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Authors

Roubinov, Danielle
Meaney, Michael J
Boyce, W Thomas

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Change of pace: How neurodevelopment accelerates or decelerates to accommodate unmet early needs

Danielle Roubinov, PhD[1], **Michael J. Meaney, PhD**[2,3,4,5], **W. Thomas Boyce, MD**[3,6]

[1]Department of Psychiatry and Behavioral Sciences, University of California, San Francisco

[2]Department of Psychiatry and Sackler Program for Epigenetics and Psychobiology, McGill, University, Montreal, Quebec H3H 1R4, Canada

[3]Child and Brain Development Program, CIFAR, Toronto, Ontario M5G 1M1, Canada

[4]Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research (A * STAR), 117609 Singapore

[5]Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, 119228 Singapore

[6]Department of Pediatrics, University of California, San Francisco

1. Introduction

Among the most prominent hallmarks of biological development is its remarkable plasticity over the entire span of individual lives (Bateson et al., 2004; Belsky and Pluess, 2009). Rather than a lockstep succession of phenotypic change, development is marked, especially in the early years, by a striking tractability in the adaptive demands and signals emanating from the individual's environment. Such phenotypic plasticity derives from the transcription regulatory capacities of the epigenome and is the centerpiece of a "developmental synthesis" describing how changes in developmental trajectories drive and constrain evolution (Gilbert and Epel, 2009). A core assertion of that evolutionary-developmental synthesis is that differences in where, when, and how genes are activated and expressed are the sources of variation in phenotypes (Muller, 2007) and that such variation is a key element in the developmental origins of human morbidities (Gluckman et al., 2009). Developmental outcomes thus serve as the primary focus for studies of phenotypic plasticity. An important but understudied dimension of such plasticity is the parameter of *pace*: alterations in the timing and tempo of developmental change.

Two unanticipated findings from our research group at the University of California, San Francisco and the University of British Columbia, Vancouver prompted a more intensive consideration of developmental pace within accessible data sets with measures of developmental timing. First, in the Peers and Wellness Study (PAWS), a prospective investigation of classroom social hierarchies and health among kindergarten children attending Berkeley public schools (see, for example: Bush et al., 2018; Obradovic and

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Boyce, 2009; Obradovic et al., 2010), dental exams conducted in a sub-sample of children during first grade yielded an unexplained, incidental finding: that children with higher basal salivary cortisol expression over three sequential school days had fewer primary teeth than children with lower basal cortisol measures ($r = -.40$, $p < .01$).[1] That is, children with evidence of greater stress-related, chronic hypothalamic-pituitary-adrenocortical (HPA) activation had exfoliated, by age 6, more of their primary dentition than had peers with more normative HPA basal activity, an association not attributable to either dental caries or tooth extractions. Second, another study by Moore and colleagues (Moore et al., 2017) examined epigenetic age data among children from a community sample of mothers and babies in whom maternal-infant contact was recorded as either unusually low or unusually high. Temperamentally fussy babies with low-contact mothers had significantly slower epigenetic "clocks," reflecting a developmentally earlier pattern of DNA methylation. Both studies thus revealed evidence of alterations in the pace of developmental change, one with dental exfoliation data demonstrating developmental acceleration and the other with epigenetic clock data suggesting developmental deceleration.

Human behavioral development is the sequential, integrative acquisition of motoric, socioemotional, cognitive, and linguistic skills, which begin prenatally, continue over the lifespan, and proceed in a time-dependent, predictable ordering. Like many biological processes, development shows extensive, normative variation and plasticity, with pathological, atypical states emerging only at the extremes of such diversity. Increasingly well-documented are the joint, interactive roles of genetic variation and environmental exposures in setting the course and endpoints of development, with epigenetic events (e.g., DNA methylation (DNAm), post-translational modifications of nucleosome proteins, and production of non-coding-, micro-RNAs) guiding the differential expression of developmentally formative genes (Czamara et al., 2019; Teh et al., 2014). Less recognized than such gene-environment (GxE) interactions and only more recently examined, time and timing constitute an essential third factor in developmental biology, comprising a previously missing vertex in triadic gene-environment-time (GxExT) interactions (Boyce et al., 2020). Differential transcription of specific gene networks by time is, of course, a fundamental driver of human embryogenesis, in which at least 200 different histological cell types are sequentially generated. Even beyond fetal embryonic development, however, time and timing may also play an essential, but not yet fully explored, role in metabolic, adaptive, and developmental processes (Boyce et al, 2021). Triadic, GxExT interactions are the basis for a set of now well-recognized, temporal events, including: critical and sensitive periods[2] (Takesian and Hensch, 2013); timed, experience-expectant processes (McLaughlin et al., 2017); optimal timing of interventions (Marin, 2016); the most injurious developmental windows of adversity exposure (Dunn et al., 2020; Riem and Karreman, 2019); and the timed emergence of developmental psychopathology (Maughan and Collishaw, 2015). Molecular events determining the timing of critical periods and the perturbations of development attending various exposures span multiple temporal scales, ranging from

[1]Boyce, Bush, and Roubinov (2020), unpublished data. See Boyce et al. (2010) for description of the dental component of the PAWS project.

[2]Both critical and sensitive periods modify the plasticity or malleability of development. Critical periods have more sharply defined beginning and end points, and plasticity is not graded over time. Sensitive periods have less well-defined onsets and endings and show a plasticity gradient over time (Columbo et al., 2019).

milliseconds in the case of neuronal oscillations to generational or even intergenerational continuities in the case of epigenetic processes (Cameron et al., 2017; Reh et al., 2019).

An enigmatic, temporal phenomenon only recently discerned and partially explained is the acceleration or deceleration of early development observed to occur under certain environmental conditions and in specific developmental periods. Such observable changes in developmental pace appear analogous to how contemporary quantum mechanics views the plasticity of time: never singular or absolute, but rather expanding or contracting as a consequence of perspective and its ontological coupling to a space-time continuum (Rovelli, 2018). Thus, in the perspective of the physical sciences, time runs measurably slower for an observer that is closer to the earth or traveling at high velocity, relative to a stationary observer located some distance from earth's surface. While the Newtonian idea that time is absolute and uniform—independent of things, their locations, and movements—is far more intuitive, the observable, objective realities of time are less instinctive, even at the macro level of organisms and planetary bodies.

In certain circumstances, it seems that *developmental* time also figuratively expands or contracts, resulting in a slower or more rapid pace of developmental change, with outcomes that are predictable and often consequential to the individual's well-being and health. To date, developmental acceleration and deceleration have largely been explained through the lens of medical models of disease (i.e., adversity "wears down" biological systems, resulting in dysfunction/death) or evolutionary-developmental theories (i.e., adversity accelerates maturation to optimize an organism's reproductive fitness). This paper advances a broadened, more explicit theoretical account for how and why variations in early environments govern alterations in the pace of neurodevelopment. More specifically, we propose a framework with five main tenets that diverge from prior explanatory theories of developmental pace changes.

First, we suggest that the parent-child dyad, rather than the individual child, is the focal unit that governs developmental pace alterations. Second, we advance an explanatory account for *why* adversity-induced changes in developmental pace occur by suggesting that accelerations and decelerations are enacted to obviate the shortfalls that emerge from children's unmet physiological and safety needs. Third, specificity in the direction of developmental pace alterations (i.e., acceleration or deceleration) is proposed to emerge from the uniquely-shaped trajectories of physiological needs versus safety needs during early childhood. Fourth, we hypothesize that developmental pace alterations emerge not only to optimize long-term reproductive fitness, but also as a response to unmet developmental needs in the short-term. Finally, we propose that linkages between early adversity exposures and developmental acceleration or deceleration involve neurobiological mechanisms operating along specific causal pathways. In order to develop this explanatory framework (see Section 4), we draw upon theoretical/conventional views of developmental needs in early childhood, as well as empirical literature on the effects of adverse exposures on aging, another instantiation of differences in developmental pace.

2. Prior Evidence of Developmental Acceleration and Deceleration

2.1 Animal models

The non-human animal literature comprises many examples of developmental acceleration and deceleration, often illustrating rapid calibrations between an organism's current energetic state and capricious environmental conditions. This homologous evidence across animal models in different species provides support for a unifying theoretical framework. For example, Western spadefoot tadpoles exhibit an accelerated larval period in response to adversely dry pond conditions, one of the greatest risks to their survival (Crespi and Denver, 2005; Denver and Crespi, 2006; Gomez-Mestre et al., 2013). This adaptive developmental plasticity is so finely attuned to the local ecology that an improvement in environmental conditions can induce a subsequent deceleration in physiological and cellular development (Sadeh et al., 2011). Evidence of developmental pace alterations has also been observed in sheep, where exposure to chronic prenatal hypoxia induces accelerated fetal relaxation of pulmonary vasculature, allowing accommodation to high altitude, low oxygen births (Blum-Johnston et al., 2016). In juvenile Coho salmon, maturational events (e.g., seaward migration) may be delayed when environments are unfavorable in order to wait for more propitious conditions (Grand, 1999).

