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Relationship Between Circadian Activity Rhythms and Fatigue in Hospitalized Children with CNS Cancers Receiving High Dose Chemotherapy

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Abstract

Purpose: Robust circadian rhythms are increasingly recognized as essential to good health. Adult cancer patients with dysregulated circadian activity rhythms (CAR) experience greater fatigue, lower responsiveness to chemotherapy, and shorter time to relapse. There is scant research describing circadian rhythms and associated outcomes in children with cancer. As part of a larger study examining whether a cognitive-behavioral intervention could preserve sleep in children and adolescents with central nervous system cancers hospitalized for high dose chemotherapy (HDCT), this study aimed to compare CAR of these children to published values, and to investigate the relationship between CAR and fatigue.

Methods: Participants aged 4–19 years wore an actigraph throughout their hospitalization (5 days). From activity counts recorded by actigraphy, six CAR variables were calculated: amplitude, 24-hour autocorrelation (r24), dichotomy index (I<O), interdaily stability (IS), intradaily

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Conflicts of Interest

Dr. Sonia Ancoli-Israel is a consultant for Eli Lilly and Co., Eisai Inc., Merck, Pfizer, and Purdue Pharma, although has no conflicts of interest related to this research. All other authors have no conflicts of interest to disclose. Dr. Mandrell has full control of all primary data and agrees to allow the journal to review the data if requested.

Ethical approval: "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

variability (IV) and acrophase. Parent-reported child fatigue and child/adolescent self-reported fatigue measures were collected daily.

Results: Thirty-three participants were included. Three CAR variables (amplitude, r24 and I<O) showed dysregulation compared to published values. Older age was significantly associated with later acrophase and greater dysregulation of all other CAR variables. Controlling for age, more dysregulated amplitude (p=0.001), r24 (p=0.003), IS (p=0.017) and IV (p=0.001) were associated with higher parent-reported fatigue; more dysregulated IV (p=0.003) was associated with higher child-reported fatigue.

Conclusions: Participants demonstrated dysregulated CAR during hospitalization for HDCT. Greater dysregulation was associated with greater fatigue. Research on circadian dysregulation and its relationship to health-related outcomes in children with cancer, and interventions to support circadian rhythmicity, are urgently needed.

Keywords

actigraphy; central nervous system cancer; chemotherapy; fatigue; circadian activity rhythm; children

Introduction

Central nervous system (CNS) tumors comprise 26% of childhood cancers [1]. The 5-year survival rate for malignant brain/CNS tumors in children 0–19 years of age currently approaches 75% [1]. Nevertheless, they are the leading cause of childhood cancer-related morbidity. Some of the most troubling symptoms reported by current patients and survivors of CNS cancers are poor nighttime sleep and daytime sleepiness, with children and their parents reporting disturbed sleep-wake cycles [2].

Maintaining a rhythm of consolidated, quiet sleep during the nighttime, and consolidated active wakefulness during the daytime is increasingly recognized as essential to physical and mental health. This rhythm of sleep and wake is reflected in our rest-activity pattern, called the circadian activity rhythm (CAR). Circadian rhythms, the physiological and behavioral changes that occur across a 24-hour period, are regulated by the central circadian pacemaker [3]. While the rhythm of sleep and wake across time is circadian, sleep itself is regulated by two processes. The homeostatic drive to sleep increases the longer we remain awake, while the circadian timing system works to consolidate the sleep and wake periods [3]. Circadian rhythms are largely regulated by clock genes, but can be influenced by social and environmental cues, known as *zeitgebers*. These include light, noise, social interactions, meals and physical activity. Zeitgebers fine-tune our not quite 24-hour circadian period to maintain synchrony with the solar light/dark cycle [4]. Critical illness and hospitalization can disrupt circadian rhythms [5].

A variety of circadian rhythms have been studied, such as temperature, blood pressure, and hormones with diurnal variation such as melatonin and cortisol. CAR is a useful biological marker for circadian rhythms in humans [6], measured using actigraphy. CAR is a frequently studied circadian marker in adult cancer patients, where dysregulation has been associated with poorer quality of life [7], greater fatigue [8], lower responsiveness to chemotherapy [9],

earlier relapse and higher risk of death [7, 9] compared to patients with healthy or *robust* CAR. Circadian disturbances in patients with CNS cancers are not surprising, considering that the central circadian pacemaker resides in the hypothalamus and that melatonin, a hormone that regulates sleep and wake, is produced in the pineal gland. The integrity of these areas can be disrupted directly during surgical resection, or indirectly through cranial radiation or chemotherapy [10, 11].

