi-system view of puberty plus recognition of the power of context in development blurs the distinction between puberty as a biological process and adolescence as a social construction, and foregrounds their biosocial, biocultural foundations. For the present, however, here we consider puberty to be the suite of biological and cognitive-behavioral changes that occur in the move from childhood to maturity, and follow global agency convention in considering adolescence as comprising the second decade (WHO, 2001).

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Population: Secular Trends and Life History

As research both has delineated context-environment relationships throughout development and across generations and has elucidated mechanisms behind them, other lines of inquiry have established an adaptive evolutionary framework that identifies design constraints and trade-offs behind these relationships. Life history theory emerged in zoology from systematic comparative analyses that identified determinants of key life course elements such as birth size, time to weaning, pace of development, time to reproductive maturation, adult body size, and life expectancy (Charnov, 1993; Stearns & Koella, 1986). Life history can be understood in terms of allocation of the finite resource, time, as driven by availability of other finite resources (energy, information) and mortality risk, to optimize life course fitness. A species' life history strategy constitutes how these resources are allocated in relation to the niche it occupies, which determines available resources and mortality risks. Life history strategy varies widely and is distinctive to each species, as illustrated by the contrast among fruit flies, mice, and elephants. Defining as it does the onset of reproductive career, the timing of reproductive maturation is a crucial element of life history strategy (Worthman, 1999b). In cross-taxonomic comparative analysis, high, stable resource availability and low mortality have been associated with a slow life history, with late maturation and reproduction.

Humans have a "slow" life history strategy, with extended childhood, late puberty, low mortality, and long life expectancy. Life history strategies furthermore show elasticity to acute conditions, known as norm of reaction, which is the range of phenotypes that can be expressed from the same genotype (Stearns & Koella, 1986). Such developmental adaptability permits the organism to accommodate the inevitable vicissitudes of living conditions, surviving to reproduce even when conditions are poor and flourishing when conditions are good. Human biological studies in the latter Twentieth Century documented a remarkably large reaction norm for menarche, spanning from median age over 18 in remote horticultural populations to under 12.5 in affluent postindustrial populations (Eveleth & Tanner, 1990; McIntyre & Kacerosky, 2011). Consistent with life history theory, accelerated growth and earlier puberty have accompanied dramatic improvements in global population nutrition and health, and the timing and pace of change in maturational schedules predictably varied in tandem with population differences in economic and health trajectories (Parent et al., 2003; Worthman, 2010). Variation in growth and maturation within populations also correlates consistently with differences in health and nutrition related to urban-rural or socioeconomic status (SES) gradients (Eveleth & Tanner, 1990). Recall the role of kisspeptin in regulating onset of puberty: it turns out that kisspeptin also plays a prominent role in regulation of food intake and energy expenditure (McCarthy, 2013), thus forming a direct physiologic link behind the association between reproduction and energetics (balance of nutrition and activity).

This takes us to the question of biodesign and how life history strategies actually are implemented. Neuroendocrine systems largely fill this role by providing the architecture for not only regulating allocation of resources and pace of development, but also mediating the relationship between context and individual (Finch & Rose, 1995; Worthman, 1999a). These systems both implement continuous acute prioritization of resource allocation, and

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orchestrate the long-term scheduling of growth, reproduction, and aging (Worthman, 2002). For example, pervasive effects of early and gestational maternal trauma are mediated largely through the HPA axis (Gunnar & Quevedo, 2007; Worthman & Kuzara, 2005), and population differences in maturational timing are indexed by shifts in HPG activity (Zemel, Worthman, & Jenkins, 1993). Consequently, endocrine measures have illuminated determinants of ongoing function, adaptation, and differential well-being, while life history draws attention to adaptive goals and trade-offs subserved by hormones.

The degree to which altered timing of reproductive maturation is paralleled by shifts in brain maturation remained unknown until recent imaging studies have enabled the study of both structural and functional brain maturation (Goddings et al., 2018), although studies at the level of populations and comparison across them are not yet available. Current evidence shows that the brain indeed undergoes a major period of development during puberty and through the second decade, and the impact of pubertal hormones on this process ensures a degree of coordination between brain and body. Nevertheless, regions involved in emotion processing and decision making mature asynchronously and continue to mature after obvious physical changes are completed. The trends in accelerated physical maturation led to concern about two forms of potential mismatch. One form is mismatch between appearance of physical maturity when psychobehavioral maturation is ongoing (Steinberg & Scott, 2003); the other entails mismatch between earlier physical and socioemotional maturity and the trend to delay social maturation (assumption of adult roles and statuses) (Gluckman & Hanson, 2006a). Such issues of synchrony among multiple maturing systems have been suggested to underlie the emergence of psychiatric and behavioral risks during adolescence (Paus, Keshavan, & Giedd, 2008).

