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The biological, biographical, and biospheric dimensions of puberty onset: Using Bio3Science to frame transdisciplinary health research on puberty

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Abstract

Introduction: This paper uses the case of puberty to characterize a new health science framework called Bio3Science and to provide an example of how trending research on biosocial mechanisms can be put to use to bridge siloed disciplines as well as the translational gap. Examined as an intricate, open-ended problem of scientific understanding, puberty offers a window to examine how three dimensions of human life – biology, biography, and biosphere – can be understood to shape human health and disease. **Methods:** Using the Bio3Science framework, a biosocial model of puberty was developed and critiqued by an interdisciplinary group of health science and social science researchers in a design studio setting. **Results:** The design and critique process resulted in a model and new conceptual framework that depicts puberty as a highly variable life experience that integrates multiple dense interactions and context-specific responses; within this model, the gene regulatory network (GRN) transformed from a biological to a biosocial mechanism, with conceptual and concrete applications. **Conclusions:** By providing a new, generalizable framework for understanding the integration of biology, biography, and biosphere in health

research, opportunities emerge for more interdisciplinary work puberty, but also and more broadly, for more collaborative, inter-epistemological health research through the Bio$_3$Science framework.

Keywords: Bio$_3$Science, puberty, biosocial, gene regulatory network, normality

Introduction

Current gaps in scientific knowledge about the human body are not solely a biological problem. Understanding differing health trajectories and individual clinical phenotypes involves a detailed comprehension of the dense interactions of a complex array of factors, which the health sciences have usually deemed *either* biological *or* social/environmental. In health and medical research, there seems to be three schools of thought regarding how to study the relevance of these dense interactions. The first school is inclined to focus only on biological measures and to leave social and environmental factors to researchers working in other disciplines. In this work, biomarkers may be seen as a proxy through which any significant effects driven by life's external context are seen and measured in the biological body (e.g., as described in Steckling et al., 2018). The second school integrates biological measures with a potentially wide array of ecological or social-environmental data known or thought to be relevant to health outcomes, which can be grouped together and referred to as biospheric. This school would include research in exposomics expanding beyond biomarkers to surveys/questionnaires, work on health in socio-ecological systems (e.g. Zinsstag et al., 2011), as well as similar kinds of geographic or spatial analytic work that tries to document the where and what of human life, (e.g., through dense data clouds or time-space analyses) in order to understand

how spatial patterns and behaviors matter to health (e.g., Hood, 2017 and see Prior, 2019 for examples). The third and most nascent school is one being developed by the current authors and has been dubbed Bio3Science. Here, the idea is to integrate and build on the two fields described above, but add a third dimension, biographical data, i.e. data related to individual life experience, which is known to have important consequences for health (Summers-Trio et al., 2019; Lobitz et al., 2019).

In this paper, puberty -- specifically scientific uncertainties regarding pubertal onset -- is used to demonstrate the potential of Bio3Science as a synthesis framework for convergence research in the area of human health and wellbeing. The U.S. National Science Foundation defines convergence research as a means of solving especially complex research problems, especially those which relate to societal needs. The NSF specifies that this type of science requires an integration of knowledge, methods, and expertise from different disciplines as well as the creation of new frameworks that catalyze scientific discovery and innovation (NSF, n.d.). Puberty was chosen strategically because of the significant impact that social norms, ecological dynamics, and individual biographies have on pubertal development; however, the Bio3Science framework, as well as the conceptual model proposed in this paper for application in health research on puberty specifically, should be broadly applicable. Bio3Science builds upon multiple existing approaches to health research, synthesizing them in part through “bridging concepts” known as biosocial mechanisms. Well-known and well-studied biosocial mechanisms include epigenetics, the exposome, the microbiome, allostatic load, and circadian rhythm (c.f. Meloni et al., 2016). This paper considers the gene regulatory network as a novel biosocial

mechanism that has yet-to-be-integrated biospheric (e.g. environmental/social) and biographical (e.g. experiential) components. Gene regulatory networks (GRN's) serve as a departure point for developing a *biosocial regulatory network* of pubertal development, which integrates biography and biosphere into an existing biological model that has advanced scientific understanding of puberty.

