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Original article

Sex- and Age-Dependent Differences in Autonomic Nervous System Functioning in Adolescents

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A B S T R A C T

Purpose: We assessed sex- and age-dependent differences in a cross-sectional analysis of cardiac autonomic nervous system (ANS) regulation during sleep in adolescents.
Methods: Nocturnal heart rate (HR) and heart rate variability (HRV) metrics, reflecting ANS functioning, were analyzed across the night and within undisturbed rapid eye movement (REM) and non-REM sleep in 149 healthy adolescents (12–22 years; 67 female) from the National Consortium on Alcohol and Neurodevelopment in Adolescence.
Results: Nocturnal HR was slower in older, more pubertally advanced boys than in younger boys. In girls, HR did not vary according to age or maturity, although overall HRV and vagal modulation declined with age. Although younger boys and girls had similar HR, the male-female HR difference increased by ~2.4 bpm every year ($p < .01$, higher in older girls). Boys and girls showed expected increases in total HRV across the night but this within-night "recovery" was blunted in girls compared with boys ($p < .05$). Also, the non-REM and REM difference in HR was greater in girls ($p < .01$). Models exploring a role of covariates (sleep, mood, reproductive hormones, activity) in influencing HR and HRV showed few significant effects, apart from sedentary activity (higher in older girls), which partially mediated the sex × age interaction in HR.
Conclusions: Sex-related differences in cardiac ANS function emerge during adolescence. The extent to which sex-age divergences in ANS function are adaptive or reflect underlying sex-specific vulnerability for the development of psychopathology and other health conditions in adolescence needs to be determined.

IMPLICATIONS AND CONTRIBUTION

This study reports an interaction between age and sex in autonomic regulation during sleep in healthy adolescents, toward autonomic upregulation (higher heart rate, lower vagal modulation) in older girls. These cross-sectional data offer a framework to understand autonomic involvement in the sex-specific vulnerability in adolescence to psychopathology, including depression and insomnia.

Conflicts of Interest: The authors have no conflicts of interest to disclose.

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Adolescence is a period of dramatic development across physiological systems including the autonomic nervous system (ANS). Abnormal ANS function is implicated in the etiology of several physical and mental conditions [1] that may emerge in adolescence [2]. Thus, effective functioning of the ANS is fundamental for maintaining an individual's mental and physical health. Understanding normal maturation of the ANS, and how behavioral and biological changes in adolescence affect its development, is crucial for timely identification of deviating trajectories in ANS function.

Cardiac ANS function is noninvasively assessed by analyzing heart rate (HR) and its beat-to-beat fluctuations, that is, heart rate variability (HRV) [3]. High frequency (HF) HRV is a well-accepted measure of vagal activity assessed in time (root mean square of differences between adjacent inter-beat intervals, RMSSD) and frequency (HF power within .15–.40 Hz power spectrum) domains, reflecting HR variation with respiration [3]. High resting HR, reduced total HRV (reflected by frequency-domain total power [TP] within the .03–.40 Hz power spectrum and time-domain standard deviation of inter-beat intervals [SDNN]), and reduced HF HRV are all associated with cardiovascular (CV) risk and mortality [1,3]. Lower HRV is also associated with mood and anxiety disorders, and is a risk factor for psychopathology in adults and adolescents [1,3,4].

Recording HRV during sleep allows the investigation of changes in ANS function across the night, reflecting ANS recovery [5], and assessment of changes between non–rapid eye movement (NREM) and REM sleep, reflecting sleep stage-dependent ANS reactivity. NREM sleep is characterized by reduced HR and vagal dominance compared with REM sleep, in which CV and ANS activity is comparable with wakefulness [6]. Sleep as a period of analysis for HRV has the advantage of being relatively free from external wake-related disruptive events that may affect HRV [7], allowing a stable measure of basal ANS tone [8].