Recent work has sought to integrate both psychobehavioral with biological dimensions of life history strategy, particularly with respect to reproductive strategies of which puberty is a vital element (Ellis, 2013). Neurobiological variation in sensitivity to stressors has been proposed to moderate life history strategies (Boyce & Ellis, 2005; Ellis & Boyce, 2011). Context sensitivity is posited to have a constitutional basis, with more sensitive individuals differentially benefiting or suffering from supportive or adverse environments (Pluess, Belsky, Way, & Taylor, 2010). Early adversity (parental harshness) furthermore has been associated with earlier menarche in western postindustrial populations (Belsky et al., 2007). This phenomenon contradicts life history expectations linking adversity to maturational delay, suggesting that under relatively low mortality and good nutrition, social adversity triggers an alternate accelerated life history strategy favoring early reproduction (Chisholm, 1993). Notably, such effects are moderated by secure parent attachment (Chen et al., 2011; Sung et al., 2016).

Summary: Interlocking Levels of Theory

While progress has been made at each level of inquiry, from physiology to individual to population, prospects for the greatest theoretical advances in the study of puberty lie in bridging across them. Unraveling proximal mechanisms regulating puberty also opened windows onto the bases of context sensitivity at the level of the individual. Moreover, tracking mechanisms behind individual-level context sensitivity has prompted discoveries at

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the molecular level that are spurring revisions of evolutionary theory. Reciprocally, applications of life history, a population-level theory, have stimulated productive lines of inquiry into contextual factors that most powerfully mobilize developmental responses. Hence, advances in theory and evidence have recast puberty as a suite of maturational processes involving not only body and brain, but also psychosocial competences that emerge through interactions between the adolescent and the material and social context (Byrge et al., 2014; Paus, 2013). They also situate the timing and course of puberty as a key element in life history strategy. Degree of synchrony among these ongoing processes, and the impact of shifting schedules of physical as well as social maturation, are important sites for inquiry to address the mental and physical health needs of adolescents. Additionally, investigators are rising to the challenge of expanding the scope of inquiry beyond the hitherto narrow focus on affluent postindustrial populations (Henrich, Heine, & Norenzayan, 2010). These issues are sharpened by evidence of rising material inequalities within and across nations (Piketty, 2014), and by concurrent evidence for the effects of adversity, including that income is most strongly associated with cortical area and specific neurocognitive capacities among the most disadvantaged children (Noble et al., 2015).

In the following section, we review methodological innovations that support these research needs by enabling researchers to tap physical processes of puberty less invasively, in naturalistic settings, and providing analytical tools required to manage the multi-system, multi-level, developmental nature of puberty. Similar advances are being made in remote sensing and portable technology that allow tracking of experience and behavior (Epstein et al., 2014; Odgers, Caspi, Bates, Sampson, & Moffitt, 2012; Shiffman, Stone, & Hufford, 2008). Used in tandem with biomarkers and appropriate statistical analysis, these techniques open powerful possibilities for understanding puberty and adolescence (Adam, 2006; Adam, Snell, & Pendry, 2007), but exceed the remit of the current review (but see Susman, Marceau, Dockray, & Ram, 2019). Taken together, such innovations reflect the value of interdisciplinary collaboration.

Methodological Advances

Biomarkers of Pubertal Onset and Progression

Biomarkers are defined as sensitive and robust signifiers of biological development and function, and these signifiers are possible at the molecular, cellular, organ and system level of physiology (Worthman & Costello, 2009). To be useful in research on puberty, biomarkers must be relevant and valid indicators of pubertal onset or progression, as adrenal androgens are, for example. Biomarkers may also be used as indicators of the action, function, and re-organization of physiologic systems that either correspond with puberty, such as changes in the hypothalamic pituitary adrenal (HPA) system (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009; Rege & Rainey, 2012), or are directly involved in its progression, such as changes in the HPG (Plant, 2015). Ideally, biomarkers are easily and repeatedly measurable, and the feasibility of the sampling and processing of biomarkers (participant acceptability and burden, sample stability, cost) is of direct relevance to how they have been incorporated in research on puberty, especially in population based studies (Granger et al., 2007; McDade, Williams, & Snodgrass, 2007). In addition to indicating

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biological processes of puberty, biomarkers have been used for decades to examine psychobiological vulnerability or resilience in relation to puberty, for example, depression, risk-taking, or aggression (Angold, Costello, Erkanli, & Worthman, 1999; Marceau, Ruttle, Shirtcliff, Essex, & Susman, 2015; Rowe, Maughan, Worthman, Costello, & Angold, 2004; Susman, Granger, Murowchick, Ponirakis, & Worrall, 1996).

Development of minimally invasive measures for biomarkers of puberty directly contributed to a resurgence of effort in mapping psychobiological processes and correlates of puberty. There are now thousands of studies that have incorporated at least one biomarker as a predictor, correlate or consequence of pubertal development (Mendle et al., 2019). Although existing methodologies to track pubertal status in population studies have been heavily deployed in psychobehavioral research, they remain underused in other population studies in social and health sciences that employ indirect morphological markers of puberty such as breast or gonadal development in girls and boys, respectively. Such indirect measures are much more convenient and less expensive, but the many factors that increase the margin of error (self report bias, observer error, contextual confounders) reduce their information value for investigating the timing, course, and causes of variation and change within and between populations (Barry & Schlegel, 1986; Parent et al., 2003). Population studies that use direct measures of neuroendocrine activity (and perhaps other biomarkers) are needed to resolve existing uncertainties about the differences in pattern and predictors of secular trends in boys versus girls, about whether secular trends are continuing or have plateaued, and about ecological factors associated with intra-population differences. In addition to their scientific merit, these questions have high salience for public health and policy, as well as for parents, educators, and clinicians concerned about what is “normal” and expectable for healthy puberty and adolescence.

