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Continuous body temperature as a window into adolescent development

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ABSTRACT

Continuous body temperature is a rich source of information on hormonal status, biological rhythms, and metabolism, all of which undergo stereotyped change across adolescence. Due to the direct actions of these dynamic systems on body temperature regulation, continuous temperature may be uniquely suited to monitoring adolescent development and the impacts of exogenous reproductive hormones or peptides (e.g., hormonal contraception, puberty blockers, gender affirming hormone treatment). This mini-review outlines how traditional methods for monitoring the timing and tempo of puberty may be augmented by markers derived from continuous body temperature. These features may provide greater temporal precision, scalability, and reduce reliance on self-report, particularly in females. Continuous body temperature data can now be gathered with ease across a variety of wearable form factors, providing the opportunity to develop tools that aid in individual, parental, clinical, and researcher awareness and education.

1. Introduction

Adolescent development is a continuous process of cognitive and physical maturation (Abreu and Kaiser, 2016; Goddings et al., 2019). Despite occurring over a protracted period of time, clinical or self-assessment (Elchuri and Momen, 2020) of pubertal status and trajectory is typically conducted via infrequent observation of external characteristics (e.g., Tanner Scale developed in the late 1960's) (Rueda-Quijano et al., 2019; Shirtcliff et al., 2009), manual ovulatory cycle tracking in girls (Fowler et al., 2020), or costly hormone measurement (Klein et al., 2017). Clinical assessment of external characteristics and laboratory hormone tests provide a relatively sparse set of markers for a lengthy process, and methods that rely on self-report are error prone (Koopman-Verhoeff et al., 2020). Today, relatively inexpensive and widely available wearable sensors capture metrics that are influenced by reproductive hormones and metabolism, such as body temperature from the core, wrist, or finger (Alzueta et al., 2022; Grant et al., 2020; Webster and Smarr, 2020). These sensors provide a surprisingly nuanced view of female reproductive state and a unique opportunity to generate markers of pubertal development in both laboratory and real-world settings. Such sensors, along with a database of normative changes, could provide

non-invasive information about pubertal development to researchers, teens, families, and clinicians (Wartella et al., 2016). Although these investigations are still in their infancy, wider adoption of wearables by preteens and teens, and further development of regulatory standards and data protection for wearable companies, may lead to reliable, inexpensive, and clinically valuable tracking of the adolescent developmental trajectory (Campbell-Page and Shaw-Ridley, 2013; Wartella et al., 2016; Herz, 2014).

1.1. Preclinical studies reveal the promise of continuous body temperature in adolescence

In laboratory rodents, day of life (e.g., postnatal day 30 or 60) is often substituted for individualized markers of pubertal onset or completion (for an overview, see (Sengupta, 2013)). When greater precision is required in animal studies, physical markers of pubertal onset, including vaginal opening (Miyakawa et al., 1991), preputial separation (Korenbrodt et al., 1977), or onset of first estrus through vaginal cell cytology assessment (McLean et al., 2012) are used. Methods that involve frequent manipulation in animal models, such as blood sampling, can be stressful and may even perturb the reproductive developmental

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trajectory (e.g., disrupt ovulation in mice) (Wagenmaker and Moenter, 2017). To avoid such manipulations, we explored whether continuous body temperature (BT) can be used to remotely monitor adolescent development in a rodent model. We selected BT because it is reliable proxy for underlying reproductive endocrine state (Goh et al., 2019; Grant et al., 2020; Webster and Smarr, 2020). For example, changes in estradiol, progesterone, and testosterone influence body temperature via actions on temperature sensitive neurons in the medial preoptic area of the hypothalamus (Nakayama et al., 1975; Silva and Boulant, 1986a; Zhang et al., 2021). Additionally, BT is influenced by metabolic rate (Calonne et al., 2019; Riccio and Goldman, 2000; Yamaoka et al., 2008) and autonomic function (Charkoudian et al., 2017; Charkoudian and Stachenfeld, 2011), providing the potential to further capture the complex pubertal transition associated with growth and reproductive system development.