The rodent literature provides evidence of developmental pace accelerations induced by differences in early life stress exposure and maternal care. For example, infant rats reared under stressful conditions (e.g., low maternal licking and grooming, limited bedding environment, maternal separation) exhibit earlier odor aversion learning (Moriceau, Shionoya, Jakubs & Sullivan, 2008) and fear retention (Callaghan and Richardson, 2012a), as well as earlier pubertal onset (Cameron, 2004) and accelerated synaptic maturity (Guadagno, Verlezza, Long, Wong, & Walker, 2020) compared to infant rats reared under normal conditions. Elevated cortisol levels have also been observed among rat pups raised in stressful environments (Moriceau et al., 2008) and exposure to the stress hormone cortisol early in life has been shown to prompt the same pattern of developmental acceleration that emerges in the context of stressful rearing conditions (Callaghan and Richardson, 2012a, 2012b). Among male mice, early weaning prompts accelerated myelin formation in the anterior part of the basolateral amygdala and more frequent anxious behaviors (Ono et al., 2008). Interestingly, there is also evidence that enriched environments (e.g., larger cages and groups, running wheels, toys) accelerate the development of the visual system in mice, potentially via higher levels of maternal licking and physical contact (Cancedda et al., 2004; Sale et al., 2004).

Developmental acceleration and deceleration are also evident in parallel, cross-species maturational processes. Among many species with a larval life cycle phase (e.g., C. elegans), a "developmentally arrested" dauer stage is observed, induced by adverse environmental conditions, including unfavorably high temperatures, humidity, and food scarcity (Karp, 2018). Dauer larvae may survive for months in disadvantageous conditions, with a relatively swift recovery and recommencement of development once environmental circumstances improve (Nika et al., 2016). In over 130 species of mammals, non-optimal environments may induce embryonic diapause, a temporary cessation of embryo development that

prolongs gestation until the prevailing context will better support offspring survival (Deng et al., 2018). Finally, both endotherms and ectotherms also enter states of metabolic suppression—topor and estivation, respectively—when environmental conditions are energetically insufficient to facilitate growth and reproduction (Staples, 2011).

2.2 Human studies

In addition to such controlled models, evidence from numerous human research domains has documented developmental acceleration and deceleration at different stages across the life course. Here, we highlight three particularly notable works that lay the foundation for the present model of developmental acceleration and deceleration. First and most notably, the recent and comprehensive meta-analytic and systematic review of literature by Colich, Rosen, Williams, and McLaughlin (2020) found that threat-related adverse exposures (e.g., childhood abuse, witness to domestic violence) were associated with earlier pubertal timing, cellular aging, and cortical thinning, especially in the ventro-medial prefrontal cortex (vmPFC) involved with emotion processing. By contrast, meta-analysis did not find childhood experiences of deprivation (e.g. neglect, institutionalization) nor low socioeconomic status to relate to metrics of developmental acceleration. Their systematic review of the literature also suggested that the area of the brain in which adversity-induced accelerations in cortical thinning occur depend on the type of adversity. This paper stands as the most comprehensive, data-centered review of studies examining developmental acceleration and deceleration in response to early life adversity.

In a second seminal contribution to recent human studies of adversity-related changes in developmental pace, the Neuro-Environmental Loop for Plasticity model advanced by Callaghan & Tottenham (2016a) suggests that the tempo of development within emotion-processing circuitry is guided by the intersection of caregiver dependence and child independence during sensitive periods. Under normative conditions in early childhood, the authors propose that a state of “semi-independence” of offspring from caregivers opens a sensitive period for the vmPFC circuitry to acquire greater regulatory capacities in response to parental inputs. This period of plasticity begins to close as the child achieves greater independence and is no longer as strongly reliant on the caregiver. The early independence from one’s caregiver that emerges under *non-normative* conditions (e.g., in settings of institutional rearing) operates as a signal to accelerate the closure of the sensitive period, contributing to early maturation of vmPFC development.

Finally, Tooley, Bassett, & Mackey (2021) focus on the pervasive effects of childhood socioeconomic status (SES). Lower childhood socioeconomic status (SES) has been associated with accelerated cortical thinning and an earlier peak in cortical surface area development, though the authors caution that the evidence is far from unequivocal and limited by largely cross-sectional study designs. Drawing upon this extant literature, they propose a framework whereby the valence and frequency of early experiences predict changes in the pace of brain maturation. More specifically, childhood experiences that are *negative and chronic* are predicted to accelerate brain development via repetitive use of regulatory circuitry, allostatic load, and (aligned with life history theory), increasing perceptions of environmental threat that suggest the need for faster maturation to facilitate

reproductive success. In contrast, *positive and rare* experiences are expected to slow brain development, as they signal greater variability in the environment that would benefit from a more prolonged period of plasticity.

Despite this strong foundation of theoretical and empirical studies reviewed by Colich et al (2020), Callaghan & Tottenham (2016a), and Tooley et al. (2021), other work has observed more variable effects of early adversity on biological and developmental endpoints, e.g., the *delayed* development of amygdala-PFC connectivity among children exposed to aversive environments. Such findings suggest that the overall direction and magnitude of adversity-related effects on the pacing of neurobiological development remain equivocal and depend upon the types of adversities encountered, the maturational parameters assessed, and the developmental age of children studied. Such variation in findings is well-represented in the assembly of other human studies summarized below.

2.2.1 Stress-induced premature birth.—Large-scale, prospective studies provide strong evidence for the influence of gestational stressors on prematurity, with findings that have been replicated across diverse types of adversity, populations, and geographic regions (Dunkel Schetter, 2011; Dunkel Schetter and Glynn, 2011; Glynn et al., 2008; Wadhwa et al., 1993). Preterm birth is frequently conceptualized using a fetal programming or fetal origins hypothesis, which describes how adverse intrauterine environments may influence fetal development, as well as offspring health and disease susceptibility (Barker, 2007; Bateson et al., 2004). Although the concept of fetal programming provides an organizational framework for research on prenatal stress exposure, premature birth can also be viewed through the lens of adaptive developmental acceleration. Early adversity may prompt accelerated fetal development, ultimately leading to delivery as an evasion of conditions threatening survival. Maternal uterine infection, for example, with its accompanying exposure to pro-inflammatory cytokines has been advanced as an explanation for prematurity (Gilman-Sachs et al., 2018; Goldenberg et al., 2008).

2.2.2 Sexual maturation.—The onset and timing of puberty have also been examined as biological processes linking early adversity and accelerated development. An extensive body of literature has observed accelerated pubertal development, resulting in earlier menarche, among girls exposed to early parental separation (Quinlan, 2003), father absence (Chisholm et al., 2005; Deardorff et al., 2011), and childhood sexual abuse (Boynton-Jarrett and Harville, 2012; Boynton-Jarrett et al., 2013; Li et al., 2014; Romans et al., 2003). Less adequate parental support and maternal depression have been associated with earlier adrenarche among children of both sexes (Belsky et al., 2015; Ellis and Essex, 2007) and maternal stress during pregnancy predicts a more advanced age at menarche among female offspring (Duchesne et al., 2017). Life history theory, rooted in an evolutionary-developmental framework, accounts for the hastening of pubertal maturation in terms of efforts to maximize reproductive fitness and avoid extinction of the lineage in harsh or unpredictable environments (Coall and Chisholm, 2003). Metabolic resources, it is argued, are preferentially allocated to pubertal maturation at the expense of other developmental processes in order to increase the probability of reproducing in environmental conditions ill-suited to reproductive efforts (Belsky et al., 2012; Ellis, 2004).

Delayed pubertal maturation, on the other hand, can be conceptualized as developmental deceleration, though the preconditions in which late maturation may occur are still unclear. Consistent research finds that serious and sustained nutritional deprivation delays puberty (Wells, 2018); beyond resource scarcity, evidence of the association between psychosocial stressors and late pubertal maturation has been somewhat more limited (Ellis, 2004). A criticism of this research has been the limited inclusion of racially and ethnically diverse samples, but in a recent study of minority children, exposure to maltreatment, violence, and other forms of trauma was associated with delays in the timing of pubertal development (Suglia et al., 2020).

2.2.3 Accelerated aging.—Successful adaptation of the brain and body to environmental stress occurs through allostasis, a process through which varied and interacting physiological systems maintain stability of function (homeostasis) through change (McEwen, 2004). However, psychosocial stressors that are severe or prolonged may lead to chronically activated or insufficient biological responses to stress; such physiologic "wear and tear" on the body, also known as allostatic load, promulgate accelerated biological aging (Juster et al., 2010). Illustratively, studies of biological "weathering" report relations among psychosocial stress exposure, heightened physiological burden (e.g., greater allostatic load), and age-related declines in health across the lifespan (Das, 2013; Geronimus et al., 2006). Compared to age-matched controls, youth reared in an international orphanage during childhood exhibited cardiometabolic health problems suggestive of advanced cardiovascular aging, even after adoption into a stable family environment (Reid et al., 2018).