Articulating a more expansive model of puberty that incorporates multiple systems, psychobehavioral capacities, and temporospecial contexts should capitalise on the wealth of extant data, led by advances in biostatistical modelling described (Susman et al., 2019). But the identification of novel biomarkers indicates opportunities to develop more comprehensive understanding of puberty. Herein we describe advances in the measurement of established biomarkers, and indicate several physiologic systems and their biomarkers that deserve attention, as they are coupled to the changes in the reproductive neuroendocrine axis at puberty.

Advances in Measurement of Biomarkers

Recent innovations in biochemical methods have directed attention to biological specimens other than saliva, blood, and urine. The choice of biological sample is necessarily determined by the conceptual model informing the research but there are opportunities to advance understandings of puberty by drawing upon sampling strategies and tissues established in animal research, including the use of nail and hair clippings. These can provide aggregate indicators of physiological function, including hormone secretion, over a longer time period, and have particular potential in population based research due to the ease of sampling and transport. A small number of studies indicate the potential of using hair and fingernail samples to gather data on biomarkers relevant to puberty; converging evidence

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indicates that steroid hormones can be measured in hair and nail clippings from children (Hubmann, 2016; Stalder et al., 2016). Levels of hair cortisol provide an integrative measure of secretion over a month and corresponds with aggregate measures of salivary cortisol taken during the same month (Short et al., 2016). Measurement of steroids in nails, including testosterone, has been possible for almost two decades (Choi, Yoo, & Chung, 2001) but the challenges of processing of nail and hair samples delayed their ready adoption in research. More recently, testosterone and dehydroepiandrosterone have been quantified in nail clippings using enzyme linked immunoassay protocols, after standard extraction procedures (Brown & Perrett, 2011; Tegethoff et al., 2011), representing a distinct advance on previous chromatographic methods. Nevertheless, greater assay sensitivity is needed for hair and nail samples. Furthermore, validation studies must demonstrate concordance with established samples of biomarkers, and use of such integrative measures must be weighed with respect to the research question and the requisite level of data granularity (Dorn, this issue).

Inclusion of biomarkers in research, especially population based studies, may be challenging for reasons including cost and participant burden (Adam & Kumari, 2009). Child and adolescent participants may find the collection of biological samples burdensome, especially in everyday contexts, and providing nail or hair clippings may be more acceptable if a marker of longer-term exposure is required. Finally, in an advance that could revolutionise research using biomarkers, lateral flow testing devices recently have been shown to provide rapid measures of steroid hormones (Shirtcliff et al.,2015) with application in research contexts. The nearly real-time measurement of biomarkers associated with pubertal development, using body fluids, or as aggregate measures of longer-term secretion using a single sample of tissue, offer exciting possibilities to understand the time progression of puberty and its biological and behavioural correlates.

Expanding the Roster of Candidate Biomarkers of Pubertal Process

Early research identified a number of biomarkers of puberty and many of these have been described in detail, notably adrenal androgens and gonadal steroids (J. L. Cameron, 2004; Panter-Brick & Worthman, 2008; Rockett, Lynch, & Buck, 2004; Worthman & Costello, 2009). Only recently has attention turned to other biomarkers as puberty onset and progression are understood to involve interlocking functional systems (Kwon et al., 2016). Secular trends to earlier pubertal onset and improved adolescent health indicators, combined with observations about the potential biological underpinnings of adolescent development and behavior, make biomarkers associated with the metabolic, microbiomic, neural, and immune systems potential candidates for targeted exploration in relation to puberty; below, we highlight relevant candidates that tap these domains.

Markers of metabolism related to puberty.—The metabolic control of puberty results from a complex interplay of signals from several biological systems (Messina et al., 2016). The interplay between pubertal and metabolic processes is exemplified in the functions of leptin, a hormone produced primarily by adipose tissue and hence an indicator of energy stores (Kwon et al., 2016). Leptin is a permissive factor for the initiation of puberty, and regulates metabolism at the hypothalamic level, increasing before the pre-pubertal rise in GnRH. The rise in leptin is sexually dimorphic; levels are lower in boys and this is related to

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testosterone levels (Ahmed et al., 1999). Leptin levels modulate kisspeptin secretion and thereby mediate metabolic control of puberty (Manfredi-Lozano et al., 2016), by stimulating hypothalamic GnRH secretion and thereby regulating pituitary gonadotropin output (Dungan, Clifton, & Steiner, 2006). Thus, leptin may serve as an upstream biomarker for the onset of puberty. Together with evidence that kisspeptin acts as a key gating factor in puberty (Clarke, Dhillo, & Jayasena, 2015; Cortes, Carrera, Rioseco, Pablo del Rio, & Vigil, 2015) and in regulation of HPG activity (Chan et al., 2011; de Roux et al., 2003), these findings suggest that both kisspeptin and leptin could prove useful in tracking pubertal onset, including delayed or precocious puberty, although the work in humans is preliminary and has been conducted among people with conditions such as hypothalamic amenorrhea or hypogonadotropic hypogonadism (Lippincott et al., 2016). Insofar as leptin and the expression of kisspeptins are influenced by stress, nutrition, obesity and other metabolic disruptions, they may be useful probes to examine multisystemic effects of health and wellbeing on pubertal development.