We were particularly interested in biological rhythms in body temperature, as rhythms change markedly across adolescent development in rodents and humans and are reflected in BT (Mohawk et al., 2012; Pronina et al., 2015; Zuloaga et al., 2009). Rhythms are coordinated across physiological systems (Goh et al., 2019; Grant et al., 2018; Mohawk et al., 2012) and occur at multiple timescales, including within-a-day (ultradian rhythms; URs), daily (circadian rhythms; CRs), and, in females, multi-day ovulatory cycles (ovulatory rhythms; ORs). These patterns of rhythmic change coordinate reproductive development (Albertsson-Wikland et al., 1997; Ankarberg and Norjavaara, 1999; Hagenauer and Lee, 2012; Norjavaara et al., 1996), synchronize internal system state to variation in the environment (Daan and Slopeema, 1978; Dibner et al., 2010; Lewis and Curtis, 2016), and can provide clinically-relevant diagnostic information in rodents and humans (Akin and Elstein, 1975; Alzueta et al., 2022; Bhavani et al., 2019; Grant and Smarr, 2021; Grant et al., 2020; Smarr et al., 2020).

To determine whether predictable rhythmic changes in BT occurred during adolescence, we first examined female rats under controlled laboratory conditions (Grant et al., 2021a, 2021b). During our initial studies, we elected to use controlled laboratory conditions to identify patterns of rhythmic change to later examine under semi-naturalistic conditions (Grant et al., 2022). This initial work uncovered reliable elevations in BT and increased circadian power (i.e., amplitude) of BT rhythms with the onset of puberty. The onset of puberty was further demarcated by 4-day rhythms of BT and ultradian power that tracked the ovulatory cycle. Ovulatory temperature patterns were coordinated with changes in reproductive hormones (Bourguignon, 1988; Grant et al., 2021a; Grant et al., 2021b), consistent with known temperature modulating effects of estrogens, which lower body temperature (Williams et al., 2010), and progesterone, which raises body temperature (both alone and in combination with estrogens) (Buxton and Atkinson, 1948; Charkoudian and Stachenfeld, 2011).

To determine whether these changes persist outside the laboratory, and whether the same strategy can be applied to track adolescent development in males, we performed an analogous study under semi-naturalistic conditions where rats were exposed to natural lighting, temperature, and humidity (Grant et al., 2022). This environment was associated with higher and more variable sex steroid concentrations (Woodruff et al., 2013, 2010) and pubertal onset timing compared to the previously reported laboratory environment (Grant et al., 2021a, 2021b). Nonetheless, patterns of BT and their rhythmic power across adolescent development mirrored that of laboratory conditions in female rats, confirming that measures of BT can be used to reliably track the female developmental trajectory.

Of note, although BT and BT rhythmic power rose across adolescence in male rats, these patterns were not temporally associated with commonly-used markers of male rodent puberty, including preputial separation or rising in testosterone concentrations. This was somewhat surprising as the neonatal testosterone surge plays an organizational role in circadian rhythms of BT in rats (Zuloaga et al., 2009) and impacts temperature sensitive neurons in the hypothalamic preoptic area (POA)

(Silva and Boulant, 1986b). However, the dynamic impact of testosterone on BT is complex, with some groups reporting substantial, irreversible dark-phase decreases in BT in calorie-restricted gonadectomized males, (Cintron-Colon et al., 2019), others reporting no association between BT and plasma testosterone concentrations (Chen and Yu, 2018), and one group reporting a small elevation in BT in gonadectomized males through brown adipose tissue activity (Lantero Rodriguez et al., 2021). Thus, whereas changes in BT represent a potential candidate to monitor human female adolescent development, this strategy may be less reliable in tracking male development and further research in this sex is required (summarized in Fig. 1).