Fatigue is a nearly ubiquitous complaint among adults and children with cancer. It frequently clusters with other cancer-related symptoms including disturbed sleep and depression [12], and sleep is hypothesized to be a predisposing or perpetuating factor in the development of cancer-related fatigue [13]. Compared to sleep, the relationship between fatigue and circadian rhythms has been less studied. However, growing evidence suggests a relationship between circadian rhythms and cancer-related fatigue [14, 15], and interventions aimed at normalizing circadian rhythms have been shown to improve fatigue [16].

There is limited research on CAR in children with cancer. One of the few studies included 82 children with leukemia on maintenance chemotherapy. Investigators demonstrated that a pulse of dexamethasone had an acute effect of dysregulating CAR compared to the period preceding dexamethasone [15]. The effects of hospitalization for high dose chemotherapy (HDCT) on children's CAR, or how sleep and CAR might best be preserved during intensive cancer treatment, are unknown. To that end, a pilot sleep intervention trial was conducted with the aim of investigating its effectiveness in preserving sleep compared to standard of care in children with CNS cancers hospitalized for HDCT. The present study reports on CAR of these children, and the relationship between CAR and fatigue.

Methods

The sleep intervention was implemented throughout a five day hospitalization for HDCT at St. Jude Children's Research Hospital. This hospitalization occurred as part of a phase III trial treating children newly diagnosed with CNS tumors (SJMB03). Treatment under SJMB03 included surgical excision of the tumor followed by six weeks of radiation therapy and four cycles of HDCT/autologous hematopoietic stem cell (HSC) rescue. Recruitment for the sleep intervention occurred from 2008 to 2011, during the second or third cycle. Methods and sleep-related outcomes of this study have been reported elsewhere [17]. Briefly, this was a randomized controlled trial (NCT00666614) testing the feasibility and efficacy of a multi-component cognitive-behavioral intervention to protect sleep in children during this hospitalization. There were no differences in CAR outcomes or fatigue scores between the intervention and standard of care groups, so analyses include the full sample. The sleep intervention was approved by the St. Jude Institutional Review Board, and the University of Maryland Institutional Review Board granted exempt status for this retrospective examination of CAR data.

Participants

Children qualified for inclusion if they were 4–19 years of age, parent and child spoke English, and children could self-report symptom. Fifty-six families were invited to participate and 43 families consented. Most refusals were related to study burden. Six

participants were removed after consent due to deteriorating clinical status. Four participants were excluded for inadequate actigraphy data for CAR analysis, resulting in 33 children for analysis.

Measures

Children wore an actigraph (Micromini, Ambulatory Monitoring, Inc. [AMI], Ardsley, NY, USA) on their non-dominant wrist throughout their hospitalization. This battery-operated accelerometer measures movement over time and transduces these data into activity counts. Data were processed using zero crossing mode, and activity counts were stored in 60-second epochs. Data were excluded for any 24-hour period having more than four hours of missing data, and for any daytime (9 am to 9 pm) or nighttime (9 pm to 9 am) period having more than two hours of missing data [18].

CAR variables were calculated by manufacturer software (AMI, Action4 version 1.16) from activity counts across all available days, using time series statistical tests. At least 72 hours of recording are required for CAR analysis. Six CAR variables were calculated: amplitude, acrophase, 24-hour autocorrelation (r24), intradaily variability (IV), interdaily stability (IS), and dichotomy index (I<O). Definitions are presented in Table 1. For calculation of I<O, daytime and nighttime periods were compared, rather than the conventional in-bed and out-of-bed time, because sleep fragmentation was severe and in-bed time was high during both periods for most participants.