From both a health science and a social science perspective, one of the most significant limitations of puberty research is the tendency to view the timing and regulation of puberty as either a normal or an abnormal process. Within the category of abnormal, studies have concluded that adolescents with testes are predisposed to "delayed" puberty while adolescents with ovaries are predisposed "precocious" puberty (e.g., Rzeczkowska et al., 2014). While these classifications are based on careful scientific observation and analysis, they fail to describe the irreducible variability that reproductive development can exhibit. Critical social scientists suggest that biological research has been unable to move beyond such dichotomies because of its entanglement with an ideology of normality that stems from a reductionist approach to studying the human body (Haraway, 1988; Hayes, 2016). Such critiques are grounded in an ethical concern that the paradigm of normal vs. abnormal, with respect to puberty, has negative real world implications for adolescents experiencing this embodied rite of passage (Roberts, 2014, 2015). It is worth mentioning that in addition to unnecessarily stigmatizing otherwise healthy bodies (most often menstruating bodies), the binary categorization of pubertal development as either normal or abnormal does a disservice to biological understanding of puberty itself by eliminating the

material complexity inherent to living matter, life systems, and lived processes.

The Bio3Science approach is used to propose an integrative model that frames the broad range of pubertal phenotypes as inherently dynamic, compensatory, and variable phenomena, relevant to the relationship between the bodies and social/biographical/environmental worlds of adolescents. In proposing such a model, *the argument will be made that mapping the biological, biospheric, and biographical factors that contribute to puberty enables a re-conceptualization of puberty as a gradient, which is best characterized as a continuous distribution of these Bio3 factors rather than as a dichotomy of normal vs. abnormal.* This proposal for the construction of a 'biosocial regulatory network' (BRN) is hypothetical and ambitious, representing the potential for a Bio3Science-based reinterpretation of the gene regulatory network (GRN) designed to better understand and predict pubertal phenotype. Depicting puberty as a BRN could also generate new, more effective exchange between and among biomedical researchers, clinicians and health practitioners, and social scientists as well as the general public (e.g. adolescents, parents, educators, and counselors). Even more broadly, the application of such a BRN could provide a new, generalized framework for both medical and social scientists to study the many components of the human condition of puberty. Roberts (2015) careful work on puberty highlights the importance of such an interdisciplinary framework for research on adolescent health and Mendle et al. (2019) have recently argued that population-wide changes in the timing of puberty necessitate new and more participatory approaches to research.

A note on terminology: This paper uses terminology that avoids gendered categorizations of pubertal and reproductive processes. This is done for a couple of reasons: to address the fact that people experiencing ovarian puberty/menstruation do not all identify as female/girls/women and people experiencing testicular puberty do not all identify as male/boys/men (i.e. trans and nonbinary, as well as some intersex individuals) and because individuals undergoing particular pubertal processes do not all have bodies that meet medical criteria for either "female " or “male.” The National LGBT Health Education Center website provides helpful guides on inclusive terminology and care practices for health researchers, clinicians, and educators.