2. The potential for wearables that measure BT in monitoring adolescent development

The widespread availability of relatively inexpensive wearable and implantable sensors that capture metrics influenced by reproductive hormones and metabolism, such as BT, may provide a convenient method to monitor adolescence in both real-world and laboratory settings. Changes in the pattern of BT can capture changes in multiple hormonal axes (reviewed in (Grant et al., 2018)). For example, parallel changes in the magnitude and direction of growth hormone and body temperature have been observed during exercise (Jørgensen et al., 2014; Pronina et al., 2015; Wheldon et al., 2006) and simulated sickness (Rettori et al., 1987) conditions. Additionally, we have shown that stereotyped changes in the rhythmic frequency of BT predict the onset of the preovulatory luteinizing hormone surge in women (Grant et al., 2020)(Fig. 2). Finally BT captures the circadian phase delay seen in adolescence (Hagenauer et al., 2011; Pronina et al., 2015; Rea et al., 2012), as well as the increases in the amplitude of hormonal rhythms and peripheral outputs (reviewed in (Hagenauer and Lee, 2013, 2012)).

Although findings in rodent models may not translate directly to teen populations, several efforts have applied measures of BT to develop algorithms to predict the preovulatory luteinizing hormone surge and confirm ovulation in adult rodents and humans (Alzueta et al., 2022; Grant et al., 2020; Majjala et al., 2019; Prendergast et al., 2012; Sanchez-Alavez et al., 2011; Smarr et al., 2017; Zhu et al., 2021), detect pregnancy prior to detection by conventional tests (Grant and Smarr, 2021; Smarr et al., 2016), detect sepsis early (Bhavani et al., 2019), and monitor fever (Smarr et al., 2020). Notably, the patterns of decreased UR power prior to ovulation, temperature elevation following ovulation, and temperature elevation early in pregnancy, are reported in rodents and humans (Alzueta et al., 2022; Grant and Smarr, 2021; Grant et al., 2020; Majjala et al., 2019; Prendergast et al., 2012; Sanchez-Alavez et al., 2011; Smarr et al., 2017, 2016; Zhu et al., 2021). These promising use cases, and the similarity of features across species and ages, suggest that continuous temperature can be a reliable and convenient mechanism for monitoring puberty. Likewise, although continuous measures of activity have been used to monitor the increase in circadian amplitude and phase delay associated with early to mid puberty (Hagenauer and Lee, 2012), activity is not as closely tied to high-frequency changes driven by hormonal systems (Smarr et al., 2017, 2016). As activity does not appear to predict individual health events like ovulation and pregnancy onset (Smarr et al., 2017, 2016) with comparable specificity (Smarr et al., 2020, 2017, 2016), and because activity does not provide signal at rest (e.g., during sleep), BT is likely a superior metric for these applications.

3. BT to monitor the impact of hormonal disruption during puberty

Temporal disruptions to metabolic and hormonal signals at hourly, daily, and ovulatory timescales are associated with negative physical and mental health outcomes in adults (Casper and Gladanac, 2014; Gibson et al., 2010; Gotlieb et al., 2018; Kalafatakis et al., 2018; Lightman et al., 2020; Wang et al., 2020; Zimmet et al., 2019).