Cancer-related fatigue was measured with three questionnaires. All items were scored on a 5-point Likert-type scale ranging from 1–5. Higher scores indicated greater fatigue. The reduced 10-item Fatigue Scale-Child is a self-report measure for ages 7–12 years. Validation of the reduced version, based on a scale of 0–4, established a cut-point of 12 for significant fatigue [19]. The present study utilized a 1–5 point scale, so the cut-point was adjusted to 22. Cronbach's alpha for this study was 0.84. The reduced 13-item Fatigue Scale-Adolescent is a self-report measure for ages 13–18 years. A cut-point of 31 indicates significant fatigue [20]. Cronbach's alpha was 0.91. The 17-item Fatigue Scale-Parent is a parent-reported measure of their child's fatigue. No cut-point has been established. Cronbach's alpha was 0.94. Children aged 4–6 years did not self-report fatigue, so parent-reported fatigue served as their proxy measure. Each questionnaire was completed daily.

Statistical analysis

Descriptive statistics including mean ± standard deviation, range and percent were used to describe the sample, CAR variables and fatigue. Age was dichotomized into children (4–12 years old) and adolescents (13–19 years old). Normality of variables and missing data patterns were evaluated. Fatigue measures had less than 5% missing data, so missing values were imputed as the within-subjects mean for that item across all other days. One child had no parent-reported fatigue measure and was too young to self-report, so was excluded from fatigue analyses. T-tests or Mann-Whitney tests were used to test group difference. Fatigue scores did not demonstrate a significant trend across hospitalization, so were averaged across the study. Age was significantly associated with all CAR variables, so partial correlations between CAR and fatigue were controlled for age. Analyses were carried out with IBM

SPSS Statistics, Version 21 (Armonk, NY: IBM Corp.). A p-value <0.05 was significant. No adjustments were made for multiple comparisons [21].

Results

Mean age of the sample was 9.5±3.9 years and 13 (39.4%) participants were female. Twenty-seven (81.8%) participants were white, five (15.2%) were black/African American and one (3.0%) was Asian. Tumor risk was classified as average for 16 (48.5%) and high for 17 (51.5%) participants.

Circadian activity rhythms

Mean CAR values of the sample, and comparison to proposed CAR cut-points or reported mean values for pediatric (where available) or adult samples are presented in Table 1. Based on this literature, participants showed substantial dysregulation of three CAR variables: amplitude, r24 and I<O. A graph of cumulative activity counts across the study, depicting the dysregulation of the rest-activity pattern of one participant, is shown in Fig 1. Dysregulation increased significantly with increasing age for all CAR variables (Fig 2), although variability was high across the sample.

Cancer-related fatigue

Fatigue was high among both children and adolescents. Significant fatigue was reported on nearly half of study days by children, and over 80% of days by adolescents (Table 2). When fatigue scores were averaged across the study, 53.3% of children and 77.8% of adolescents had significant fatigue. Parent-reported fatigue was significantly associated with child-reported fatigue ($r=0.850$, $p<0.001$) and adolescent-reported fatigue ($r=0.882$, $p=0.002$). Parent-reported, but not self-reported fatigue, was associated with age ($r=0.395$, $p=0.025$) such that as age increased, parents perceived greater fatigue in their child.

Circadian activity rhythms and fatigue

Associations between fatigue measures and CAR variables are presented in Table 3. Parent-reported fatigue was significantly, negatively associated with amplitude ($p=0.001$), r24 ($p=0.003$) and IS ($p=0.017$) and significantly positively associated with IV ($p=0.001$). Child-reported fatigue was significantly, positively associated with IV ($p=0.003$). Adolescent fatigue was not associated with CAR although approached significant negative associations with three variables: amplitude, IS and I<O. Parent-reported fatigue scores of the youngest children (4–6 y) were not associated with any CAR variable. No fatigue measures were associated with acrophase. These findings suggest that fatigue increased as CAR became more dysregulated.

Discussion

In this study, children and adolescents with CNS cancers receiving HDCT demonstrated dysregulated CAR, and dysregulation increased with increasing age. Greater CAR dysregulation was associated with greater fatigue, particularly as reported by parents.