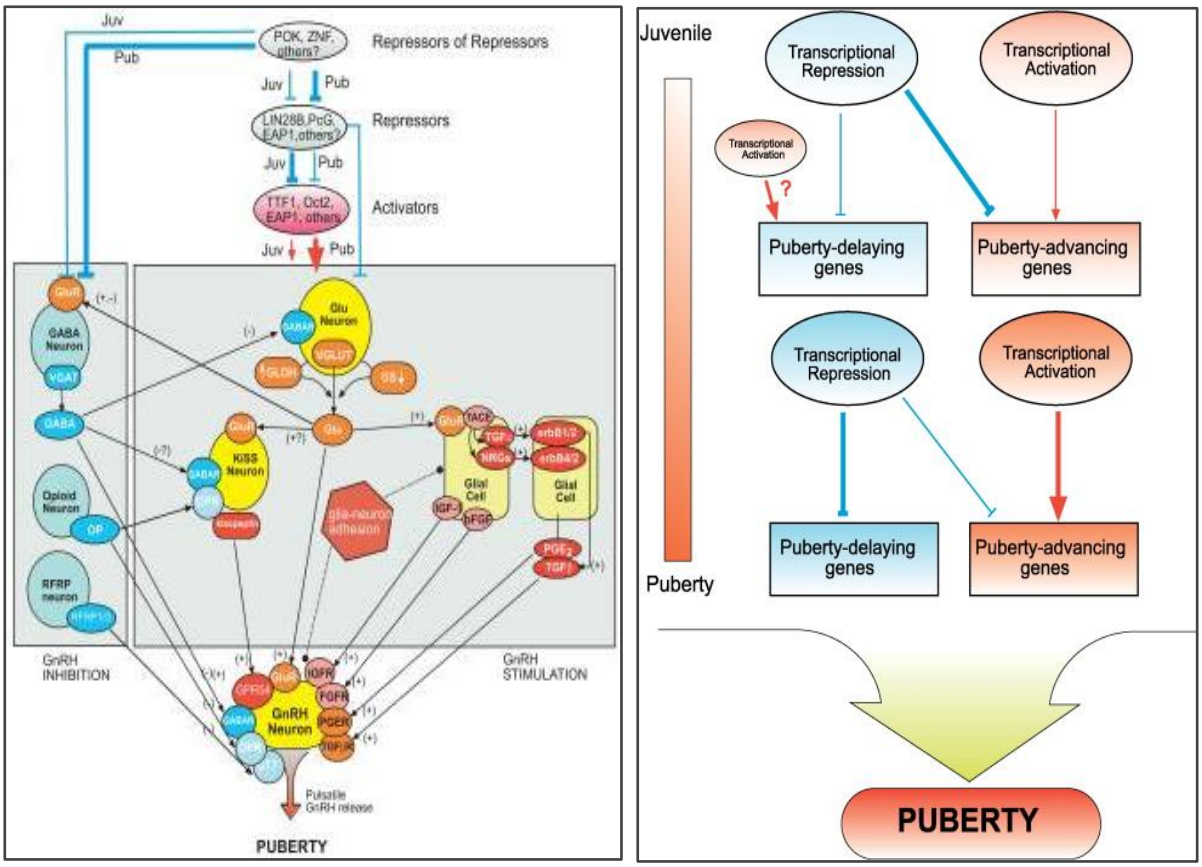
State of Research and Clinical Practice

While there are currently no cases of collaborative and inter-epistemological team-research on puberty, there have been an influx of researchers considering how external factors might influence puberty, which provides a solid foundation for the kind of work described above. In contrast to reductionist scientific models based on binary biological states, these researchers are part of a broader paradigm shift in biology that moves towards a recognition of the environmental permeability and fluidity of biological organisms (c.f. Wiese et al., 2018). In the case of puberty research, this work advances an interaction framework in which genetic and external factors modulate a continuous pubertal process. With respect to the schools of thought mentioned above, this shift might be understood as a move beyond “biology only” research and into an integration of biology x biosphere.

Currently, a variety of molecular frameworks exist that view gene expression as mutable by both internal and external factors. The gene by environment (GxE) framework and, less commonly, GxExE, are certainly relevant here (as in Keers & Pluess, 2017), as is the field of molecular epigenetics, which studies how gene expression is modulated by DNA modifications often induced by factors from the environment (Jaenisch & Bird, 2003). One example from puberty research is Rzeczkowska et al. (2014) who view epigenetics as an important step towards deepening understanding of puberty's complexities and layers of regulation (p. 148). Ojeda et al. (2010) concur that the coordination and transcriptional plasticity of genes that control puberty is likely to be offered by epigenetic factors, although more research is needed to determine why and how.