Research has also identified associations between adversity and shorter telomere length, a marker of cellular aging (Epel and Prather, 2018). Telomeres are the protective ends of chromosomes, which shorten progressively with each cell division and, can lead to cellular death or senescence (Frenck et al., 1998). Telomere erosion has been observed in relation to varied types of early life stressors (for review, see Price, Kao, Burgers, Carpenter, & Tyrka, 2013), and across numerous developmental periods, including infancy (Entringer et al., 2013), childhood (Drury et al., 2014), and adolescence (Humphreys et al., 2016; Theall et al., 2013). Beyond discrete indicators of aging, a novel, algorithmically-derived "pace of aging" measure based on eighteen biomarkers revealed an accelerated rate of aging among young adults with exposures to adversity in childhood (Belsky et al., 2017). In the accelerated group, 75% of individuals were exposed to at least one childhood risk factor, and aging occurred at a pace more than 1.4 years faster than average. Risk exposure was markedly lower among individuals with an average (50%) or below average (43%) pace of aging (Belsky et al., 2017). Greater exposure to threat-related adverse childhood has also been associated with accelerated aging across studies of telomere length and DNA methylation age (Colich et al., 2020)

Recently, novel methods have yielded an intriguing measure of biological aging in children. Based on normative patterns of age-related changes in DNAm, research has identified epigenetic "clocks" serving as highly accurate predictors of chronological age (Horvath and Raj, 2018). An epigenetic clock-based prediction of age that exceeds actual age is believed to reflect developmental acceleration, which has been associated with maternal risk factors

during pregnancy (Girchenko et al., 2017), maternal prenatal anxiety (McGill et al., under review), and children's exposure to neighborhood violence (Jovanovic et al., 2017).

2.2.4 Accelerated maturation of brain circuitry and structure.—A recent study by Gur and colleagues (Gur et al., 2019) revealed a compelling illustration of adversity-induced, developmental acceleration by directly comparing effects associated with low SES with those linked to traumatic life events—two different, albeit inter-correlated, aspects of adverse early environments. The study replicated the effects of early life adversity on the timing of puberty, with more widespread effects in females. The authors then analyzed MRI data from individuals 8 – 21 years of age to test for accelerated development. The age range permitted the use of machine learning approaches to classify adult vs non-adult brain structural and connectivity profiles using a range of parameters. A significantly higher proportion of the low SES or traumatized individuals in the younger ages were (mis)classified as adults compared to controls.

Maternal prenatal depression associates with alterations in microstructure and functional connectivity of the amygdala at birth (Hay et al., 2020; Rifkin-Graboi et al., 2013; Scheinost et al., 2016), greater functional connectivity of the amygdala in 6-month-old infants (Qiu et al., 2015) and 4-years-old children (Soe et al., 2018), a larger right amygdala volume in young girls at age of 4 and 7 years (Buss et al., 2012; Wen et al., 2017), and alterations of the amygdala-prefrontal structural circuit from birth to early childhood (Lee et al., 2019). The effects are largely specific to the right hemisphere where there is a specialization for the processing of threat (Fox and Davidson, 1986). Importantly, these effects are apparent in neuroimaging studies performed with neonates, thus confirming prenatal influences that persist beyond birth. Studies from Tottenham and colleagues (Gee et al., 2013a; Gee et al., 2013b) provide what may be the most compelling evidence for adversity-induced developmental acceleration. Under typical rearing conditions, children exhibit positive coupling of amygdala-mPFC activation when viewing fearful faces, while adolescents and adults exhibit negative coupling. However, children exposed to institutionalized rearing have been shown to exhibit negative amygdala-mPFC connectivity when viewing fearful faces, demonstrating a pattern characteristic of normally-developing adolescents (Gee et al. 2013a). This pattern suggests accelerated maturation of amygdala-PFC circuits following exposure to the severe adversities associated with institutional care.

2.2.5 Psychosocial short stature.—Empirical studies of developmental *deceleration* are more limited than those providing evidence of accelerated developmental pace. Some of the most compelling examples of developmental deceleration may be observed from research on psychosocial short stature, a phenomenon first documented over 70 years ago, in which reduced growth is found among children reared within emotionally deprived environments (Gohlke et al., 2004; Talbot et al., 1947). A variety of stress-sensitive biological mechanisms have been advanced to explain the growth effects of neglectful conditions, which appear to emerge independent of adequate nutritional supply (Johnson et al., 1992; Muñoz-Hoyos et al., 2011). In humans, fetal growth retardation in response to nutrient deprivation or placental insufficiency, followed by postnatal catch-up growth, may represent another such phenomenon (Baschat, 2014).

2.2.6 Decelerated aging.—Research on the epigenetic clock suggests that negative epigenetic-to-chronological age deviations (i.e., age deceleration) may be associated with risk in a manner similar to the previously reviewed positive deviations (i.e., age acceleration). Prenatal risk factors, for example, have been associated with both epigenetic age acceleration and deceleration. Offspring born to mothers who experienced heightened prenatal depressive symptoms showed lower epigenetic gestational age (age deceleration based on DNAm of fetal cord blood DNA), compared to women without depression (Suarez et al., 2018). Further, evidence of lower epigenetic age has also been observed in highly distressed infants who experience lower maternal physical contact, compared to those with more extensive maternal-infant contact (Moore et al., 2017).

3. Deficiencies in existing explanatory accounts of changes in developmental pace

Existing explanatory accounts for observable shifts in the pace of development include the psychosomatic medicine or social determinants of health models, as well as evolutionary developmental theory. These frameworks are largely descriptive in character, and description has become conflated with explanation.

3.1 Psychosomatic medicine and social determinants of health models

The psychosomatic medicine model views cellular aging and bodily “weathering” as the biological consequences of chronic exposures to adversity, and a social determinants orientation has pointed to poverty and disadvantage as impediments to normative acquisition of developmental skills. Primarily used to account for developmental acceleration, these frameworks are difficult to reconcile with empirical evidence of developmental deceleration. Moreover, they suggest disparate types of adversities compromise development through a similar, singular pathway of stress exposure and do not consider the nuanced implications of different dimensions of adverse exposures. Recent empirical studies find variable implications of environmental adversity on developmental pace, depending upon whether adverse exposures represent sources of threat (e.g., physical abuse, interpersonal violence) or sources of deprivation (physical neglect, institutionalization, low family socioeconomic status (Sumner et al., 2019)). As elucidated by McLaughlin and colleagues, the dimensional model of adversity and psychopathology (DMAP) argues that experiences of threat and deprivation differentially influence mechanisms of developmental plasticity that link adverse exposures to health and developmental outcomes (McLaughlin and Sheridan, 2016; McLaughlin et al., 2014; Sheridan and McLaughlin, 2014, 2016). In a meta-analysis and systematic review of the literature, adversity type moderated the direction of adversity-induced developmental pace changes: early experiences of threat were associated with accelerated development across indicators of puberty and cellular aging, but there was no association of these metrics with childhood deprivation or SES (Colich et al., 2020; see Section 2.2 for more information). Although a comprehensive discussion of the varied neurodevelopment pathways that link threat/deprivation to health is outside the scope of the current paper (for review, see Sheridan & McLaughlin, 2020), we underscore the importance of this dimensional perspective on adverse exposures: not all adversities are comparable in the demands they place on the developing organism nor, necessarily, in their outcomes.

3.2 Evolutionary developmental theory

Evolutionary developmental theory has been proposed to explain both acceleration and deceleration in developmental pace—each framed as means for optimizing reproductive fitness. In a seminal 1991 paper, Belsky and colleagues (Belsky et al., 1991) advanced an evolutionary interpretation for why girls from harsh, insensitive families appeared to follow an accelerated pace of pubertal development, relative to those from more supportive, securely attached family environments. Invoking life history theory (e.g., Coall and Chisholm, 2003), which views developmental resource allocations as a preconscious optimization of fitness, the authors proposed that girls reared in adverse family conditions utilized a "reproductive strategy" of early pubertal development and precocious sexuality as means of promoting reproductive success. A similar evolutionary interpretive lens is used to describe delays in pubertal timing: In a context of deprivation and scarce bioenergetic resources, late maturation is posited to conserve resources until the emergence of environmental conditions that are more conducive to reproduction (Ellis et al., 2012).

The nearly exclusive focus of life history theory on reproductive benchmarks, such as menarche or sexual debut, does not address broader maturational markers, such as exfoliation of deciduous teeth, the acquisition of executive functioning, or shifts in the pace of an epigenetic clock. Although well-grounded in evolutionary biology, life history theory places principal focus on *eventual, future* outcomes, narrowing its utility for understanding the implications of adversity across the full range of development and into adulthood. Also common across extant frameworks is a predominant focus on the *individual:* how adversity operates to inhibit *individual* functioning or constrain *individual* patterns of resource allocation in service of reproductive goals. Notwithstanding such person-driven processes, these accounts largely ignore the essential dyadic nature of early rearing experiences, namely, the ways in which children's development is powerfully shaped by primary caregiver relationships. Particularly during infancy and childhood, children's most basic needs for physiologic resources and safety are fulfilled within the context of transactions with primary caregivers (Roubinov et al., 2021). Thus, it is reasonable to consider ways in which the insufficient fulfillment of needs within this dyadic context may be instrumental in determining developmental pace changes. Without explicitly conceptualizing a central role of the parent-child dyad, extant frameworks may omit one of the most central influences on developmental pace.