No cut-points for identifying dysregulated CAR in children are available, so interpreting our findings is challenging. There are limited studies reporting CAR values in children, so adult studies reporting CAR values or proposed cut-points for dysregulation are also included against which to compare our sample. Amplitude was evaluated in children and adolescents with acute lymphoblastic leukemia preceding a pulse of dexamethasone, where they achieved a mean amplitude of 114 [15]. Although these children might not be considered truly healthy in that they were receiving treatment for cancer, they were in the maintenance phase of chemotherapy, living at home and in stable health at the time of participation. In comparison, the mean amplitude of our sample was well below that value.

Mormont, et al. [22] suggested that an r24 above 0.28 represents well-defined CAR in adults, a value that matched our sample mean. Nevertheless, over half of our sample had r24 values below this cut-point, suggesting dysregulation was present for many children. Pediatric studies reporting r24 values are lacking. However, younger age was associated with higher r24 values, suggesting that the mean r24 of healthy children and adolescents would likely be higher than that of adults, and the true degree of dysregulation of r24 may be underestimated.

The I<O of all participants fell below the adult cut-point of 93.6% [22]. Children are active sleepers and might be expected to have lower I<O than adults, as actigraphy cannot distinguish between movement during active sleep and wake. Instead, we found the opposite association, with I<O being highest in our youngest participants, then decreasing significantly with increasing age. In light of this finding, our low I<O is not explained by our young sample. I<O is recognized as one of the most clinically relevant CAR variables for predicting prognosis, and for its association with disease symptoms [7, 23]. The low I<O in our sample, then, is likely a valid reflection of circadian disruption experienced during HDCT, suggesting that I<O may be a useful CAR measure for future childhood cancer studies.

In a study of healthy children and adolescents, a mean IV of 0.76 was reported by Mitchell et al [24]. In another study, a mean IV of 0.31 was reported among healthy adolescents and young adults by Castro et al. [25]. Hospitalized children removed from their normal routines, such as school attendance, that help impose regularity to their lives, are already at risk for circadian dysregulation. Given the physical and mental stressors of HDCT, its adverse effects such as vomiting and fever, and disruptions for nursing care, we expected fragmentation of sleep and subsequent high IV. Therefore, it is difficult to interpret our results, which fell between values reported in these studies. It is possible that the high IV reported by Mitchell et al. [24] relates to their shorter actigraphy recording requirement of at least 10 hours/day, compared to our minimum of 10 hours of recording during each daytime and nighttime period. The IV measures fragmentation of the rest-activity pattern across the 24-hour period. A day lacking adequate recording during both periods might be inadequate to reliably calculate the IV. Therefore, it is possible that their reported IV value was overestimated.

Finally, the IS of our sample was slightly higher than the mean values of 0.4 reported for healthy children [24] or 0.55 for adolescents and young adults [25]. As a measure of the

stability of the rest-activity pattern, it is not surprising that children on HDCT would achieve scores well below 1.0. It is surprising that they would achieve scores similar to published means of healthy child and young adults. This could indicate that sleep fragmentation in our sample, while abnormal, was stable across the study. It may also reflect the small sample sizes and diverse ages included in these studies, which may have resulted in imprecise estimates of IS.

Much about this hospitalization contributed to a disrupted sleep-wake cycle. Nursing care, HDCT and its adverse effects, psychological stressors related to cancer and this treatment cycle, and other factors fragmented children's sleep. As the rhythm measured in this study was activity, sleep fragmentation with higher than normal nighttime activity and lower daytime activity could have biased our calculated CAR values. However, while circadian rhythms are regulated by clock genes, they are also responsive to alteration by zeitgebers as a means of optimizing our synchrony with the solar light/dark cycle [4]. Numerous zeitgebers including light, noise, social patterns such as school attendance, use of electronic equipment, meal timing, and physical activity are altered during hospitalization, potentially disrupting circadian timing. Indeed, we hypothesize that these alterations not only disrupted CAR during hospitalization, but may lead to longer-term circadian dysregulation following discharge.