Epigenetic research is particularly relevant because puberty is thought to be controlled not by one gene or a single set of genes, but rather through complex gene regulatory networks. Gene regulatory networks, or "GRNs", are road maps of genetic interactions that biologists use to model how information is spatio-temporally directed within the cells of the body. These networks comprise of multiple genes and proteins that are known to influence each other in positive (activation) or negative (inhibitory) manners. GRNs can be large, consisting of tens or hundreds of genes, or very small, consisting of just a few genes. A typical GRN is structured with central "hubs" which control the flow of information out to several smaller "nodes" located across various levels within the network (Ojeda et al., 2010). The flow of information is directional and can be depicted as arrows that typically start at the hubs and flow out to the nodes; but the passage of information can also flow back to the central hubs from the nodes, or in between the nodes

themselves. Basically, a GRN will look much more like a spider web than a one-way street (as seen below in Figure 1a).



Figures 1a and 1b. Example of a Gene regulatory network (GRN) modeling pubertal development (taken and modified from Ojeda, et al., 2010). This GRN models genetic and hormonal interactions that occur in neurons primarily located in the medial basal hypothalamus, culminating in the neuroendrocrine release of the gonadal release hormone (GnRH).

Researchers have begun to model the GRN involved in puberty, as pictured in the genetic model shown in Figure 1, which depicts the gene-hormone interactions involved in the onset of puberty (Ojeda et al., 2010). However,

such modeling work is yet to fully incorporate external factors (biosphere and biography) that may regulate gene expression. Moreover, while the GRN makes clear that there are more than a dozen interactions responsible for initiating puberty, it also highlights the pulsatile release of the Gonadotropin-releasing hormone (GnRH) as the single, defining moment at which puberty occurs. As seen in Figure 1, this hormonal release depends on a balancing act of GnRH inhibition (smaller shaded lefthand box in Figure 1b) and stimulation (larger shaded righthand box in Figure 1b). This focus on such singular events often accompanies an ideology of normality in biology, and in the case of puberty, provides a motivation for drug intervention.

The most common drug prescribed to individuals experiencing precocious puberty is a GnRH agonist (GnRH-A), which downregulates the GnRH receptor, thereby delaying pubertal development (Carel & Ledger, 2008). It is important to note that GnRH agonist drugs are used not only on pubescent individuals treated for precocious puberty, but also on individuals treated for various cancers as well as trans and gender nonconforming adolescents considering gender reassignment. In the case of precocious puberty, however, biologists and social scientists have expressed concerns about its overuse in otherwise healthy adolescents displaying early signs of ovarian puberty (Carel & Leger, 2008; Hayes, 2016). These concerns include a high prevalence (upwards of 50% of all cases) of initial signs of precocious puberty either regressing or ceasing to progress, inconclusive data on comorbidities of precocious puberty and their levels of severity, and potential detrimental psychosocial and physical effects of drug treatment (Carel & Leger, 2008). In light of the uncertainties around categorizations of and interventions into pubertal onset, one of the potential benefits of the current

research is to extend the use of the puberty GRN as primarily a tool for drug development to providing a conceptual foundation for researching the inherently variable pathways of puberty and pubertal health. The overall task of the research was to configure a robust model of puberty which demonstrates the ability of the Bio$_3$Science framing to incorporate an understanding of genes, hormones, and their interactions with each other and within the context of the biosphere and the biographies in which they exist. This was accomplished through a collaborative interdisciplinary methodology, which is discussed in the following section.

Methods

The BRN model is the conceptual outcome at the center of this paper. The model (both the visual and, critically, the conceptual synthesis behind it, as described in this paper) was developed in a studio setting through a design-based collaboration between a microbiologist, genomicist, and three human geographers, each with different disciplinary training and epistemological stances. The design studio training method originated in architecture and has since been expanded to other disciplines, including STEM (Cennamo & Brandt, 2012), at the suggestion that the studio's more open, problem-centered approach to learning and discovery could benefit a wider population of scholars and researchers (Schön, 1985). Design-based, team-driven collaborations are a rising mechanism for training and productive output in academia (Brandt et al., 2013). The team (comprised of the authors of this paper) worked within a broader studio in which design-based activities represented concrete means to catalyze convergence science on a variety of topics related to the human body. The studio was funded through the National Science Foundation (Abstract