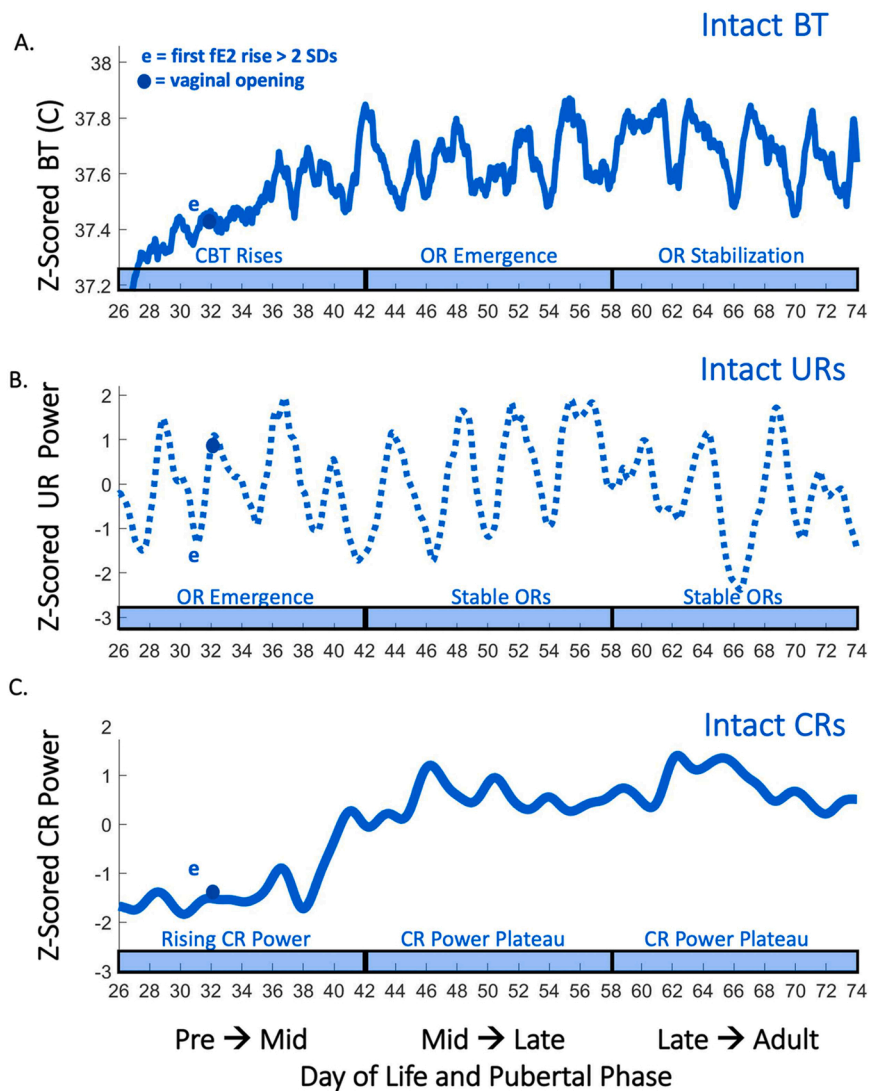


Fig. 1. Summary of BT Features Associated with Adolescent Development in an Intact Female. Features of BT and BT rhythmicity can be used to complement and extend hormonal and external markers of adolescence. Presented here are derived features for an intact female rat from postnatal day 26 (p26) to p74, with a rise in fecal estradiol (fE2) and vaginal opening occurring on p31 and p32, respectively. Dots indicate vaginal opening and “e” indicates first rise of fE2 > 2 SDs. Rising BT, emergence of ovulatory rhythms (ORs) in UR power, and rising circadian rhythm (CR) power can be used to characterize pubertal onset. Mid to late adolescence is characterized by a plateau of CR power as well as the emergence of ovulatory rhythms (ORs) in raw BT and persistence in UR power. From (Grant et al., 2021a, 2021b).

Adolescence may be a sensitive period where such disruptions have rapid (Jain Gupta and Khare, 2020) and long-term health consequences (Carskadon et al., 2002; Crowley et al., 2015; Logan et al., 2018; Pereira et al., 2019). For example, the hormonal contraception commonly used by teen girls for pregnancy prevention (Apter, 2018), treatment of menstrual symptoms (Adeyemi-Fowode et al., 2017), or acne (Mwanthi and Zaenglein, 2018), disrupts typical rhythms observed in hormones of the reproductive axis. Many hormonal contraceptives, for example, aim to prevent ovulation and implantation by maintaining elevated progestin levels (with or without estrogen derivatives) akin to the post-ovulatory, luteal phase of the cycle (Gemzell-Danielsson, 2010; Krishnan and Kiley, 2010; Li et al., 2018). As these hormones are delivered at static or once daily bolus concentrations that differ from the endogenous, multiscale rhythmic pattern of release (Naqvi et al., 1984; Strom et al., 2010; Zhou et al., 1998), hormonal contraceptives can be considered a form of *temporal* endocrine disruption (Landersoe et al., 2020; Lucaccioni et al., 2020). Hormonal contraceptive use is associated with elevated body temperature (Baker et al., 2001), decoupling of follicular maturation cycles within the ovary (Achari, 1969; Baerwald and Pierson, 2004; Crosignani et al., 1996; Landersoe et al., 2020), weight change (Lopez et al., 2016; Okunola et al., 2019), mental health risks (Fruzzetti and Fidicicchi, 2020; Skovlund et al., 2018, 2016), potentially lasting luteal phase deficiency (Gnoth et al., 2002), and a variety of other off target effects (Barr, 2010; Benagiano et al., 2019).