In support of this hypothesis, there is significant research on critically ill patients during hospitalization [26], and post-discharge demonstrating long-term sleep disruptions [27], and growing evidence of circadian disruptions [5, 26] where rhythms have been found to be abolished or phase delayed [28–30]. There is also growing evidence of long-term sleep disruption in adult survivors of HDCT/stem cell transplant [31, 32]. It is plausible that at least some of the sleep-wake disturbances transplant survivors experience may be driven by circadian dysregulation. This could, in turn, explain the difficulty in treated their sleep disturbances with established sleep-promoting measures [31], as therapies for circadian rhythm disturbances differ from those for sleep. Long-term studies serially following children during hospitalization and post-discharge, and including multiple measures of circadian rhythms, are needed to better understand the effects of different cancers and treatments, hospitalization, and intrinsic stressors on disruption of sleep versus circadian dysregulation, to improve targeting of treatment strategies.

It is unknown whether dysregulation of CAR as seen in our study is transient, with potential to recover between cycles of HDCT, or is more enduring. There is evidence from adult cancer research that CAR dysregulation progresses across treatment cycles [33, 34]. Adult HDCT/stem cell transplant studies have demonstrated that changes in sleep following transplant persist long-term in many survivors [31]. Thus, regardless of recovery between cycles, there appear to be long-term disturbances of the sleep-wake cycle following HDCT/stem cell transplant. Additionally, there is a growing body of research, albeit mainly in animal models, that chronic sleep loss can damage neurons and other non-neuronal brain cells, causing neurobehavioral impairments including long-term disturbance of sleep-wake patterns [35]. Sleep loss during critical developmental periods (such as childhood) in particular appear to have lasting detrimental effects [35]. Considering the high degree of sleep-wake disturbance in our sample, exploring long-term effects of cancer treatment and

hospitalization on disruption of sleep and CAR in children with CNS cancer, their health consequences and interventions to improve them is imperative.

We found that as age increased, CAR became more dysregulated. While the reason for this is unclear, it may be partially explained by the physiological lengthening of the circadian period during adolescence, resulting in a delayed circadian phase that contributes to later bedtimes and rise times [36]. This shift in circadian timing may not synchronize well with hospital routines. Additionally, as children age, their social focus shifts from the family to friends. Loss of engagement with this social support system during hospitalization, combined with loss of routines such as school attendance, could have acted both as stressors and as loss of social zeitgebers, increasing circadian disruption. Few age-based CAR values exist for healthy children and adolescents, so it is impossible to know whether this age-related pattern is concerning, or reflects normal developmental changes. The lack of normative values limits our ability to use CAR variables as biomarkers with which to identify children with dysregulated CAR who could benefit from supportive interventions. Large studies of healthy children are needed to establish age-based normative values and clinically meaningful cut-points for CAR variables that could suggest dysregulation of these rhythms and the need for intervention.

We found that greater fatigue was associated with greater dysregulation of several CAR variables. This relationship was particularly strong for parent-reported fatigue. In support of our finding, higher fatigue has been associated with lower CAR values in women receiving treatment for breast cancer [37] and in patients with metastatic colorectal cancer [8]. In children with leukemia [15], higher parent-, child- and adolescent-reported fatigue were all significantly associated with less robust CAR. The sample size of the present study was small compared to this study, however, so likely lacked power to achieve significant associations among children and adolescents.

These findings should be interpreted in light of study limitations. Our participants spanned a wide age range, and therefore a wide range of physical and neurological developmental stages. As age was significantly associated with all CAR variables, this may have affected our results despite statistically controlling for age. Several CNS cancers were represented in our sample. Although all participants were treated under the same SJMB03 protocol, radiation doses varied by high versus average risk classification. CAR variables did not differ between risk classification groups, yet it is possible that tumor location and/or radiation dose may have affected the CNS of children differentially, potentially affecting CAR differently. Additionally, there are multiple endogenous factors including pain, depression, anxiety and others that were not measured in this study but would likely have affected sleep, and may also have affected CAR.

We hope that this report raises awareness of sleep and circadian disturbances among children treated for CNS cancers, their potential negative health outcomes, and the need for interventions to support circadian rhythms during and after treatment. Using current evidence-based strategies for managing sleep and circadian disorders, interventions could currently be implemented in the hospital and in outpatient and home settings that exploit zeitgebers that help maintain our circadian alignment with the solar light/dark cycle. At

night, these interventions could include maintaining consistent bedtimes and routines conducive to children's sleep; and establishing protected sleep periods with minimal light, noise and sleep interruptions, with care delivered between protected periods to maximize sleep while taking safety into consideration. During daytime, exposure to natural light could be promoted, and children engaged in out-of-bed activities to promote exercise and social engagement, and minimize napping. Participation in interventions could be modified according to children's condition, rather than being disregarded until their condition improves. Future research should also investigate ways to modify childhood cancer treatment protocols to decrease toxicities and side effects, such as chronotiming of chemotherapy and radiation therapy, which has shown potential for lower dosing with equivalent effectiveness and lower toxicities [38]; and melatonin supplementation, capitalizing on its role in sleep and circadian regulation while leveraging its potent anti-inflammatory properties, which appear to play a role in reducing sleep-disturbing side effects of many cancer therapies [39].