#1545309). The research process was design-based in the broadest sense. Schon (1988) explains that design work involves juggling multiple and sometimes conflicting factors and values in order to create new artifacts despite the inherent challenges and constraints. The design-based collaboration that produced the BRN model took the following steps: *Brainstorming*: Prior to forming of the research group; the wider training studio, consisting of eleven scientists from widely different disciplinary backgrounds and epistemological starting points, went through a two-day brainstorming process where hundreds of “fuzzy problems” relevant to the human body were developed, debated, and discarded. Fuzzy problems are those that are complex, not sufficiently understood, and, in the case of the collaborative design studio, have multiple dimensions that seem to demand input from a variety of disciplines. The problems that were chosen were both problems of understanding (i.e., conceptually complex) and problems of action (i.e., lack of full understanding has created concrete challenges). *Assembling a Research Team*: After the wider studio settled on a half-dozen fuzzy topics, research groups teamed up based on the broad relevance of their domain expertise and research interests. The team that conducted the research presented in this paper converged on a common interest in deepening existing understandings of puberty. The reasons behind this interest varied widely, from a desire to understand and improve the lived experience of individuals going through puberty to an interest in expanding what biological measures can tell us about human growth and development. The inclusion of qualitative social science expertise at the earliest stages of the scientific research process is notable, as social fields are frequently viewed as an accessory in life and biological sciences, and

social expertise is rarely considered at the stage of hypothesis development or concept modeling (Rose, 2013).

Literature Synthesis: The team reviewed literature on puberty and pubertal timing from within each individual team members broad expertise. The intent was not to provide a systematic review, but rather to identify and extract different hypotheses from the literature in order to synthesize these hypotheses, whether incongruent or overlapping. This process involved much epistemological and dispositional opening (e.g. critical social scientists coming to terms with the merits of integrating social critique into traditional scientific modeling or geneticists learning to fully embrace the idea that the "epi" in epigenetics could include structural forces such as sexism, racism, or economic inequity). It was through this literature synthesis that the focus on GRN's of puberty became clear, as the GRN was agreed upon as the ideal concrete concept through which to merge wide-ranging hypotheses into a comprehensive model.

Iterative Modeling and Critique Sessions: The critique session, which supports feedback and iteration, is a central feature of the design studio. The creation of the conceptual model underwent five rounds (three formal and two informal) of critique and revision, with critiques coming from social sciences, biology, and medicine. Each of the revisions improved and refined the visual model's ability to illustrate the convergence of discipline-specific hypotheses into a meta-conceptual framework for understanding puberty and pubertal timing. The resulting model and conceptual synthesis are detailed in the next section.

Results

The collaborative and inter-epistemological research process produced the following biosocial regulatory network (BRN) of puberty, depicted visually in Figure 2. The BRN model utilizes the network format of the traditional gene regulatory network (GRN) but builds this network out into the three dimensions of Bio3Science: biology, biosphere, and biography.

Figure 2. Biosocial regulatory network (BRN) developed by the current authors. The model integrates components of a biological gene regulatory network of pubertal onset (e.g., key elements originally depicted by Ojeda et al., 2010) (in green), biographical aspects of the specific individual's life (e.g., social relationships and social structures, feelings, and emotions) (in red), and examples of elements of the biosphere (e.g., air pollution, chemical exposures like phthalates, and water quality) that surrounds and penetrates the biographical and biological dimensions of the puberty experience (in blue).

As previously mentioned, GRNs do not yet integrate social or biographical components and have only relatively recently begun to consider external factors. Yet, due to their familiarity and value in biological research, as well as their ability to map out rather than categorize bodily phenomena, for the design collaboration they provided a means to conceptualize puberty as an inherently variable process. As seen in Figure 1, the typical GRN exists as a series of genetic components that may not be able to account for influences that outside factors may play a dynamic role in, such as epigenetic gene silencing that results from a particular social environment or stressor. Epigenetic marks, such as methylation and histone acetylation, can be induced by the environment and subsequently can alter the state of a gene and suppress its expression.