Furthermore, women under 21 are more likely to exhibit anovulatory cycles following birth control cessation than are older individuals (Blanc et al., 2009; Brandt et al., 1981; Pinkerton and Carey, 1976), suggesting that contraceptives taken during late adolescence may be more disruptive than in adulthood. In rats, we recently showed that combined contraceptive administration disrupts the rhythmic ovulatory-cycle-associated pattern of BT, and that this disruption persists beyond their cessation (Grant et al., 2021a, 2021b). Although currently considered safe, discontinuation rate is high (Blanc et al., 2009; Coukell and Balfour, 1998) and impact on the temporal progression of human development is unclear due to lack of longitudinal studies with high temporal resolution data.

Additionally, the increasing rate of young people identifying as transgender (youth age 13–17 make up ~18% of the U.S. transgender population in 2022, up from ~10% in 2015 (data from the Williams Institute, 2022) suggests that variability in pubertal trajectory, and the rate of altered pubertal trajectories, may be increasing, and will continue to increase through the use of pubertal blocking hormones and gender affirming hormone treatment (Rew et al., 2021). These treatments underscore the need to understand the impact of exogenous sex steroids on cognitive and hormonal development. Continuous BT measurement may provide an inexpensive and convenient method to monitor pubertal progression in children and teens who delay puberty through gonadotropin-releasing hormone agonists, or who are