A cast of trillions: puberty and the microbiome.—The human microbiome, the relatively enormous genome of a human's microbiota, holds great potential to inform understandings of pubertal development and adolescent health and behavior. Trillions of microbes inhabit the human body, and new sequencing technologies have demonstrated that these microbes not only influence many aspects of physical health, but also are related to psychological wellbeing and behavior (Allen, Dinan, Clarke, & Cryan, 2017; Fung, Olson, & Hsiao, 2017). Puberty prompts changes in the microbiome, perhaps in response to altered patterns of activity of the neuroendocrine system, including changes in levels of sex steroids (Markle & Fish, 2014; Oh, Conlan, Polley, Segre, & Kong, 2012; Yurkovetskiy et al., 2013).

The gut microbiota, a regulator of the gut-brain axis, has received the most attention as a biomarker of risk and resilience at puberty. Bidirectional communications run between the gut and the brain, and this axis integrates signals from the endocrine, metabolic and immune systems, potentially affecting both multiple metabolic pathways and behavior at puberty and adolescence (Allen et al., 2017; Cryan & O'Mahony, 2011). It is likely that the microbiome interacts with the HPG axis to modulate gonadal hormones, and alter the brain and behaviour of adolescents. Intriguingly, research in animal models has demonstrated that a change in the gut microbiota following transplant of fecal material from an opposite sex animal, can result in increased production of androgens (Markle, Frank, Adeli, von Bergen, & Danska, 2014), and other studies have shown that some microbiota can convert glucocorticoids to androgens (Markle et al., 2014). Consequently, the microbiota may have the capacity to regulate sex steroids.

The gut microbiota may influence puberty by another pathway, via effects on metabolism and energetics (Le Chatelier et al., 2013). Increased weight and obesity have been associated with earlier puberty in both girls and boys (Ahmed, Ong, & Dunger, 2009; De Leonibus et al., 2014), and individual differences in body weight have been linked to differences in composition of the gut microbiome. Fecal transplants from lean to obese individuals have been associated with reduction in recipient body weight, and vice versa (Garrett, 2013; Ridaura et al., 2013). In turn, the gut microbiota is shaped by a host of factors, including birth mode, infant feeding, diet, antibiotic use, and household ecology, many of which are

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undergoing dramatic changes with globalization (Bokulich et al., 2016; David et al., 2014; Maslowski & Mackay, 2011). Childhood body mass index (BMI) was linearly and negatively associated with age at onset of puberty among Scandinavian schoolchildren monitored 1930–1969, suggesting the importance of weight per se rather than overweight (Aksglaede, Juul, Olsen, & Sorensen, 2009). Hence, more "thrifty" microbiota may contribute to weight gain and thereby modulate pubertal timing.

So far, much of the microbiome research relating to puberty has been conducted in animal models, but the theoretical models emerging from such work (Neufeld, Luczynski, Oriach, Dinan, & Cryan, 2016) signify the potential of the microbiome as a biomarker in future studies of health during puberty in humans as well. Early indications from the pace and direction of microbiome research are that findings may radically transform understandings of puberty, behaviour and health. Sample collection protocols will need to be fielded, but initiatives such as the Earth Microbiome Project have demonstrated the feasibility and global reach of human microbiome sampling (Gilbert, Jansson, & Knight, 2014).

Puberty and the nervous system.—The need for research to capture the unique and coordinated development of all neural systems during pubertal development long has been recogized (Dahl, 2004), because pubertal processes have transformative effects on the brain, changing both neural architecture and biochemistry, and affecting processes including apoptosis, myelination, neuropeptide expression, and neurotransmitter receptor sensitivity (McEwen & Alves, 1999). A body of work has mapped out the synaptic pruning and myelination that occur in the second decade (Blakemore & Choudhury, 2006; Goddings et al., 2014; Sisk & Zehr, 2005), and regionally specific differences in brain volume have been related to circulating levels of testosterone and estradiol (Neufang et al., 2009; Peper, Hulshoff Pol, Crone, & van Honk, 2011) as well as to sex and pubertal stage (Bramen et al., 2011). Gonadal steroids act on the brain in both organizational and activational ways; they alter brain structure by, for example, influencing myelination, dendritic branching, and the addition of neurons in specific regions (Ahmed et al., 2008; Ladouceur, Peper, Crone, & Dahl, 2012). They furthermore can alter the activity of neural systems (Koolschijn & Crone, 2013). Direct measurement of the activity in the central neuroendocrine system is difficult, although application of novel functional techniques such as optogenetics offers powerful means to track functional pathways (Le Tissier et al., 2017), and there is much to be discovered about the timing and magnitude of pubertally mediated changes in the nervous system. Tracking such processes is made more complex by differences in the timing and degree of sensitivity to the effects of hormones at different stages of pubertal development (Schulz, Molenda-Figueira, & Sisk, 2009). The congruence of sample timing and pubertal events must be carefully gauged, and the potential upstream and downstream correlates specified for biomarkers to have maximal value (Worthman & Costello, 2009). Changes in brain architecture and function, for instance, may occur after a pubertal biomarker is obtained (Belchetz, Plant, Nakai, Keogh, & Knobil, 1978; Moenter, 2015). Algorithms to model associations of puberty and brain development (Faghih, Dahleh, Adler, Klerman, & Brown, 2015) may be used to address such challenges, and to design studies that capture the temporal associations of pubertal processes and changes with neural architecture, neurotransmitters and neural systems.