The BRN model that was created (Figure 2) heuristically incorporates the potential influence and variability of the individual relationship with environment and of an individual's life experience. This systematic, yet variegated and dynamic BRN for pubertal development was configured using some of the most well categorized genes known to play a role in the initiation of pubertal timing. A BRN for pubertal development might highlight, for example, cellular specificity by portraying these networks in structures located in the brain where much of the relevant gene communication and hormone signaling occurs. These structures include various neurons, glial cells, and the pituitary gland, all of which are themselves enmeshed in dense, dynamic interactions with a wide array of external factors. By explicitly highlighting BRNs in specific regions of the body, interdisciplinary science can develop a more realistic representation

of how these networks might interact with specific environmental/social factors.

The significant modification (and scientific challenge) in BRNs involves the integration of biological, biospheric, and biographical factors. The heuristic BRN that was developed provides a mere foundation for identifying how social and environmental spheres could feasibly impact the functionality of certain genes in the gene regulatory network. The inclusion of these social modifiers on gene expression is innovative, but still hypothetical, and seeks to drive further transdisciplinary research on gene regulation in puberty. The BRN establishes an outline for integrating a wide variety of mundane but significant biographical and biospheric circumstances such as daily nutrition and vitamin intake, parental occupation, familial economic stress, feelings/emotions associated with significant social relationships, daily exposure to traffic pollution, toiletry and cosmetic use (particularly those including endocrine-disrupting chemicals), UV light exposure, physical activity, and household use of pesticides as events that could trigger a molecular epigenetic event such as methylation or demethylation. All of these factors (and more) have been listed as potentially implicated in the complex and multi-dimensional epigenetic regulation of puberty (Aksglaede et al., 2009; Kinsey-Jones et al., 2010; Lominiczi et al., 2015; Gunes & Arslan, 2016). For example, Aksglaede and colleagues (2009) argue that while body weight and nutrition matter for pubertal timing, they do not explain it. Other factors that they mention, including those that specifically increase exposures to a large number of endocrine disrupting chemicals, are important to include in the model. In another example, Lominiczi and colleagues (2015) cite environmental inputs ranging from nutrition, to

toxins, to light exposure, and even social interactions as potential influencers of puberty's architecturally complex regulatory network. In short, a BRN could intricately map pubertal timing as an inherently biosocial phenomenon, shaped by a plurality of dense interactions, spanning time and context, between the body, the individual's biography, and their environment.

Furthermore, by showing how everyday circumstances, such as diet or pollution exposure, can affect just one part of the network, it must be emphasized that such networks are subject to an incredible number of dense and dynamic external circumstances, each of which may combine to significantly alter communication within the network itself. Hence, by extending the GRN to a more comprehensive BRN, it becomes possible to illustrate the fluidity and malleability of a single measurable process, such as pubertal timing. It is already known that Polycomb group (PcG) silencers can repress the puberty activator gene, *Kiss1*, through the hypermethylation of *PcG* gene promoters (Lomniczi et al., 2013). Yet, several other pathways influence the neuroendocrine control of pubertal onset (Ojeda et al., 2006). Identifying these pathways, the molecular bases of their GxE regulatory control, and the environmental factors that can induce this control, remains a critical but unanswered challenge to fully developing a biosocial regulatory model of pubertal development. Such work will demand critical transdisciplinary research to generate nuanced, contextualized data, document dense interactions, and incorporate multiple kinds of data-sets towards the understanding and accurate prediction of pubertal phenotypes (c.f. Horwitz et al., 2017).

In summary, the gene-hormone interactions that constitute the biological dimension of puberty, the ecological components that constitute the biospheric dimension of puberty, and the life stories and experiences that constitute the biographical dimension of puberty, have all been studied but have never before been integrated into a single conceptual model. The BRN does not draw conclusions about how all of these factors interact, but instead provides a visual, meta-conceptual, multi-hypothesis model for guiding transdisciplinary research inquiries around the Bio3 elements of puberty. Like the Bio3Science framework itself, the BRN model can be viewed as a first step toward constituting a new body of scientific literature on biosocial mechanisms; however further commentary about the critical ethical dilemmas involved in recent biosocial research is provided below.