Life history theory also contends that developmental pace adjustments are adaptive because they reliably predict future environmental conditions. Evolutionary strategies, termed "predictive adaptive responses (PAR)," operate through developmental plasticity to modify an organism so that the resulting physiology "matches" (or is advantageous within) the environment that is expected later in life (Gluckman et al., 2005). Within such a framework, environmental matches (i.e., a harsh early environment and a harsh future environment) should be more advantageous than environmental mismatches (i.e., a supportive early environment and a harsh future environment), even when early life conditions are favorable (Rickard et al., 2014). Although often relied upon as a guiding theoretical framework, there are limited empirical tests of PAR, and those that have been conducted yield inconclusive results. For example, an experimentally-manipulated mismatch of prenatal and postnatal

nutrient environments induced cardiovascular dysfunction in a sample of sheep that was not observed under matched prenatal-postnatal environmental conditions (Cleal et al., 2007). Yet in an analysis of a well-documented famine in preindustrial Finland, Hayward, Rickard, and Lummaa (2013) found that individuals born during “lean years” did not experience better survival or fertility rates despite the “match” of early and later life conditions. Rather, it was those individuals who experienced more favorable, nutrient-rich early life conditions (“mismatches”) who fared better during the famine. Overall, research into PAR bears the same weakness of the life history approach: it predominantly focus upon the relation of exposures to outcomes, rather than the developmental processes that lie between.

Notably, under each of the aforementioned extant theoretical accounts, adversity-induced health consequences may be promulgated as “trade-offs” or costs of survival in non-optimal conditions. None of the existing accounts of plasticity in developmental pace have offered a clear, heuristic explanation for: a) why development can be either accelerated or decelerated or b) what common underlying mechanism(s) might allow pace shifts in either direction.

4. A novel explanatory framework of developmental pacing

Although the presented theory rests on a foundation of evolutionary principles, there are a number of ways in which the ideas presented here distinguish themselves from past views. Our objective is not to challenge or supplant life history theory, but to provide a possibly more nuanced and mechanistic explanatory framework that places developmental time in the foreground of studies examining maturational pace. Below, we outline the features of this novel framework, highlighting the fundamental ways in which the present theory diverges from life history theory.

4.1 The parent-child dyad is the focal unit of influence

An alternative account for environmentally driven shifts in the pace of early development might center upon parent and caregiver provision for the needs of young children. The canonical 1943 paper by psychologist Abraham Maslow advanced a theory about such needs that became deeply rooted within developmental science (Maslow, 1943). Developmental needs, Maslow argued, are arrayed in a pyramidal hierarchy in which the earliest, most fundamental necessities (physiological and safety needs) must be first addressed in order for the child to progress to the fulfillment of higher-order psychological needs (love and self-esteem) and ultimately to self-actualization (see Figure 1). Others have suggested that the intensity of early needs follows specific developmental trajectories but is not necessarily hierarchical; rather, physiological needs (for sustenance, hydration, warmth, human contact) begin high and steady and decrease through middle childhood, and safety needs (for protection, security) remain relatively low in the first several years but peak in adolescence (Figure 2).

The first two decades of life are also characterized by changes in the balance between caregiver needs provision and offspring autonomy: a gradually diminishing of parental provision for children’s needs, as the child’s own ability to meet needs increases over time, ultimately exceeding parental contributions (see point A in Figure 3A). The displayed models in Figures 3, 3A are based not on data describing measured needs provision,

because, to our knowledge, no such data presently exist. Rather, the dual trajectories of needs provision and needs fulfillment within the dyad have been drawn based on conventional understandings of the shape of their developmental courses (see, for example, Krech et al, 1962). Empirical data robustly demonstrate that parents' capacities for meeting early childhood needs can be compromised by the presence of poverty, mental disorders or addictions, social isolation, or other forms of family adversity, resulting in a systematic down-shift in parents' abilities to provide for children's needs (e.g., Madigan et al., 2019; Stein et al., 2014). As shown in Figure 3B, the modeled trajectory of parents' capacities for such provision is depressed over the full range of children's early development, reflecting the obstacles encountered by parents experiencing economic disadvantage, substance dependence, psychiatric impairments, or other forms of adversity (Reiss, 2013; McLaughlin et al., 2011). As we outline below, the parent-child dyad occupies a more central operational role in change of pace theory than has been the case within traditional evolutionary perspectives. Change of pace places the dyadic relationship (and needs deficits therein) squarely at the heart of adaptive change, rather than more conventionally regarding the individual child as the unit of conditional adaptation and the child's developmental traits as the target of natural selection.

4.2 Need shortfalls are obviated via alterations in developmental pace

In this theoretical account, compromised parents' diminished capacity for needs provision results in a shortfall of needs satisfaction for both physiological and safety needs over early development (Figures 3 and 4, respectively). Due to the distinctive trajectories of these two categories of needs over early development, the shape and timing of the two areas of red denoting provision shortfalls are also distinctive in shape and timing. As a consequence and as shown in Figures 3 and 4, two different developmental strategies are employed for overcoming the problem of unmet needs. In the first (Figure 3B and 3C), unmet *physiological* necessities—resulting, for example, from parental or caregiver neglect of a child's nutritional or interpersonal needs—could be surmounted by a strategy of developmental *deceleration*. Such slowing of physiological requirements over time would result in both delayed maturation of a child's autonomous needs provision (dashed green line) and a diminution in physiological needs themselves (dotted black line). Together, these two alterations in pace would result in an ablation of the needs provision shortfall caused by diminished parental capacities (Figure 3C). The result of a deceleration strategy might be viewed as analogous to survival by the physiological slowing that attends cold water immersion (Daanen and Van Marken Lichtenbelt, 2016; Tipton et al., 2017). In a meta-analysis of studies across 21 mammalian species, prenatal maternal stress induced deceleration in offspring growth (Berghänel et al., 2017). Notably, Bergähnel et al. found that adversity-induced deceleration was less pronounced at higher levels of offspring autonomy, a process captured by the current framework: Figures 3 and 4 illustrate a lessening of the effect of adversity later in development, as the nature of dyadic transactional exchanges shifts from reliance on primary caregivers toward children's autonomous needs provision. Similarly, some studies of low childhood SES and accelerations in cortical thinning have failed to replicate in adolescent samples (Tooley et al., 2021). While this may be explained by the rate of cortical thinning (which slows in adolescence), it may also

relate to changes in the balance of needs provision between caregivers and offspring across development.

In the second developmental strategy, unmet *safety* needs—due to insufficient parental protection or support in the face of threat or adversity—might be overcome by an engagement in developmental *acceleration*. Consistent with the basic, unperturbed trajectories of early physiological needs, the graphical representations of children's safety needs, autonomy, and needs fulfillment (Figure 4A) draw upon conventional wisdom as opposed to empirical data. As shown in Figure 4, such accelerated change in the pace of a child's autonomous needs provision would result in an obviation of the needs fulfillment shortfall (dashed green line) and a shift to an earlier temporal point at which a child's capacity would override parental contributions (point A in Figure 4C). Acceleration might be expected to result in a later stunting of developmental autonomy (i.e., the downturned segment D on the child's developmental curve in Figure 4C). Accelerated development to meet early, immediate environmental demands or threats has been observed in prior studies to have longer-term effects on cardiometabolic risk (Reid et al., 2018), the integrity and functioning of limbic circuitry (Callaghan and Tottenham, 2016b), and physical growth (Berghänel et al., 2017), in both humans and non-human models (Ludewig et al., 2017; Metcalfe and Monaghan, 2001). In describing developmental pace changes (Figures 3C and 4C, respectively), we distinguish between the existing empirical data that documents the occurrence of these purposefully slowed and more rapid maturational patterns (e.g., Colich et al., 2020; Sumner et al., 2019) and what remains more theoretical in nature, which are the rationale, function, and mechanistic underpinnings of such strategies that are proposed by the present framework.

4.3 Unique trajectories of early physiological versus safety needs underlie the directionality of pace changes

This "change of pace" model provides a rationale for the discrete responses that emerge in the context of unmet physiological needs (i.e., neglect, deprivation) versus unmet safety needs (i.e., protection from threat). The distinctiveness of these responses is commensurate with reports that neglect and physical abuse are only moderately linked in studies of child maltreatment (e.g., Castro et al., 2017) and is aligned with the dimensional model of adversity and psychopathology (McLaughlin & Sheridan, 2016). This model stipulation also builds upon prior theory of the importance of early parental care (Callaghan & Tottenham, 2016a); here, we indicate that specificity in the direction of developmental pace changes depends upon the *domain* of children's needs in which caregiving deficits emerge. The current model postulates that the direction of developmental pace changes are determined, at least in part, by the unique trajectories of physiological versus safety needs. Physiological needs begin high and steady early in life and decrease during middle childhood; thus developmental deceleration averts the deficiencies that would appear under a normative developmental trajectory (Figure 3C). In contrast, unmet safety needs begin lower in the early years of life and rise as offspring mature; thus an acceleration strategy precludes the shortfall that would emerge if developmental pace were unperturbed (Figure 4C). Although threat and neglect can co-occur within individual family units, the predominance of one over the other may be reflected in directional changes in developmental tempo of children.

Most importantly, the model's predictions match previous findings that threat-related early life adversity is associated with accelerated epigenetic age (DNA methylation within an epigenetic "clock" array) and advanced pubertal development, while deprivation is linked to slowed pubertal maturation (Sumner et al., 2019), and also extend this work by proposing a unified account that describes *why* directional differences in pace changes may emerge under varied conditions. A model based on the trajectories of early needs provision may also more easily account for the striking individual differences in susceptibility to early life adversity by positing that some individuals may be more sensitive to aversive stimuli in both the external environment (i.e., threat) and the internal milieu (i.e., physiological deprivation; Boyce, 2016; Ellis et al., 2011; Rickard et al., 2014).