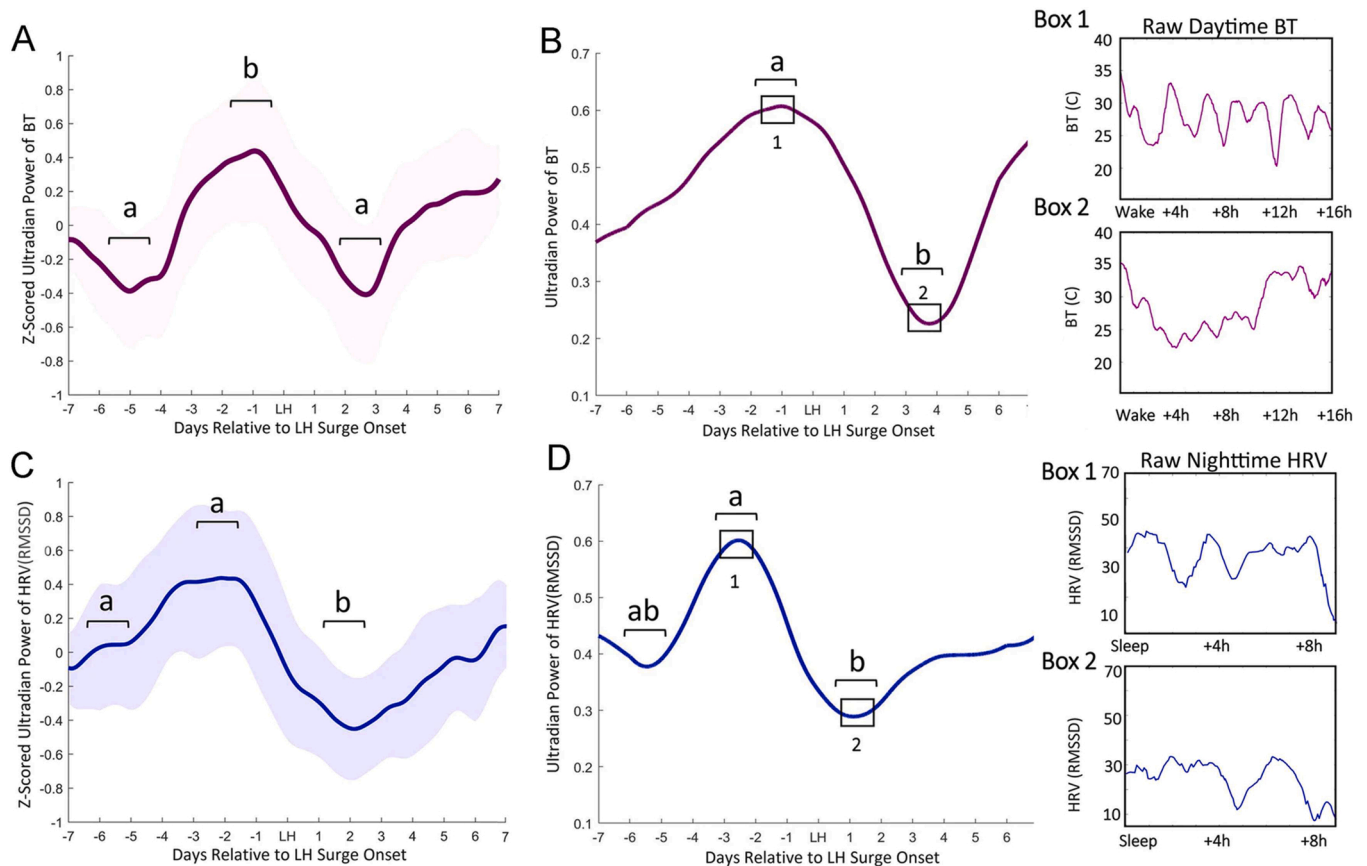


Fig. 2. Ultradian power of distal BT and heart rate variability (HRV) anticipates LH surge onset. Mean BT (A) and HRV (C) ultradian power (z-scored) \pm standard deviation for cycles within one week of the LH surge in women. BT UR power peaks exhibit an inflection point $5.82 (\pm 1.82)$ days prior to LH onset, a peak a mean of $2.58 (\pm 1.89)$ days before LH onset and a subsequent trough $2.6 (\pm 1.02)$ days after surge onset. Ultradian HRV power inflects an average of $5.82 (\pm 1.53)$ nights prior to LH surge onset, exhibits a subsequent peak $2.58 (\pm 1.59)$ days prior to the surge onset and a trough $2.11 (\pm 1.27)$ days after surge onset. Representative individual example of raw BT ultradian power within one week of LH surge onset (B). Black squares in B and D correspond to Boxes 1 & 2 that show linear waking BT and HRV from which ultradian power in B and D were generated. From (Grant et al., 2020).

undergoing delayed puberty and gender affirming hormone treatment. These adolescents may also allow a dissociation of changes in BT resulting from maturational events independent of reproductive axis development. To our knowledge, no studies to date have used continuous measures of BT to monitor developmental trajectories in transgender youth. The use of BT may help to identify treatment options that mimic the typical developmental tempo seen in biological males and females and may generally help characterize the impact of novel hormone administration protocols. For example, BT may be used to identify if the rhythmic trajectory of trans-identifying youth during and prior to puberty differ from a typical trajectory. If exogenous hormones or puberty blockers are introduced, BT could aid in characterizing how exogenous agents modulate circadian amplitude and phase characteristic of typical puberty, and may help to guide the optimal timing of hormone administration.