Discussion

The BRN model addresses a specific set of critiques and limitations of existing puberty research revolving around both social science and biological/health research that questions whether or not it is possible to actually mark the moment of pubertal onset and/or deem it either abnormal or normal. In the interdisciplinary research team's collective synthesis of wide-ranging literature on puberty, it was noted that online resources that educate young people and their families about puberty often do highlight the role of variation in pubertal experiences (e.g., www.kidshealth.org), while most biomedical research about puberty timing, treatment options, and outcomes continues to highlight thresholds of normalcy rather than unqualified variation. This discrepancy is not surprising as classical genetics typically begin with a basic assumption of duality: that there exists a "normal" phenotype (i.e., "wild type") that contrasts phenotypically with an

abnormal or unusual phenotype (i.e., “mutant”). This binary phenotypic model is applied across all aspects of modern genetics—and now genomics—from mutational analyses in model organisms to GWAS (genome-wide association studies) studies across cohort populations. While classifying a complex phenotype into two separate classes increases the power of genetic analysis, the continued categorization of the materiality of life as either normal or outside established norms: 1) ignores the diversity of genes, genetic interactions, and the variability of network modulators in a changing and heterogeneous environment 2) has real life, potentially detrimental implications for individuals experiencing this process, and 3) limits what researchers can interpret from the data and how it gets applied to both the field and practice of medicine. Therefore, the proposed BRN model depicts puberty as an interactive and ongoing experience within an individual’s biological and biographical development, and avoids binary depiction of puberty occurring in either a normal or abnormal trajectory.

In addition and related to replacing the normal-abnormal dichotomy with a depiction of puberty as a nuanced and environmentally permeable process, the model also addresses uncertainty in the scientific literature over whether it is possible to actually mark the moment of onset. Traditionally, the age of onset determines whether a young person is “officially” experiencing puberty in a normal or abnormal way (Eugster & Palmert, 2006; Carel & Leger, 2008; Neely & Crossen, 2014). Typically, ovarian puberty displayed before the age of eight is classified as “precocious puberty” (aka abnormal), and individuals are often administered several tests that may lead to the prescription of drugs that inhibit continued

pubertal development (Hayes, 2016). More recently, however, the clinical community has begun to question the existing timing guidelines for puberty, especially in the context of ovarian puberty. This questioning was spurred by the Lawson Wilkins Pediatric Endocrine Society's 1999 recommendation that the age milestone for precocious ovarian puberty be lowered to reflect current statistical trends. Responses to this report have varied over the years, with some researchers agreeing that the age limit should be lowered (Kaplowitz et al., 1999), and others expressing doubts about the data and instead concluding that girls might be experiencing thelarche earlier, but not necessarily comprehensive precocious puberty (Sørensen et al., 2012). While much research has been conducted in response to the 1999 Lawson Wilkins study and cohort studies continue to suggest higher prevalence of pubertal onset before the age of eight than existing models indicate, abnormal/precocious puberty continues to be set at this age limit (Hayes, 2016). As a result, under current categories of pubertal onset, the pubertal experiences of many young people are classified as abnormal.

The fact that different studies have used different milestones (rather than a common single event) to mark pubertal onset further underscores the limitation of researching puberty as a *normal or abnormal* timed arrival at a *normal or abnormal* bodily state. In ovarian puberty, for example, researchers alternate between menarche (the first menstruation), thelarche (initial development of breasts), and pubarche (growth of pubic hair), as well as other milestones (Witchel, 2016). With regard to the variety of markers of pubertal onset, Tena-Sempere (2012) describes puberty as a culmination of several events that start *in utero* and are shaped by gene-environment interactions (p. 300). From this explanation, puberty and

pubertal timing begin to take on a more broadened and potentially biosocial meaning, necessitating new models for and approaches to research. Indeed, Rzeczkowska et al. (2014) have recently called for a broader approach in studying puberty, pointing out that genome-wide association studies (GWAS) have identified alleles that only account for seven percent of the total phenotypic variation in pubertal timing. This means that despite the existence of so much variation in pubertal onset, scientists still cannot identify associated genetic signals across genomes. Because of the lack of a strong genetic signal, it has been proposed that there must be other factors accounting for the disparities among an individual's pubertal onset, which are more likely to be identified through transdisciplinary collaborations.