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Tracking interactions of puberty and neural development faces twin challenges to feasibility for obtaining appropriate measures of puberty, and assessing brain morphology, chemistry and activity in humans. Collecting data about brain structure and function in large scale studies has been difficult, but research consortia currently are compiling imaging databases with thousands of participants, capturing ages representing puberty and adolescence and often focused on mental health. Examples include IMAGEN, a longitudinal imaging and genetics study (Schumann et al., 2010), and the ENIGMA major depressive disorder consortium (Schmaal et al., 2017). Other examples of data aggregation and meta-analytic work examining brain structure and function also serve as useful models for researchers interested in puberty (Biswal et al., 2010; Choudhury, Fishman, McGowan, & Juengst, 2014). Despite existing administrative or other barriers to access, the principles of data sharing, cooperation, and research investment should direct efforts to make use of the trove of data already collected (Poline et al., 2012). Aggregation and mining of extant data afford opportunities to accelerate research on puberty and the nervous system that are as great, or greater, than newly generated data and techniques. We note that these opportunities do not rely on technical advances in measurement, but arise directly from data sharing collaborations across research fields and laboratories, along with the application of novel or underused statistical approaches. However, the various measures used to assess puberty tap different relevant processes, and although they are related, they are not necessarily equivalent. Harmonisation of data across studies is crucial for future progress in this area, and requires exacting precision to define measures with equivalence in quality, specificity, and representation of pubertal process or stage.

Puberty and the immune system.—The complexity of dynamics between the reproductive endocrine system and the immune system is indicated by the immunomodulatory effects of sex steroids (Grossman, 1985; Kane & Ismail, 2017; Trigunaite, Dimo, & Jorgensen, 2015) but rarely studied in relation specifically to puberty (Shanahan et al., 2013). The mapping of the interactions between the immune and reproductive neuroendocrine systems does not as yet suggest strong candidate biomarkers for studies focussed on puberty, but there are several promising directions for research. The effects of gonadal steroids on the immune system are dimorphic; estrogens have immune-enhancing effects and progesterone and androgens, including testosterone, are more often associated with immunosuppression, and these effects become apparent after puberty (Lamason et al., 2006). However, it still is not standard practice in research on immune responses to examine sex differences or interactions of other factors with sex, even less common to include measures of reproductive hormones or pubertal status. As with other candidate biomarkers that can contribute to a systems based study of puberty, significant efforts are needed to map the interactions of pubertal and immune processes in humans. Here again, interdisciplinary collaboration is essential.

Biomarkers of puberty may prove valuable to probe the pathways underlying sex-based differences in innate and adaptive immune responses, perhaps especially insofar as they may be related to the sex differences in depression and other psychopathologies. Onsets of psychobehavioral disorders that characterize the second decade peak at age 14 among U.S. adolescents (Paus et al., 2008), and direct relationships to gonadal hormones have been

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identified. These hormones, in particular testosterone, have known relationships to limbic system maturation and changes in reward processing at puberty (Bramen et al., 2012; Spielberg, Olino, Forbes, & Dahl, 2014). Moreover, the neural circuits associated with threat and reward processing involve two major systems that are directly implicated in development of depression (Stringaris et al., 2015; Swartz, Hariri, & Williamson, 2017; Swartz, Knodt, Radtke, & Hariri, 2015), are furthermore linked to increased susceptibility to stress (Nikolova, Bogdan, Brigidi, & Hariri, 2012; Swartz et al., 2015), and finally are sensitive to changes in inflammation (Eisenberger et al., 2010; Harrison et al., 2016; Inagaki, Muscatell, Irwin, Cole, & Eisenberger, 2012; Swartz, Prather, Di Iorio, Bogdan, & Hariri, 2017). Gender differences in these relationships have been identified but are not consistently studied. Together, these intersecting lines of evidence suggest that further inquiry into interactions of puberty, immune activity, psychobehavioral regulation and mental health risk will yield important insights that also will inform prevention and intervention efforts.

Advances in Biostatistics

Expanded use of biomarkers for measuring puberty, along with new studies capable of integrating across data streams and including genetic information, have necessitated concomitant advances in biostatistics. As technology and computing resources continue to expand, so do the possibilities for increasing the scope and complexity of the longitudinal study designs required for investigating developmental processes. The use of historical databases in conjunction with current studies now allows for comparisons of pubertal trajectories across generations (Walvoord, 2010). The increasing ease of technologically-mediated global collaborations allows for cross-cultural comparisons of puberty. Continual expansion of technological resources facilitates generation and aggregation of ever more data to test theories of pubertal development. Core methodological issues and exciting future directions are discussed in detail in Susman et al. (2019). Here, we highlight two major recent biostatistical contributions to our understanding of puberty: modeling developmental processes themselves, and capitalizing on new interdisciplinary techniques in genetics.