4.4. The short- and long-term functionality of pace alterations

The change of pace theory focuses more intensively upon the implications of immediate, unmet physiological and safety needs on developmental processes, rather than on the longer term, eventual outcomes that are central to life history theory. We contend that failures to fulfill key early needs figure prominently in developmental accelerations and decelerations, and the character of the unmet needs, as explicated in Figures 3 and 4, determine the direction of change in the pace of development. As such, the presented theory offers a more explicit account of the temporal mechanisms at work within changes of developmental pace.

5. Neurobiologic Mechanisms

A "change of pace" or temporal plasticity framework rests inherently on an understanding that all complex forms of life express the capacity to alter phenotypic development in response to environmental conditions. Studies reviewed above illustrate the impact of environmental circumstances on the timing of developmental processes as a specific form of such phenotypic plasticity. A key question concerns the biological signals by which environmental conditions might influence the pace of development—mechanisms that would have widespread, coordinated effects across multiple systems. The hypothalamic-pituitary-adrenal (HPA) axis may operate as one such illustrative mechanism for determining developmental pacing across a range biological systems and phenomena.

An extensive literature in non-mammalian species has identified neuroendocrine systems affecting the timing of life history transitions (Denver, 2009b; Wada, 2008). These studies illustrate the critical and evolutionarily conserved role of the HPA axis, a classic example being the advanced timing of metamorphosis apparent in tadpoles in response to environmental adversity (Denver, 2009a). Tadpole development occurs in aquatic environments, such as ponds, which contain the nutrients required for normal development. Evaporation of the pond and dwindling nutrient resources trigger the release of corticotrophin-releasing factor (CRF), a hypothalamic peptide that ultimately stimulates the release of both adrenal glucocorticoids and thyroid hormones. These hormones act in synergy to accelerate the timing of tadpole metamorphosis and to stimulate the transition to a developmentally mature stage, permitting independence from the pond and promoting survival through the alternative foraging capabilities. These findings are consistent with those from a remarkable range of vertebrates, revealing the importance of glucocorticoids in

pacing the major life course transitions from the earliest stages of development to the end of the life cycle (Wada, 2008).

5.1. Parturition and fetal development

While findings with tadpoles might seem remote to those focused on human development, the processes are remarkably similar to those governing parturition in humans, as well as the effects of environmental adversity on the timing of parturition (Liggins et al., 1977; Smith and Nicholson, 2007). CRF and CRF-induced levels of glucocorticoids normally rise over the course of human pregnancy. The associated glucocorticoid action on conceptual tissues provides the basis for parturition timing. Glucocorticoids facilitate the cellular effects of pro-inflammatory cytokines on prostaglandins, among other mediators (Challis et al., 1999; Challis and Smith, 2001), and prepare the fetus for 'life on the outside' through advancing maturational effects on lung, liver, kidney and other organs (Liggins et al., 1977). Adverse conditions such as maternal infections, malnutrition and stress can all drive increased release of CRF, and the resulting glucocorticoid action serves as a basis for premature birth by enhancing the actions of pro-inflammatory uterine signaling. Importantly, the placenta is the source of CRF, and the timing of parturition is governed by a fetal signal that uterine conditions no longer support growth and/or threaten survival. The fetal signal is transmitted to conceptual tissues to promote the early exit and the transition to postnatal conditions.

The increased levels of glucocorticoids triggered by adversity in utero influence the timing of birth, as well as fetal growth and birth weight. The highly catabolic glucocorticoids constrain fetal growth (Meaney et al., 2007). Low birth weight in humans associates with increased cord blood levels of both CRF and cortisol (Goland et al., 1993). Prenatal administration of glucocorticoid receptor agonists, such as dexamethasone or betamethasone, produce fetal growth retardation in humans and other species (Price et al., 1992). An exhaustive meta-analysis of the effects of prenatal maternal stress across 21 nonhuman mammalian species (Berghänel et al., 2017) revealed evidence for both an initial dampening of fetal growth, a developmental constraint associated with limited maternal investment, followed by an adaptive calibration of a developmental trajectory marked by acceleration (catch-up) of growth and advanced reproductive maturation. Here, two points are critical. First, this profile was a common outcome across multiple forms of prenatal maternal adversity. Second, both the initial deceleration of fetal growth and the later acceleration (i.e., 'catch-up growth') were replicated in studies using only fetal glucocorticoid exposure without exposure to external maternal stressors. Fetal exposure to increased glucocorticoid levels restrains fetal growth and produces sustained hyperinsulinemia— a function of insulin resistance in selected tissues—which then promotes postnatal, accelerated somatic growth. Hence fetal glucocorticoids are positioned to establish both an initial growth retardation as well as a later acceleration of growth. The glucocorticoid-mediated hyperinsulinemia also associates with accelerated pubertal development (Dunger et al., 2005; Morton et al., 2001).

5.2. Maternal care and postnatal development

While the level of HPA activity during the prenatal period is linked to maternal signals associated with the quality of the uterine environment, the maternal role extends into the

postnatal period. The mammalian mother provides thermoregulation, nutrients, protection from predators, and even regulates cardio-metabolic function (Hofer, 1970, 1975). The mother thus spares the rodent pup the need for independent HPA activity. This period of HPA quiescence associated with maternal 'buffering' ensures that growth proceeds without interruption of the highly catabolic glucocorticoids, a period referred to as the 'stress hyporesponsive period' (Sapolsky and Meaney, 1986). Under optimal conditions, activity of the HPA axis and its capacity to respond to stressors emerge as the developing animal advances towards weaning, a stage of independence that requires physiological and behavioral self-sufficiency. However, pups deprived of maternal care for abnormally extended periods of time are obligated to physiologically 'fend for themselves', in part by advancing the maturation of the HPA axis and enhancing the response of the adrenal cortex to CRF-induced pituitary adrenocorticotropic hormone (ACTH). Maternal separation accelerates adrenal maturation of the steroidogenic response to ACTH, enabling the synthesis and release of glucocorticoids. The HPA axis is thus able to meet the demands of adversity with an increase in circulating glucocorticoid levels.

5.3. Developmental timing of fear behavior

Maternal pacing of the development of defensive responses includes neural circuits implicated in the activation of 'innate' behavioral fear responses activated during periods of stress, avoidance of cues associated with pain as well as fear conditioning (Callaghan et al., 2014). These responses comprise a highly adaptive set of defensive behaviors that allow for the avoidance of conditions (e.g., predation) that imperil survival. These responses function in the form of stable differences in fearfulness that enhance the avoidance of novel, uncertain conditions and in the capacity for avoidance learning. The capacity for the expression of such defensive responses is critical for the successful transition to independence from the parent.

This maternal regulation of HPA maturation timing is produced in part by downstream effects on amygdala-mediated fear behaviors. Such behavior in the developing rat pup emerges towards the beginning of the third week of life, thus mapping nicely onto the timing of weaning and, not coincidentally, HPA development. This timing of development anticipates the transition of weaning that requires independence of the offspring well served by the coincident development of HPA responsivity and fear behaviors. The temporal coordination of these effects on defensive systems is reflected in studies showing accelerated onset of fear behaviors in pups treated with glucocorticoids during the period of normal HPA quiescence; blocking glucocorticoid signaling prolongs the immaturity of the fear behavior system (Moriceau et al., 2006; Takahashi et al., 2005). Infusion of glucocorticoids directly into the amygdala accelerates the onset of fear behaviors, and glucocorticoid receptor antagonism produces the opposite effect. Further, genomic analyses of neuroimaging data obtained from human newborns implicates glucocorticoid signaling as a mechanism for inter-individual variation in amygdala structure (Ong et al., 2019). These findings are consistent with those of Buss and colleagues (Buss et al., 2012) showing that maternal cortisol levels during pregnancy associate with fetal amygdala development. A more recent report from this group reveals a comparable influence of pro-inflammatory cytokines,

thus once again reflecting the glucocorticoid-inflammation pathways (Gyllenhammer et al., 2020).

Recent studies provide insights into cellular mechanisms underlying variation in developmental pacing of the onset of fear-related behaviors. Bath, Walker and their colleagues (Guadagno et al. 2020; Nieves et al., 2020) used a mouse model of early life adversity that involves limiting the bedding material provided to the mother for nesting. The limited bedding delayed the ability of peri-weanling mice to express an auditory conditioned fear memory, which would normally be apparent by this stage of development. Importantly, the effect was apparent in the timing, but not the ultimate developmental outcome: by 50 days of age there was no longer any effect of the resource limitation. The limited bedding condition accelerated the developmental emergence of parvalbumin (PV)-positive cells, a marker for inhibitory neurons, in the BLA. The delay in the expression of the condition fear response was reversed through optogenetic inactivation of PV-positive cells in the BLA in the Nieves et al. (2020) study.

The focus on the PV-positive cells in these models provides an important bridging to the developmental pacing. Hensch (2005) have provided compelling evidence for the importance the GABAergic PV-positive cells in the timing of critical periods in neurodevelopment. Benzodiazepines prematurely open critical periods of plasticity in the visual system by acting through GABA-receptors (GABARs) containing the subunit α1 (Fagiolini et al., 2004), which is a primary target of PV-positive interneurons. Genetic manipulations directed towards glutamic acid decarboxylase 67 (GAD67), a GABA synthesizing enzyme, delay the onset of this critical period of plasticity (Chattopadhyaya et al., 2007). Thus, GABAergic signaling affecting excitatory/inhibitory balances provides a molecular mechanism for developmental pacing.