While the biological research and medical communities have tended to respond to these new complexities/variations by shifting age milestones of normal vs. abnormal puberties, social science and more interaction-based biological frameworks suggest that bodies are inherently variable and relational. Therefore, a phenomenon such as puberty may be better understood as an open and constantly shifting network of interactions rather than a single event marked as either normal or abnormal (Levins & Lewontin, 1985). Importantly, such a shift in approach mirrors recent attentiveness to the dense interactions between a body and its (external and internal) environment, and ultimately, to the importance of understanding dense interactions for phenotypic prediction and clinical decision-making (Latour, 2004; Mansfield & Guthman, 2015; Weise et al., 2017; Wivel et al., 2017; Bachur et al., 2018). This shift also overlaps with recent attention to biological plasticity and its inherent mechanisms

including epigenetics, from both social scientists and life scientists interested in human health (e.g., Meloni, 2016; Kuzawa & Sweet, 2009). The BRN model presented in this paper is the first to actually visualize the networks and dense interactions that underlie puberty.

Finally, the BRN model should also be useful in clinical and educational settings, specifically for its ability to depict puberty as a biological and biographical journey that an individual goes through within a given context (see comparable push for context-based medicine in the management of infertility in Macklon & Fauser, 2019). One of the hopes of the current research is that the BRN could address Mendle et al. (2019)'s call for puberty researchers to use community-based participatory methods in order to capture new types of data on this dynamic, biologically driven process while also acknowledging the reality that puberty is both universal and individualized. This underscores the fact that population-wide changes in pubertal onset necessitate new, more participatory, and more socially contextualized research approaches.

Conclusion

Bio$_3$Science has interdisciplinary benefits in and beyond puberty research. Reformulating existing models of pubertal mechanisms through a revised BRN provides an example of what Bio$_3$Science can do for health research. Such design-based, scientific collaboration also addresses recent calls for the social analysis of science to move beyond critique and toward a collaborative reconstruction of the science itself (Rose, 2013). In the case of puberty, the intent of this paper is to demonstrate how such collaboration could not only address the social repercussions of standard approaches to

puberty, but also and more emphatically, how it could catalyze more nuanced, context-informed attempts at phenotypic prediction. In reconstructing a regulatory network of pubertal timing from GRN to BRN, the argument is made that mapping the social, environmental, and lived experiences of adolescent development alongside its biological mechanisms would necessarily shift puberty research toward a paradigm of regulatory modulation and healthy variability, and away from a decontextualized normal vs. abnormal dichotomy. This shift is possible through the regulatory network's ability to exhibit puberty as a highly variable, even *intra-active*, biosocial process (Barad, 2007) models alone will not abolish the bodily norms that continue to impact research and embodied lived experiences, nor will they automatically assemble transdiscplinary research collaboration. Still, the idea being presented is that this integrative BRN provides an important stepping stone that can used for further research into the biosocial dynamics of many complex diseases as well as for science communication among and between researchers, medical practitioners, and the public they serve. The BRN, as well as the broader Bio$_3$Science synthesis framework aim to encourage collaborative, convergence research that moves beyond disciplinary critique in order to reshape pathways in the service of life (Rose, 2013, p. 22).

Conflict of Interest to Declare

The authors have no conflicts of interest to disclose.

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*The authors choose to use the FLAE (first-last-author-emphasis) norm (Tscharntke at al., 2007), with Hayes-Conroy as senior author.

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