HRV decreases with age but the effect of aging on HRV is not linear during the life span [9,10]. There is extensive literature about cardiac ANS control in healthy adults but less is known about ANS control within adolescence [10]. HR progressively slows across childhood and adolescence [11] and HRV peaks in late childhood (between 15 and 18 years), and then declines with advancing age [10–12]. This age-related ANS maturation is also evident during sleep [13–15] and is hypothesized to reflect enhanced efficiency of neural integrative mechanisms [11]. It remains unclear whether there are sex differences in ANS development [10]. Few studies have focused on adolescence, and findings are mixed, indicating higher HR in girls than in boys [9,16,17], age-dependent sex differences in HR [18], or no sex difference [19]. Similarly, some studies report lower HRV in girls [9,20,21], age-dependent sex differences in HRV [22], or no sex differences in HRV [11,19]. Sex differences in HR and HRV measures are evident in adults [23], with women having a faster HR, lower total HRV, and greater vagal activity than men, but when these differences emerge is not clear. This state of relative vagal dominance in adult women (despite a higher resting HR) could protect them against CV disease [23].

Hormonal factors (along with anatomical and genetic factors) are implicated in sex differences in ANS and CV function [24]. Estrogen affects electrophysiological properties of the myocardium [25] and sex steroids increase cardiovagal baroreflex sensitivity [26,27]. Sex differences in the hormonal milieu during puberty and differences in pubertal timing (starts later in boys), therefore, may impact the ANS over and above age in adolescents. Sex and age differences in ANS functioning could also be mediated by differences in activity or anthropometric factors, which change across adolescence, such as sleep [28], body composition, and lifestyle factors [10]. For example, sleep duration [29], fitness, and physical activity [30] are associated with ANS activity in healthy children and adolescents, and obesity in children is associated with reduced vagal functioning [10]. Substance use is also related to a poor ANS profile in adolescents [31].

The current cross-sectional study aims to investigate sex- and age-dependent differences in HRV measures in a large sample of healthy adolescents (12–22 years) participating in the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA). HRV measures were obtained during undisturbed NREM and REM sleep, and across hours of the night. We hypothesized that older age and advanced pubertal development would be associated with a slower HR and that girls would have a faster HR than boys overall. We also investigated the influence of sleep, reproductive hormones, body mass index, depressive symptoms, physical and sedentary activity, and alcohol exposure on HRV.

Methods

Participants

A total of 149 healthy adolescents participated in a sleep component of the multi-site longitudinal NCANDA study at SRI International (N = 119) and University of Pittsburgh (N = 30). Details about NCANDA methodology [32] and the sleep project [28] are described elsewhere. Sample characteristics are from data-release version NCANDA_DATA_00010_V2. The study was approved by institutional review boards at both sites. Adult participants consented to participate, and minors provided written assent along with consent from a parent or legal guardian.

Participants had an in-person visit that included weight and height measurements (body mass index was calculated and converted into a body-mass-for-age percentile according to US reference standards) and validated questionnaires, including Pubertal Development Scale (PDS) [33], a self-report measure of pubertal stage; National Youth physical activity and nutrition survey, to assess self-reported physical and sedentary activity; Pittsburgh Sleep Quality Index, to assess perceived sleep quality; and Center for Epidemiologic Studies Depression Scale, to assess depression symptoms. Twenty-six adolescents exceeded baseline alcohol and drug use criteria for no-to-low exposure [32]. Participant characteristics are reported in Table 1. Participants were free from severe medical conditions, current or past DSM-IV Axis-I disorders, and sleep disorders, assessed by an in-laboratory clinical polysomnographic (PSG) evaluation. None of the participants was using medication known to affect sleep (e.g., hypnotics) or the CV system (e.g., antihypertensives).

All but eight participants had a clinical (adaptation) night a few nights before the PSG recording night. Girls who were postmenarche were studied irrespective of menstrual cycle phase; however, only five girls (of 116 sampled) had saliva progesterone levels >40 pg·mL^{-1}, reflecting probable recordings in the luteal phase. Each night, a breath alcohol test (S75 Pro, BACtrack Breathalyzers) and urine drug test (10 Panel iCup drug test, Instant Technologies, Inc.) confirmed the absence of recent alcohol or drug use.