Batista and Hensch (2019) provide evidence for a distal signaling mechanism that targets the timing of critical periods through the PV-interneurons. Interestingly, this proposed mechanism, thyroid hormone signaling, brings us full circle back to the amphibian models noted at the outset of this section (Denver, 2009b; Wada, 2008). While these models emphasized the role of CRF in morphogenesis, thyroid hormones serve as a critical trigger for CRF. Likewise, thyroid hormones are regulators of the pacing of the critical periods for imprinting in chicks (e.g., Yamaguchi et al., 2012) as well as neural circuitry in rodents (Gould et al., 1990; Koibuchi, 2008). Batista and Hensch (2019) mobilized compelling evidence in support of the idea that thyroid hormone regulation of PV neurons and thus GABAerigc signaling can determine the timing of critical periods and thus developmental pacing: 1) thyroid hormones regulates GAD expression in the brain, an effect that is particularly pronounced in early life (Wiens &Trudeau, 2006); 2) thyroid hormones shape the morphology and connectivity of GABAergic cells during development, an influence mediated by the mTOR signaling pathway (Westerholz et al., 2013). The mTOR pathway also underlies the plasticity during imprinting in chickens (Batista et al., 2018). Thyroid hormones control a switch in GABAa/GABAb receptors to open the critical period for imprinting in chicks (Aoki et al., 2018). Finally, in rodents, thyroid hormones regulate neural PV expression in multiple brain regions (e.g., Gilbert et al., 2007; Royland et al., 2008; Sawano et al., 2013; Harder et al., 2018).

The thyroid hormones also emerge as regulators of the effects of maternal care in the rat. Hellstrom et al (2012) showed that the influence of maternal licking on glucocorticoid receptor expression in hippocampal neurons is initiated by activation of the thyroid hormones receptors in the raphe with subsequent serotonergic activation of a signaling cascade that involves the transcription factors CBP and NGFI-A. Importantly, Hellstrom et al. showed that the tactile stimulation derived from pup licking was the critical signal for the maternally-regulated increase in circulating thyroid hormones. An intriguing, but as yet unanswered question, is whether maternal licking might regulate the ontogeny of PV-interneurons and thus, influence developmental pacing. Such studies might mechanistically link the human research on parental care or deprivation thereof to developmental pacing (see Hostinar et al., 2014; Tottenham et al,. 2019; Sullivan & Opendak, 2021).

5.4. Pubertal development

We previously noted the influence of parental care on the timing of pubertal development in human females (Coall and Chisholm, 2003). Conditions of parental neglect and/or abuse, for example, are linked to deviations in the timing of pubertal development in human females. There are comparable effects observed in the same rodent model of maternal care that features effects on HPA development. Female offspring of rat mothers that exhibit low levels of pup licking and grooming enter puberty significantly earlier than do those reared by high licking mothers (Cameron, 2004). The effect is driven by increased hypothalamic expression of the gene for the alpha subtype of the estrogen receptor, which serves as a basis for the activation of gonadotropin releasing hormone (GnRH) neurons that drive the onset of the hypothalamic-pituitary-ovarian function defining the onset of puberty. The increased hypothalamic expression of estrogen receptor alpha associated with low maternal investment emerges early in postnatal development as a function of the differential methylation of the estrogen receptor alpha gene promoter region. This region is hypomethylated in the female offspring of low-licking mothers (Champagne et al., 2003), leading to increased estrogen sensitivity and an earlier onset of puberty. The same effect produces increased sexual behavior and fecundity in the female offspring of low licking mothers (Cameron, 2004), an effect that is also supported by the greater acute stress-induced HPA activity in the offspring of low licking mothers.

Active maternal care ‘buffers’ the young from adversity and promotes the physiological conditions allowing growth. Levine and Gunnar (Gunnar et al., 1981) anticipated the framework presented above by positioning the mother and maternal care as the relevant environmental signal that determined the timing for HPA maturation, reflected in the capacity for mobilizing an adrenal corticosteroid response to stress. Hostinar and colleagues (Hostinar et al., 2014) provide a compelling review of the evidence for maternal “social buffering” of the young across multiple species, including humans. The critical role for the mother in modifying the development of ‘defensive responses to threat was first elucidated in studies dating back almost seven decades, where Levine (Levine, 2002), Denenberg (Zarrow et al., 1968) and their colleagues documented what, at the time, was an unexpected level of phenotypic plasticity in the HPA axis in rodents. These studies revealed that brief periods of postnatal handling in rodents increase mother – pup interactions and, in doing so, regulate the pace of HPA maturation, as well as HPA function over the life course (Liu

et al., 1997). The enhanced tactile stimulation derived from handling-induced increases in mother–pup interactions in the rat is critical for sustaining the stress -hyporesponsive period. Thus, greater maternal investment ensures the availability of energy to sustain growth, as well as protection from threat. Offspring so indulged can afford to prolong HPA immaturity and invest in growth supported by maternal contact-induced release of growth hormone (Schanberg et al., 1984; Schanberg et al., 2003).

The increased maternal stimulation, in the form of licking, induced with brief periods of postnatal handling, has long term consequences for HPA function, which ultimately determine the later pace of brain aging (Meaney et al., 1988). Maternal licking alters intracellular signaling processes in hippocampal cells in the pup that results in a reduced methylation of glucocorticoid receptor gene promoters and increased glucocorticoid receptor expression. In adulthood, the increased hippocampal glucocorticoid receptor signaling provides more effective feedback regulation of HPA function. With age, the rat shows increasing basal levels of HPA activity, increased exposure to glucocorticoids, and glucocorticoid-induced atrophy of hippocampal neurons (Meaney et al., 2000). Postnatal handling spares animals the exposure to increased glucocorticoid levels and hippocampal atrophy. Thus even in the later stage of the lifecycle animals that were handled in early life show little evidence of hippocampal neuron loss nor of aged-related impairments in hippocampal-dependent forms of learning and memory, all of which become increasingly apparent in non-handled animals by mid-life (Meaney et al., 1988). Maternal care in early life is thus registered on HPA function to alter the timing of biological aging.

5.5 Summary and future directions

Work described above on the HPA axis and glucocorticoid influences on developmental pace emphasizes resource availability, or metabolic demands, and safety/threat, which implicates biological defenses. The HPA axis lies at the fulcrum of these systems. A wealth of HPA hormones not only regulate the activation of stress responses, the body’s primary line of defense, but the adrenal glucocorticoids are also major regulators of cardio-metabolic function resulting in altered resource availability and, in synergy with catecholamines, the circulation of energy substrates. This system, proposed by Meaney, Szyf, and Seckl (2007) as a mechanism for fetal programming of developmental outcomes, is thus ideally positioned as a biological mediator of the trade-offs ultimately defining developmental pace. Interestingly, low birth weight, which reflects glucocorticoid-mediated effects on somatic growth, is also associated with advanced pubertal development, increased HPA responses to stress (Phillips and Jones, 2006), as well as the later risk for stress-related psychopathology.

There is compelling evidence for the importance of glucocorticoid signaling in regulating the pace of development in multiple biological systems, stemming from a wealth of science in multiple disciplines. Nevertheless, there is considerable reason to assume that glucocorticoids account for only a portion of linkage between exposure and developmental outcomes (O’Donnell and Meaney, 2017). For example, studies suggest importance of inflammatory signals as a mechanism for the pacing of development within the systems described above (Danese et al., 2009; Kuhlman et al., 2017). A further consideration is the topic of gender and gender-specific effects. The associations between maternal adversity

and the development of amygdala – PFC circuitry, for example, is largely apparent only in girls by the time of childhood (Wen et al., 2017). This finding is consistent with the association between maternal depression and risk for depression in the offspring, which is likewise mostly apparent in daughters. Studies of the developmental outcomes associated with birth weight and prematurity are similarly replete with examples of gender differences. These findings seem to suggest that effects on the pacing of development would, likewise, be gender dependent. Future research is well-poised to explicate the varied biological pathways through which adversity determines developmental pace alterations. Studies of gender dependency will add a fascinating dimension to these analyses.

6. Conclusions

Developmental time, in a manner analogous to the plasticity of physical time, might be usefully viewed as expanding or contracting adaptively in response to early life environmental signaling. Such temporal elasticity, if present, would reveal itself in observable decelerations or accelerations among maturational events—changes in developmental pace that adaptively accommodate the child to the conditions of early life. Evolutionary biology (e.g., Gilbert and Epel, 2009), life history theory (e.g., Ellis and Del Giudice, 2019), and developmental origins research (e.g., Fleming et al., 2018) have all attributed such alterations in the pace of development to "tradeoffs" in the allocation of limited metabolic and energetic resources—tradeoffs that are responsive to the assets and liabilities, supports and adversities that together characterize early rearing environments. These tradeoffs, it is argued, are enacted to maximize reproductive fitness, but result in shifts in the timing of events, such as birth and sexual maturation, that are consequential to both health and development. Here, a heuristic, mechanistic extension of this theoretic account is advanced, centering upon how *unmet, early developmental needs* operate as key determinants of the direction and timing of changes in developmental pace. Further, we summarize emerging evidence describing how *neurobiological processes* may guide developmental pace.