Modeling developmental processes.—Biostatistical advances for modeling phenotypic measures of pubertal maturation have advanced our understanding of puberty as a process, enabling investigators to gauge the tempo or rate of development, often through the use of growth curve modeling(Beltz, Corley, Bricker, Wadsworth, & Berenbaum, 2014; Keenan, Culbert, Grimm, Hipwell, & Stepp, 2014; Mendle, Harden, Brooks-Gunn, & Graber, 2010). A small body of work has sought to apply nonlinear modeling techniques and better match current models of puberty to theoretically nonlinear trajectories that have been described for decades (Greulich, Dorfman, Catchpole, Solomon, & Culotta, 1942). Nonlinear growth curve models have been used to examine pubertal timing (age at the mid-point of puberty) and tempo (number of stages each individual progresses through per year), and generally have been found to fit repeated measures data better than linear models across different time scales and pubertal measures (Beltz et al., 2014; Eaves et al., 2004a; Marceau, Ram, Houts, Grimm, & Susman, 2011; Susman et al., 2010). Nevertheless, nonlinear growth curve models still simplify pubertal maturation in such a way as to miss important variation in pubertal onset and course. First, in the aforementioned studies, the sigmoid-shaped course of development is assumed to be symmetrical: youth start development slowly, mature the

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fastest in the middle, and slow down again toward the end. This pattern is unlikely to reflect the development of most (if any) individuals. Ellis, Shirtcliff, Boyce, Deardorff, and Essex (2011) used piece-wise growth curves to estimate separate rate parameters for early vs. late puberty, showing differential prediction of rate changes over development. Although the method allows for asymmetrical development (e.g., starting slow and finishing quickly), their inclusion of only two "pieces" assumed a single rate change and was driven by modeling decisions rather than underlying theory of pubertal processes. Testing various forms of growth curve modeling constitutes an important first step towards better characterization of puberty, but future work can do much better in terms of identifying important theoretical characteristics of puberty that should be explicitly modeled. For example, the degree of synchrony in adrenal and gonadal development remains relatively understudied in longitudinal research on puberty; consequently, its significance is scarcely understood (Susman et al., 2010). Future work explicitly could model synchrony in multiple growth characteristics that change during the pubertal process (e.g., skeletal maturation, Flor-Cisneros et al., 2004, height). Analysis of different maturation patterns-including characterization of time to each of several distinct pubertal milestones (e.g., through survival analysis), and the number and spacing of inflection points marking shifts in the rate of change in metrics of maturation-would provide new theory-based measures of puberty that would advance our understanding not only of predictors of pubertal trajectories, but also of outcomes from different maturation profiles.

Capitalizing on genetics to illuminate pubertal process.—Genetic analysis further illustrate biostatistical innovations that greatly have advanced the understanding of puberty. Expanded computational resources have allowed twin studies effectively and efficiently to examine the contributions of genetic and environmental influences on multiple aspects of pubertal development in large samples (Eaves et al., 2004b; Mendle et al., 2006). Genome-wide association studies have identified novel genes linked to puberty (e.g., Cousminer et al., 2013; Elks et al., 2010; He & Murabito, 2014; e.g., Liu et al., 2009; Perry et al., 2014). This population-based research identifies genetic contributions to pubertal onset, tempo and timing, and has revealed an intricate and coordinated network of genes that control physiological processes of puberty (Cousminer et al., 2013; Day et al., 2017; Elks et al., 2010). These include genes that encode leptin and kisspeptin and their receptors (e.g., LEP/LEPR; KISS1/KISS1R[GPR54])(Rostami, Kohan, & Mohammadianpanah, 2015; Seminara et al., 2003), as well as those that control the sensitivity of the GnRH feedback loop (e.g., GNRH1)(Day et al., 2017).

Given the enormous number of candidate genes, a vigorous field of research aims to identify which genes are critical to puberty. Collating data from 40 studies with >370,000 European women, a research consortium has identified 389 independent genetic signals for age at menarche (Day et al.,2017). These signals account for just 25% of the estimated heritability of age at menarche, a mere 7.4% of the total variance in age at menarche (Day et al., 2017). In addition to consortium-based and meta-analytic approaches, novel computational methods have facilitated formulation of biologically relevant methods that inform the biology of puberty, including gene enrichment and over-represention analysis, gene set and network-based analyses, and other systems-biology techniques. Gene set (using an *a priori* set of

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genes) and network-based (a parallel but more data-driven approach) analyses examine associations of DNA variation at the level of the gene or a network or set of genes (e.g., testing the joint associations of all included markers with puberty), rather than at the level of specific single nucleotide polymorphisms (or other markers), and can be a useful tool for reducing the type-1 error rate and increasing power (de Leeuw, Mooij, Heskes, & Posthuma, 2015; Jia & Zhao, 2014). Gene enrichment, or over-representation analysis, is a systems-biology tool that aids interpretation of gene lists, like those generated from GWAS, to determine whether particular biosystems or biological pathways (cascades of actions or interactions among molecules that lead to assembly of proteins, fats, or other changes like gene expression and cell movement) include a statistically significant proportion of genes on the target list. These analyses provide a broader picture of the biological systems in which genes (e.g., that have been empirically linked to puberty) operate, and has been used to generate hypotheses about how specific genes are related to puberty phenotypes (Cousminer et al., 2013; Zhu et al., 2010).