In conclusion, in this sample of hospitalized children with CNS cancers undergoing HDCT, several CAR variables showed signs of dysregulation compared reported pediatric and adults studies. Greater dysregulation of CAR was associated with greater fatigue. Investigation into the short- and long-term consequences of circadian dysregulation in children with cancer, and interventions to maintain circadian rhythmicity during treatment are urgently needed, and have the potential to improve health and survival outcomes.

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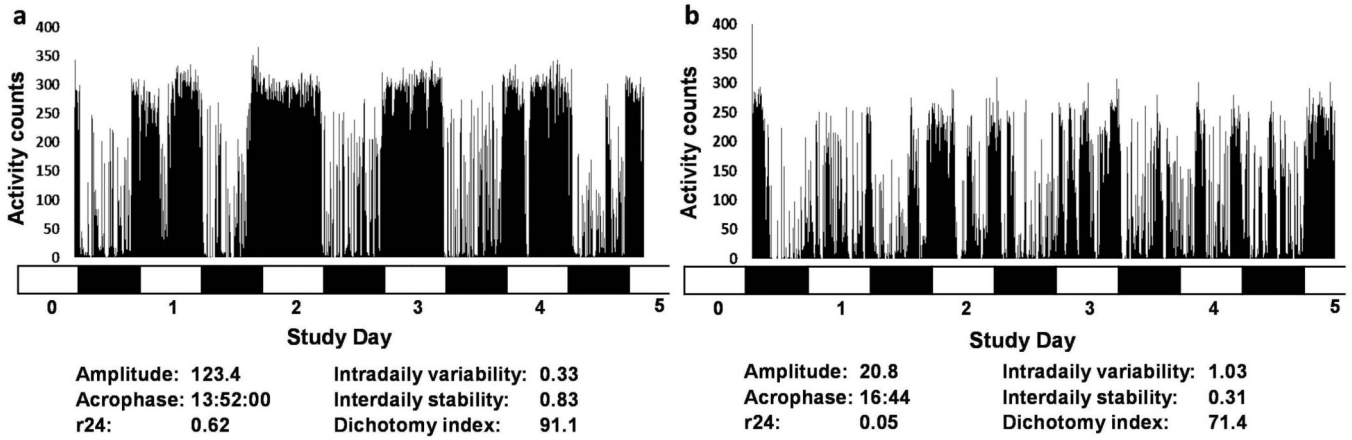

Figure 1.

Graphs of activity counts across time measured by actigraphy and corresponding circadian activity rhythm (CAR) values for two participants. a A 7-year-old female whose activity level is high during the daytime, relatively lower during the nighttime (although higher than during healthy sleep), and has a pattern that repeats predictably from day to day, indicating some preservation of CAR. b A 13-year-old male for whom daytime and nighttime are indistinguishable on most days, indicating severely dysregulated CAR. White rectangles below graphs denote 9 am to 9 pm; black rectangles denote 9 pm to 9 am