This "change of pace" theory of developmental acceleration and deceleration takes as its point of departure several extensions or annotations of classical evolutionary, life history, and developmental origins frameworks. First, the focal unit of influence on developmental pace is deemed to be *the parent-child dyad*, rather than the individual child in isolation. Whereas the life history perspective centers upon an *individual's* expenditures of effort and energy in the service of reproductive fitness, the present theory regards the transactional relationship between parent and child as a key determinant of developmental pace. Second, change of pace theory offers an explanatory account for *why* poverty, social isolation, and other adversities contribute to the tempo of maturational change by interceding in families' responsiveness to early developmental needs. Poor, disadvantaged parents sustaining multiple adversities and/or symptoms of mental illness are simply unable to provide the resources and supports that young children require, especially in the early childhood years. Alterations in developmental pace operate to obviate such shortfalls, either via a decelerated pace that reduces children's overall physiological needs or via an accelerated pace that increases children's overall capacity for autonomous safety needs provision. Third, an accelerated or decelerated pace—that is, the *direction* of the change in developmental

maturation—is proposed to occur by virtue of whether physiological needs (i.e., nutrition, metabolic stability, and parental care) or safety needs (i.e., protection, harm reduction, and shelter from threat) are slighted or neglected within early family environments. As suggested by recent evidence (Sumner et al., 2019), exposures to physiological deprivation can result in developmental slowing and delays, while exposures to threat and adversity may bias development toward acceleration and hastened maturation. This specificity in how different categories of early environmental experiences affect developmental acceleration or deceleration has been extensively reviewed in prior literature (Colich et al., 2020); we draw upon this supportive information but importantly, do not assert it as a novel component of our proposed framework. Rather, key determinants of developmental pace, we argue, are the differentially-shaped trajectories of physiological needs versus safety needs during early life and parental capacities for sustained fulfillment of those needs. It is not enough to consider only the balance of caregiver dependence-child independence early in life (i.e., Callaghan & Tottenham, 2016a); rather, we must address whether premature independence from caregivers occurs in the domain of physiological or safety needs, as this differentially affects the pace of development. Fourth, while life history theory attends principally to the optimization of *long-term* outcomes (i.e., reproductive fitness), the present amendment also attributes differences in pace to the sufficiency of the family's efforts to meet *immediate, short-term early developmental needs* (i.e., Maslovian needs for physiological stability and safety from threat). Fifth and finally, the theory promulgated here is closely tied to increasingly known *neurobiological mechanisms* by which accelerations or decelerations in developmental pace could be induced. The effects of early environments signaling insufficient resources for meeting physiological and safety needs are demonstrably mediated by systematic changes in developmental brain circuitry, prompted most likely by epigenetic processes guiding direction and pace. Related to this point is the concept of the "experience expectant" brain, which relies upon the environment to provide key pieces of information required for optimal development. Over time, evolutionary processes are assumed to have "canalized" brain development, producing phenotypes that are optimized for regularly encountered environmental conditions (McGrath, Hannon, & Gibson, 2011). When particular genotypes are exposed to environments that deviate from the expected, the brain may "decanalize" away from normative trajectories of development (Burrows & Hannon, 2013). It has been proposed that GxE interactions operate via decanalization to influence the development of neurodevelopmental disorders (Burrows & Hannon, 2013). Decanalization that occurs in response to non-normative, adverse environmental conditions may be akin to processes of developmental acceleration or deceleration (deviations from normative pacing), which we propose emerge when children's fundamental needs are not met.

This novel framework accounting for shifts in developmental pace rests upon tenets supported by research across a variety of disciplines, including epidemiology, neuroscience, psychiatry, pediatrics, and epigenetics, among others. The presented evidence, while compelling, is drawn from discrete studies that generally address only singular aspects of the model. Collaborative, team science efforts are ideally suited for studies that comprehensively explore the calibration of developmental pace on the basis of unmet needs. The features of such studies, while ambitious, are achievable with current, methodologically

accessible approaches. For example, future research must thoughtfully measure diverse qualities of early adverse exposures and the manner in which they variably inhibit parents' provisions for children's early needs. There is compelling evidence of non-uniformity in the consequences of different types of adverse conditions, with some that may inhibit the fulfillment of physiological resources and others that may hinder the procurement of safety needs. Summative measures of adversity exposure cannot offer the nuance to disentangle these effects. Similar careful assessment is required of developmental outcomes; such measures should be inclusive of (but not limited to) reproductive milestones and span multiple temporal scales across the full life course. This may also necessitate the development of novel measures of accelerated or decelerated development, beyond traditional measures of precocious maturation or aging. To achieve this, longitudinal designs are imperative.

Future studies should also adopt a reconceptualization of changes in pace as context-dependent. In other words, the implications of developmental acceleration and deceleration should not be deemed advantageous nor deleterious per se, but rather must be evaluated by considering their function within the early rearing conditions in which they emerge. As evidence of developmental acceleration and deceleration continues to accumulate, studies may advance the field not by simply continuing to document these main effects, but by pursuing evidence of processes that explain, exacerbate, diminish or reverse developmental changes of pace. We have reviewed the potential explanatory power of neurobiological mechanisms, but urge consideration of other mediators and moderators that span biological, psychological and social domains relevant to the pace of children's development.

Finally, this change of pace theory offers, as well, a richer framework for conceptualizing the content and timing of preventive interventions. Such interventions might, for example, utilize the signaling inherent in developmental pace alterations or might identify novel means of addressing unmet early needs. The change of pace perspective suggests potential ways of incorporating sensitive or critical period biology into explanations for developmental acceleration and deceleration. Variations in pace may occur predominantly in the early years of life, for example, due to the unique, developmentally-influenced shapes of curves describing early needs (Figure 2) and child versus parent capacities for provision for such needs (Figure 3 and 4).

Developmental science has conventionally viewed children's acquisitions of competencies over time as a linear, ordinal progression varying only modestly from child to child, in the absence of neurodevelopmental pathology. However, like the process of human growth (Caino et al., 2006; Hermanussen et al., 1988), evidence now suggests that trajectories of development can be non-linear and uneven in configuration, with differences in timing and pace from one child to another. Further, findings reviewed here indicate that such temporal differences can be systematically linked to the environmental conditions of early life. Specifically, the pace of development over time may reveal the proximal social environment's capacity or incapacity for fulfilling a child's the most basic, early Maslovian needs: those for physiological resources and protection. In their most fundamental forms, developmental acceleration and deceleration may constitute not only a salient and useful bioassay for the adequacy of parental care but also an evolutionarily conserved mechanism

for mitigating shortfalls of parental provision for needs. Careful attention to inter-individual changes of pace in early development might thus offer new clinical and research windows onto the character and efficacy of early parent-child relationships.

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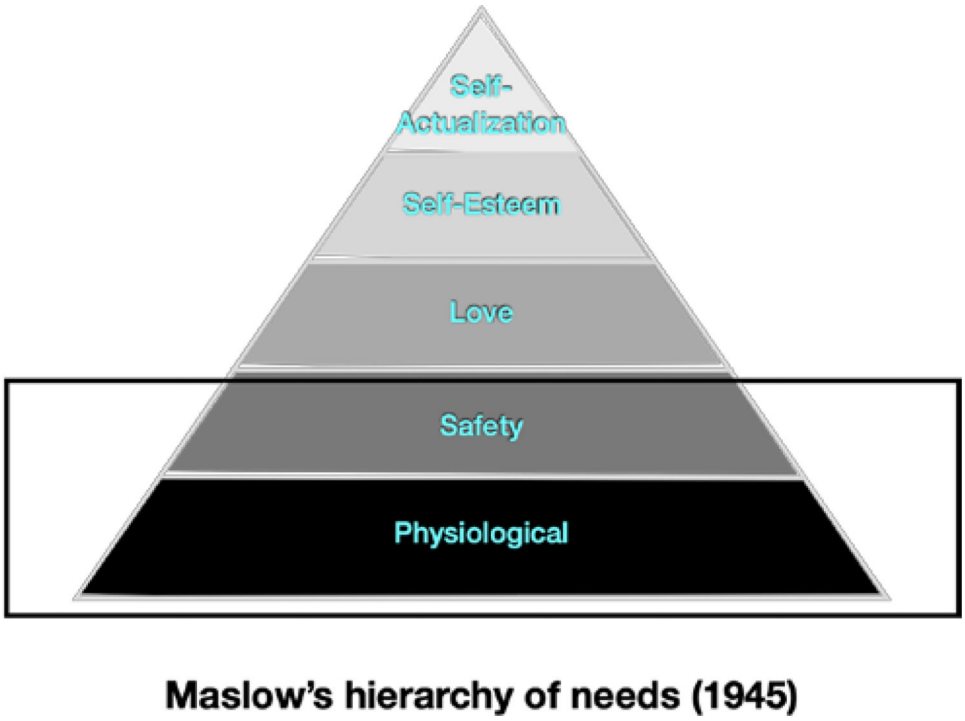

Figure 1.
Maslow's hierarchy of needs
Abraham Maslow's hierarchy of needs. An ordered ranking of needs, ranging from the earliest and most fundamental (e.g., physiological and safety needs) to the later and most complex (e.g., self-esteem and self-actualization). Early physiological needs compromised by food insecurity and other forms of deprivation. Early safety needs compromised by threat or adversity (Maslow, 1943).