Nonetheless, much of the work on the genetics of puberty has focused on one sex (most often females) and been conducted within ethnicity (most often Caucasian). Consequently, even these ‘best’ estimates may not be as robust in populations with high racial/ethnic diversity (Cousminer, Widen, & Palmert, 2016). In addition, sex specificity has been reported, such that signals identified in females may have greater or lesser effect in males. Indeed, genome-wide association studies have identified only a few loci that contribute to pubertal timing in males, and with fewer signals (Cousminer et al.,2016). Many promising paths of inquiry are suggested by such sex specific genetic variability in pubertal timing and tempo, and in differential sensitivity to rearing conditions. For instance, the exact primary mechanisms that underlie activation of HPG axis maturation and regulate the onset of puberty remain to be discovered, although recent discoveries about the role of epigenetic mechanisms (Messina et al., 2016) and the nature of neuroendocrine regulation are taking us closer. Further investigation of the maturation of GnRH secretion and pituitary responsiveness is vital to understanding the mechanisms of the wide spectrum of pubertal development.

Less than five years ago, little was known about the role of epigenetic mechanisms in the development of neuroendocrine reproductive function. The availability and affordability of epigenetic assays allow for the examination of specific molecular mechanisms linking genetic and environmental influences to pubertal maturation. As reviewed above and elsewhere in this issue (Aylwin et al., 2019), identification of epigenetic and other non-genomic mechanisms is delineating how environmental and metabolicfactors act as crucial regulators of the HPG axis including the timing and initiation of puberty. application of epigenetics to puberty continues to expand, we will gain insight into tissue- and timing-specific mechanisms contributing to normative and abnormal variations in pubertal maturation. Here again, biomarkers will be useful in elucidating intricate person-context dynamics across development and leveraging predictive and real-time interventions to enhance pubertal outcomes.

Summary: methodological advances.—In sum, although accumulated data focused on the reproductive neuroendocrine system provide opportunities for collaborative

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approaches and the application of new analytical techniques discussed elsewhere in this issue (Aylwin et al., 2019; Susman et al., 2019), additional biomarkers can more expansively map the multiple and interactive actions of biological systems that influence puberty. Puberty research in recent decades has concentrated on GnRH and sex steroids, using both animal and human models to articulate the role of the endocrine system in puberty, and on improving our statistical methods of longitudinally quantifying the pubertal process. However, as demonstrated by the advances in our understanding of the genetics of puberty in the field of statistical genetics, adopting a systems biology approach is necessary to parse the complex interactions of genes, cells, tissues and organs involved in puberty. Additionally, extant and emerging arrays of biomarkers and functional measures suited to ambulatory application in everyday settings offer tremendous potential for research that integrates biological processes with cognition, affect, behavior, and context across time and space (Baum et al., 2014; McDade et al., 2007; Shiffman et al., 2008). Such capabilities are especially valuable for expanding research on puberty to more geographically and culturally diverse populations, a need discussed in the next section.

Puberty in Global Context

These are exciting times in developmental science, when empirical, conceptual, and methodological advances greatly have expanded knowledge about ontogeny itself, resolving entrenched debates and challenging or modifying established views in the process. Old nature-nurture distinctions have receded, as evidence at many levels of granularity-from molecular to evolutionary-points to mutual interdependence of biological and contextual sources of information throughout development and across generations. Such foundational insights have fueled surging attention to supporting youth strengths and needs across the globe (UNICEF, 2011; WHO, 2001), and to bringing developmental science into conversation with global health and policy actors to inform this enterprise (Patton et al., 2016; Sawyer et al., 2012). Advances in adolescent health and survival have not matched the great gains realized for infants and children, even as those gains have increased the numbers surviving to the second decade (Hill, Zimmerman, & Jamison, 2015; UNICEF, 2012). Adolescents' welfare is in everyone's interest (Kleinert & Horton, 2016), but neglect of their needs arises from relatively low mortality risk in this period although it is known to harbor the roots of long-term chronic diseases. Moreover, ascendant challenges to adolescent health differ from those encountered earlier in life, and involve sexual and reproductive risk, mental illness, injury, and lifestyle formation (Mokdad et al., 2016). Recent insights in pubertal and adolescent development offer translational opportunities to more effectively address adolescent health needs (Patton et al., 2016).

Other considerations spur the drive for global action: these also are challenging times for youth. Rapidly shifting geopolitical, climatic, demographic, and global economic conditions challenge youth's crucial project of life construction (UNICEF, 2012; Worthman, 2011). Macro-level forces shape the landscapes that adolescents must navigate to build their lives, raising an imperative for large societal discussion and action within and among nations to negotiate societal goals and opportunities with individual youth interests and needs. Many forces have converged to urge the importance of attending to adolescence: as the drive moves forward, we point to three significant knowledge gaps that merit attention: cultural

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factors, the impact of "mismatch" in maturational components of puberty, and multidimensional studies of puberty embedded in the broader social context.