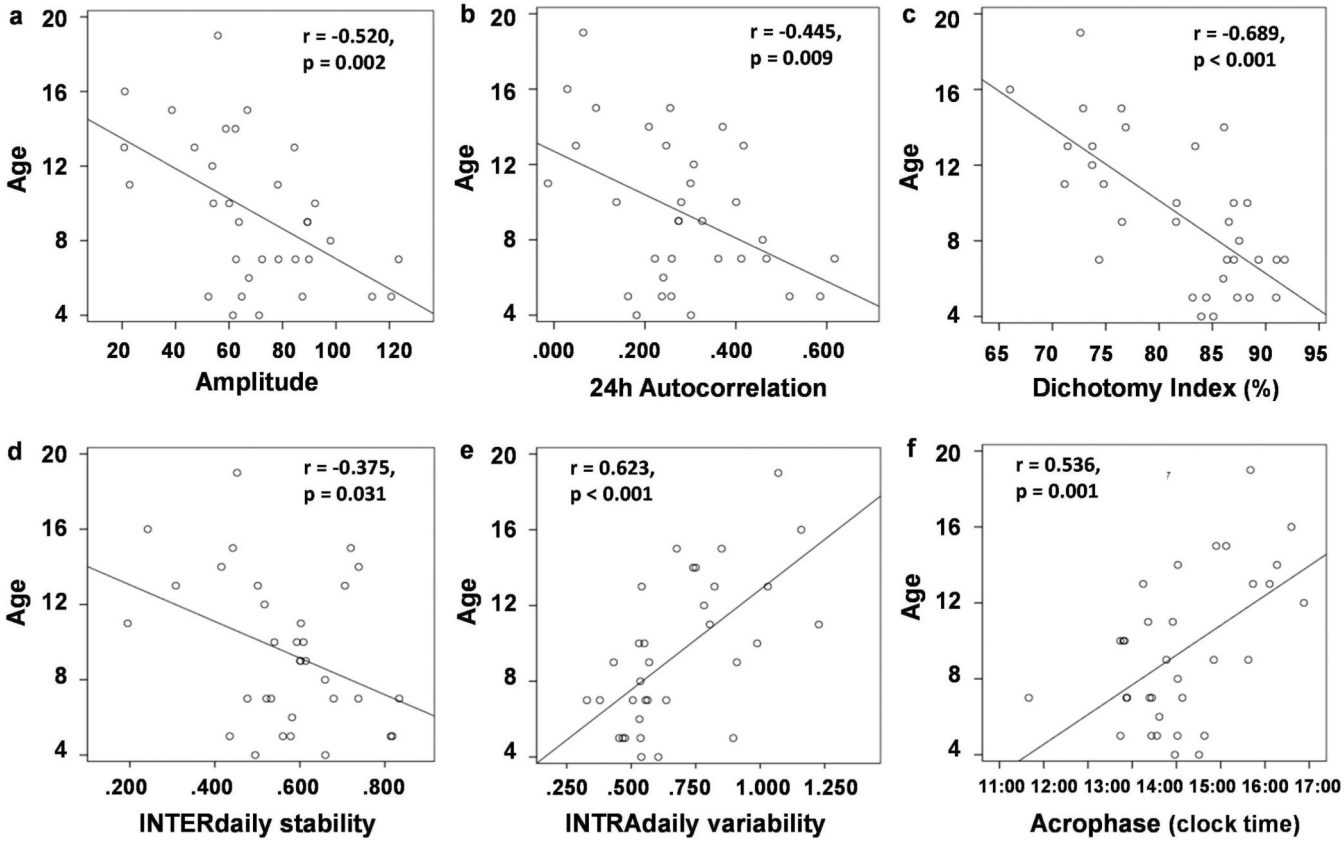

Figure 2.

Scatterplots of age and circadian activity rhythm (CAR) variables. a-e Increasing dysregulation of CAR with increasing age. f Increasingly delayed circadian phase with increasing age. Correlations: a r = −0.520, p = 0.002; b r = −0.445, p = 0.009; c r = −0.689, p < 0.001; d r = −0.375, p = 0.031; e r = 0.623, p < 0.001; f r = 0.536, p = 0.001

Table 1

Circadian activity rhythm variables of children and adolescents with CNS cancers (N=33) and comparison to reported values