Finally, even unmodified puberty exhibits greater variability and earlier onset in today's adolescents. Children in developed nations begin puberty at an earlier age than in past decades, attributed to increased body fat (Reinehr and Roth, 2019), stress-related factors (Bellis et al., 2006; Chittwar et al., 2012; Delemarre-van de Waal et al., 2002; Herbison, 2016; Parent et al., 2015, 2003), and potentially exposure to endocrine disrupting chemicals (Fudvoye et al., 2019). Additional temporal insults, including light at night (Casper and Gladanac, 2014; Jain Gupta and Khare, 2020; Smarr and Schirmer, 2018), late meals (Jain Gupta and Khare, 2020), and sleep loss from early school start times (Berry et al., 2021) may contribute independently to alter cognitive (Migueles et al., 2021) and metabolic development (Lin et al., 2022;

Sundaram et al., 2020). In adolescents, BT could be used to track individual pubertal trajectory (e.g., rate of growth; onset and stability of menstrual cycles) to provide a continuous, personal view of development at a time marked by anticipation and changing expectations. BT logs and features may additionally be aggregated to create a more detailed population description of what currently constitutes typical pubertal development, and how features of pubertal onset and ovulatory cycle stabilization change over the coming decades.

4. Strategies to measure continuous temperature in human populations?

While specific patterns of core body temperature during adolescent development observed in preclinical rodent work may not translate directly to peripheral measures in human populations, the availability of wearables providing continuous temperature measurement, such as those from the iButton (Hasselberg et al., 2013) or Oura Ring (Chee et al., 2021; Grant et al., 2020; Majjala et al., 2019), could be used to develop population-wide datasets during typical adolescent development and pubertal onset. Using this approach would allow a determination of whether reliable patterns of BT, or their rhythmic power, can be identified. Whereas peripubertal ovulatory cycles are irregular and often anovulatory (Schmalenberger et al., 2021), continuous temperature monitoring may permit tracking the transition to more consistent, ovulatory cycling. Although requiring open validation, numerous other wearables, including the Ava Bracelet, Whoop4.0, Apple Watch, and Biostrap collect temperature data, providing further opportunity for

identification and independent validation of features associated with adolescent development. In addition to being informative on a population level, individual tracking can be empowering to young people following their own pubertal trajectory, in anticipation of menarche (Fowler et al., 2020; Wartella et al., 2016) or in identifying potentially adverse reactions to disruptive behavior (e.g., drug or alcohol use, sleep loss) (Asimes et al., 2018; Logan et al., 2018) and medication (Apter, 2018). If adopted broadly in teen populations, these metrics could be used to generate high-temporal-resolution images of healthy adolescent development to aid in early detection of deviations from normative and personalized trajectories.

5. Challenges

Generating markers of adolescent development from continuous signals requires regular data detection over long periods of time. In pre-teens and teens, initial interest in self tracking may wane quickly. Although ring form factors may be associated with greater retention, resizing across adolescence may be required to compensate for growth spurts, and companies using this form factor might consider discounted opportunities to increase ring size. Temporal disruptions from environmental factors (e.g., light at night; nighttime use of electronic devices) may alter circadian patterns of adolescent development, creating challenges for data interpretation. Defining new markers of adolescent development in a population whose developmental trajectories are increasingly variable is a long-term, challenging prospect. As reviewed herein, the development of algorithms that consider not only phase and raw amplitude of BT (and other continuous measures such as heart rate, heart rate variability, etc.), but also rhythmic power across frequencies, represents an opportunity to further inform normative developmental tempo and atypical trajectories. We believe an approach that combines commonly worn devices with traditional methods for pubertal assessment, can aid clinicians, researchers, parents, and teens to define reliable relationships among body temperature, classic physiological markers, and the continuous process of adolescence development.

6. Conclusions

Chronic observation of temperature change and rhythmic amplitude represent promising metrics for monitoring adolescent development and the detection of pubertal onset in females. Future work is needed to determine the extent to which such features are consistent across individuals and coordinated with markers of puberty in teens, but findings to date in rodents suggest the feasibility of such an approach. Wearable devices that capture continuous body temperature may provide considerable value if incorporated into longitudinal studies of adolescence.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Azure Grant now works at Levels Inc. Although Level Inc does not engage in the monitoring of puberty and adolescence, the company does promote personalized, self monitoring.

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