The first concerns integration of cultural factors in studies of puberty and adolescent development. We have emphasized the need for systematic incorporation of biomarkers in longitudinal population studies of puberty, and pointed to the many advances made by doing so in psychobehavioral research. Expansion of research on puberty and its relationships with psychobehavioral development to a wider range of cultural contexts within and across societies is needed and feasible. Development of field-friendly sampling methods has facilitated inclusion of biomarkers in large scale international programs such as the Demographic and Health Surveys (Garrett, Sangha, Kothari, & Boyle, 2011; McDade et al., 2007). Biomarkers have been incorporated extensively by anthropologists for population research in non-western settings (Gurven et al., 2017; Leonard et al., 2015; Worthman & Panter-Brick, 2008), including in large birth cohort studies (Bui et al., 2012; Gettler, McDade, & Kuzawa, 2011; Kuzawa, Gettler, Muller, McDade, & Feranil, 2009; McDade et al., 2017). Nevertheless, our present understanding of human development-both biological and psychobehavioral-is recognized as limited by reliance on a narrow sampling from the wide sociocultural diversity that humans inhabit. This is particularly true of puberty and adolescence in the contextualized body-brain-psychosocial sense as they are now understood. Given what has been learned about the significance of spatiotemporal contexts, priority among developmental scientists should be given to tapping strategically the enormous human diversity to understand its correlates in puberty, beyond mere timing of menarche or height gain.

Second, evidence is needed about the impact of "mismatch" brought on by shifting schedules in components of maturation in puberty, particularly in view of dramatic secular trends to faster growth and earlier puberty even as rising bars for adult independence delay attainment of social maturity (McCarthy, 2013; Sawyer et al., 2012). Asynchrony among elements of brain maturation have been proposed as grounds for rising rates of mental disorders beginning at puberty (Paus et al., 2008), but inquiry into patent questions about the extent and possible effects of asynchrony among physical, psychobehavioral, and social maturational schedules has been largely focused on studies of effects of early vs. late puberty on behavior and attainment within western populations (Angold, Costello, & Worthman, 1998; Keenan et al., 2014; reviewed in Dorn & Biro, 2011; Marceau et. al., 2011). The very social and technical advances that brought about improvements in nutrition and health that, in turn, prompted earlier onset of puberty, also occurred alongside demographic, economic, and educational changes that have altered cultural maps for the life course including adolescence. Social scripts for the transition to adulthood have both changed and become less orderly (Furstenberg, 2013). Very few studies have integrated biological, behavioral, and cultural factors in the study of puberty and adolescence in non-western settings (Worthman, 1993), though a growing number comes from western populations (Sweet, 2010; Telzer, Fuligni, & Galván, 2016).

Third, multidimensional studies of puberty are needed which probe the impact on youth of social systemic forces such as socioeconomic inequality. We have seen that recognition of the powerful role of context in trajectories and outcomes of development is one of the great

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advances in developmental science. Indeed, growth rates and timing of maturation have come to be regarded as indicators of environmental quality, even across generations (Perkins, Subramanian, Davey Smith, & Ozaltin,2016). Key ingredients of environmental quality comprise not only access to material resources or exposure to insults, but also availability of social-emotional resources and societal affordances and opportunities. Differential distribution of important affordances or challenges becomes embodied through developmental processes, leading to disparities in capability, function, and health (Hertzman & Boyce, 2010; Nussbaum, 2011). The wealth of global data on factors influencing child growth, maturation, and health is not matched by similarly robust data on issues heavily explored in postindustrial settings, such as pathways to differential vulnerability to stress and its long-term outcomes in areas of well-being, function, resilience, and health. As a recent review observed: “The health of adolescents is strongly affected by social factors at personal, family, community, and national levels.” (Viner et al., 2012, p. 1641). But health is not the only or necessarily the most important outcome from puberty; rather, others such as ability to achieve personal and socially desirable goals, or a sense of meaning and value, may be significant (Petersen, Koller, Motti-Stefanidi, & Verma, 2017; Worthman, 2011).

In sum, we have discussed key theoretical and methodological advances in puberty research, and the importance of continued growth in these areas combined with inclusion of diversity in a global context. We have argued that puberty is a multidimensional interacting suite of maturational processes in body, brain, and socioemotional capacities that is important at the individual level, for example, in shaping the likelihood of realizing full potential and the capacity to capitalize on developmental gains, and at a very broad social level, with implications for improving adolescent morbidity and mortality, and economic conditions. Theoretical and conceptual advances bridging the levels of physiology, individual, and population have been supported by concurrent methodological advances in use of biomarkers from multiple coordinated biological systems, and ever-growing computational capacities mapped onto developmental and systems biology approaches. As developmental science related to puberty continues to advance, we challenge researchers to take and expand the examples of integrative conceptual models and new and ever-evolving technological advances to a wider range of cultural contexts. Integrated study of biological, psychobehavioral, and contextual dynamics in puberty and adolescence offers tremendous opportunity to tackle these issues at a pivotal, and hence highly informative, point in the life cycle. Skillful application of insights and methods from developmental science to investigate these important dynamics in diverse sociocultural settings will advance capacity to promote both well-being and health, and will require continued expansion of multi-national, multi-ethnic human capital and interdisciplinary collaboration.

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