CAR variable	Definition	Reported CAR cut-points or mean ± SD	Sample mean ± SD (range)	N (%) below reported cut-points or mean
Acrophase[a]	Clock time of peak activity; suggests whether a person has a morning or evening chronotype. Change during treatment can indicate an advance or delay in the circadian period.	• 14:52 ± 1:3 (82 stable children and adolescents 5–17y with ALL) [15] • 15:17 ± 1:29 (58 healthy children and adolescents 11.6 ± 3.8y) [24]	15:08 ± 1:21 (11:40–17:53)	1 earlier than 14:00 16 later than 15:00
Amplitude	Difference between the highest point of the cosine-fitted curve of activity counts (peak activity) and its mean. Higher values suggest a more robust rest-activity pattern with higher activity during the day and lower activity during sleep.	• 112.4 ± 4.9 (healthy adults) [40] • 114 ± 24 [15]	69.9 ± 25.4 (20.8–123.4)	31 (93.9) with amplitude <114
24-Hour Autocorrelation (r24)	Compares activity counts within an epoch to that of epochs separated from it by precisely 24 hour increments. Reflects the stability of the rest-activity pattern across time. Values range from −1 (no rhythm) to +1 (perfect rhythm stability) [41].	Well-defined CAR >0.28 (adults) [22]	0.28 ± 0.15 (−0.01–0.62)	19 (57.6) with r24 <0.28
Dichotomy index, % (I<O)	Compares daytime to nighttime activity, as the percent of activity counts during sleep that are lower than the median activity during wake. A score of 100% indicates the most robust CAR (activity during sleep consistently lower than activity during wake), 50% indicates no rhythm, 0% indicates a completely inverted rhythm (activity during sleep consistently higher than activity during wake) [42].	• Well-defined CAR >93.6 [22] • ≥97.5 best predicted survival (cancer patients) [43]	81.7±7.0 (66.0–91.8)	33 (100) with I<O <93.6
Interdaily stability (IS)	Compares the rest-activity pattern of one day to that of all other days, reflecting its stability across time. Values range from 0 (no rhythm) to 1 (perfect rhythm stability) [44].	• 0.49 ± 0.12) [24] • 0.55 ± 0.13 (20 healthy AYA 13–27y) [25]	0.57 ± 0.15 (0.19–0.83)	8 (24.2) with IS <0.49 14 (42.4) with IS <0.55
Intradaily variability (IV)[b]	Quantifies the frequency and length of transitions between rest and activity across a 24-hour period. Values range from 0 (perfect sinusoidal waveform or rhythm) to 2 (no rhythm), with higher values reflecting greater rhythm fragmentation [45].	• 0.31 ± 0.05 [25] • 0.76 ± 0.20 [24]	0.68 ± 0.23 (0.33–1.23)	33 (100) with IV >0.31 11 (33.3) with IV >0.76

Note: ALL, acute lymphoblastic leukemia; AYA, adolescents and young adults; CAR, circadian activity rhythm; CNS, central nervous system.

[a] 24-hour clock time, with standard deviation in hh:mm;

[b] Lower value reflects more robust CAR.

Table 2

Measures of fatigue in children and adolescents with CNS cancers receiving high dose chemotherapy

Fatigue measure	Mean ± SD or N (%)
[a]Child self-report	
Total fatigue score	22.2 ± 4.8
Days with significantly fatigue (80 daily reports)	38 (47.5)
[b]Adolescent self-report	
Total fatigue score	40.6 ± 8.7
Days with significant fatigue (48 daily reports)	40 (83.3)
Parent-report total fatigue score (123 daily reports)	
[c]Full sample	48.7 ± 10.5
[d]Children 4–6 y	49.4 ± 4.8
[a]Children 7–12 y	43.6 ± 9.7
[b]Adolescents	57.3 ± 9.9

Note. N=32;

[a]ages 7–12 y, n=16;

[b]ages 13–19 y, n=9;

[c]ages 4–19 y,

[d]n=7. Total fatigue score reports the mean of daily total fatigue scores.

Table 3

Partial correlations between circadian activity rhythm variables and fatigue

	Amplitude	24-h auto-correlation	Intradaily variability	Interdaily stability	Dichotomy index
Parent-reported fatigue (n=32)	−0.576 p=0.001	−0.517 p=0.003	0.587 p=0.001	−0.425 p=0.017	−0.347 p=0.056
Child-reported fatigue (n=16)	−0.474 p=0.087		0.738 p=0.003		−0.465 p=0.094
Adolescent-reported fatigue (n=9)	−0.665 p=0.072			−0.680 p=0.063	−0.664 p=0.072

Note: All correlations controlled for age. Child-reported fatigue only included children aged 7–12 years of age. Correlations with p-values <0.10 are presented.