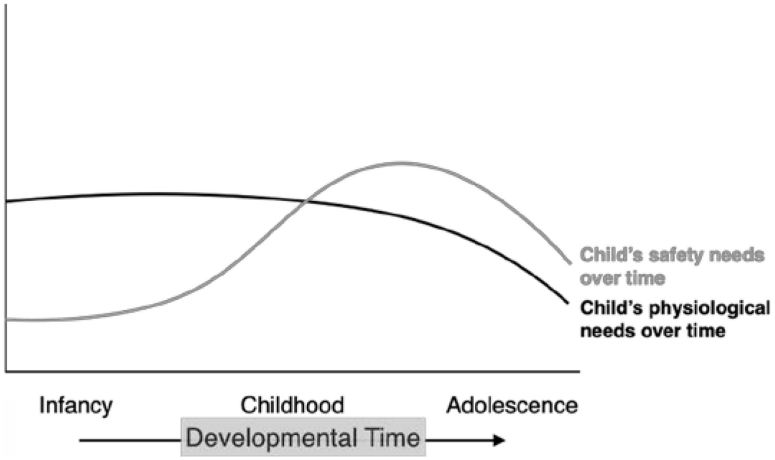

Figure 2.

Trajectories of early, physiological and safety needs over developmental time. Physiological needs are high and sustained early in development, diminishing as a child matures into adolescence. By contrast, safety needs are relatively low and easily met early in development but increase later, peaking in adolescence (Krech, Crutchfield, Ballachey, 1962).

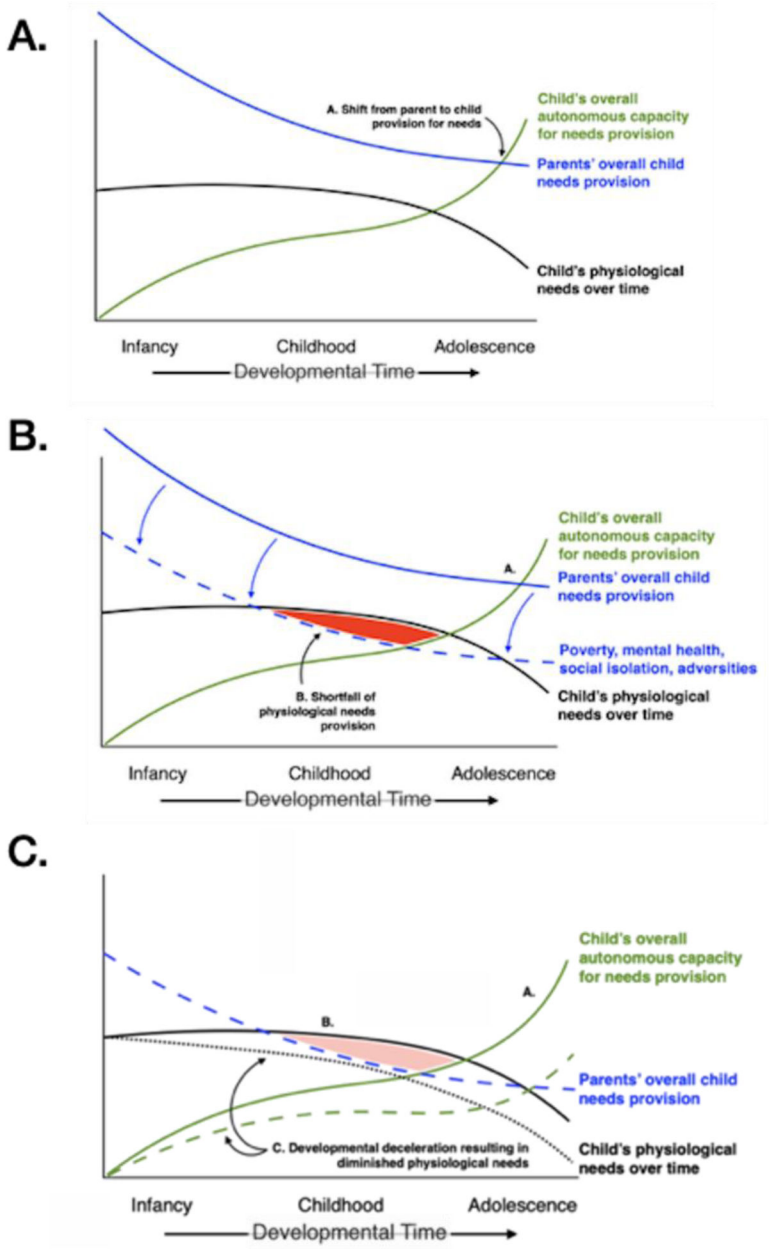

Figure 3.

Developmental deceleration as a response to unmet physiological needs.

A. Trajectories of parental and child provisions of needs. Parents' provisions gradually diminish over time as the child's capacity for meeting needs increases in adolescence. Point A depicts the position in developmental time when needs provision shifts from mostly parental to mostly child.

B. Under conditions of poverty, disordered mental health, social isolation, or adversity, parents' capacities for meeting a child's needs become systematically lower, resulting in (Point B) a shortfall of physiological needs provision.

C. Such deprivation is countered by an evolutionarily conserved developmental deceleration strategy, in which slowed developmental maturation results in diminished physiological

needs over time (Paths C), obviating the needs provision shortfall. Such a developmental strategy is comparable to the diminution in metabolic needs that attends cold water immersion.

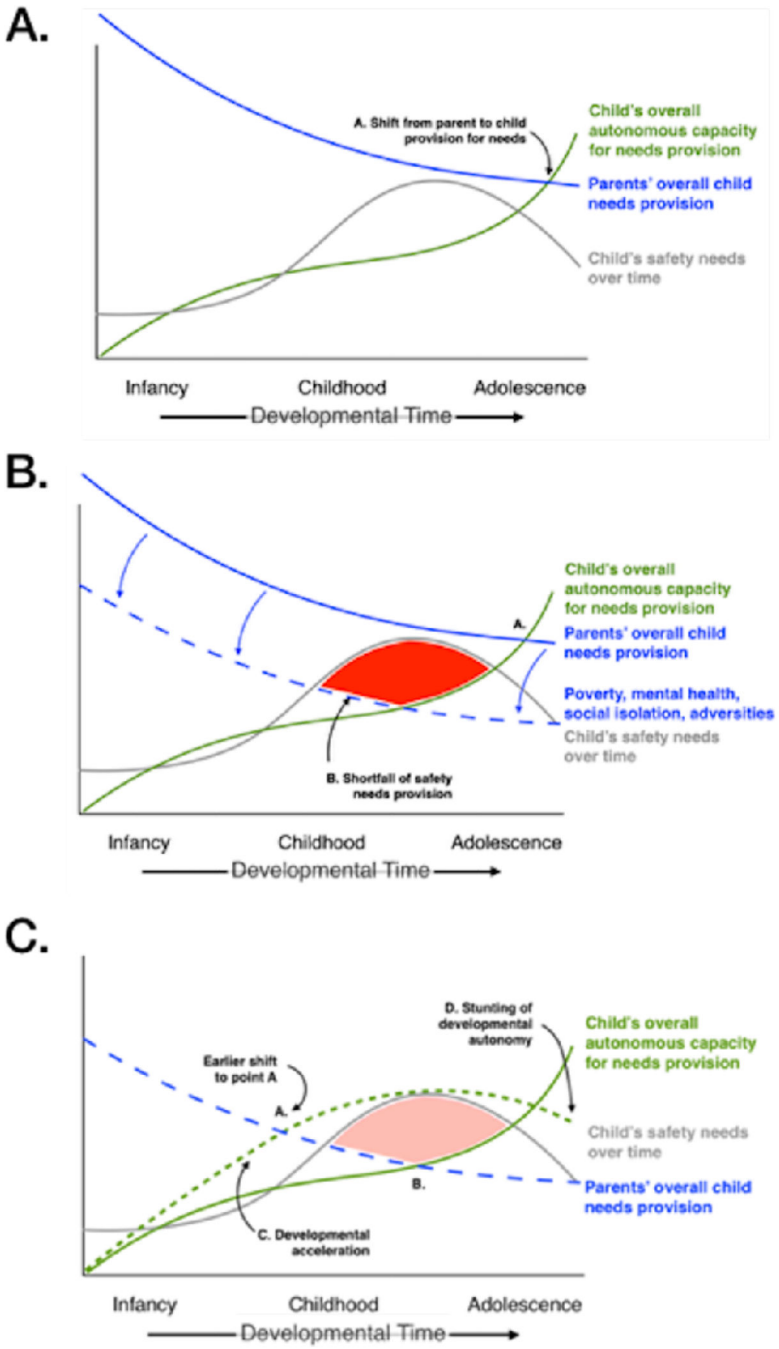

Figure 4.

Developmental acceleration as a response to unmet safety needs.

A. Trajectories of parental and child provisions of needs. Parents' provisions gradually diminish over time as the child's capacity for meeting needs increases in adolescence. Point A depicts the position in developmental time when needs provision shifts from mostly parental to mostly child.

B. Under conditions of poverty, disordered mental health, social isolation, or adversity, parents' capacities for meeting a child's needs become systematically lower, resulting in (Point B) a shortfall of safety needs provision.

C. Such a safety needs provision shortfall under threat is countered by an evolutionarily conserved developmental acceleration strategy, in which more rapid maturation (Path C) results in an earlier shift to predominantly child-derived needs provision (Point A), a meeting of developmental safety needs, and an eventual stunting of developmental autonomy (Point D). Such a developmental strategy entails a life history tradeoff between earlier safety needs provision and longer term autonomy.