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Adolescents at Clinical-High Risk for Psychosis: Circadian Rhythm Disturbances Predict Worsened Prognosis at 1-Year Follow-up

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Abstract

Background—Individuals with psychotic disorders experience disruptions to both the sleep and circadian components of the sleep/wake cycle. Recent evidence has supported a role of sleep disturbances in emerging psychosis. However, less is known about how circadian rhythm disruptions may relate to psychosis symptoms and prognosis for adolescents with clinical high-risk (CHR) syndromes. The present study examines circadian rest/activity rhythms in CHR and healthy control (HC) youth to clarify the relationships among circadian rhythm disturbance, psychosis symptoms, psychosocial functioning, and the longitudinal course of illness.

Methods—Thirty-four CHR and 32 HC participants were administered a baseline evaluation, which included clinical interviews, 5 days of actigraphy, and a sleep/activity diary. CHR ($n = 29$) participants were re-administered clinical interviews at a 1-year follow-up assessment.

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Conflict of Interest

Dr. Mittal serves as a consultant to Takeda Pharmaceuticals. There are no other conflicts of interest to report.

Contributors

Authors Lunsford-Avery, Gonçalves, and Mittal conceptualized and designed the study. Authors Lunsford-Avery and Gonçalves performed the statistical analyses, and Dr. Lunsford-Avery wrote the initial draft of the paper. Authors Mittal, Brietzke, Bressan, Gadelha, and Auerbach contributed to results interpretation and drafting of the manuscript. The submitted manuscript reflects the contributions of all of the authors, who unanimously approved the final draft for submission.

Results—Relative to HC, CHR youth exhibited more fragmented circadian rhythms and later onset of nocturnal rest. Circadian disturbances (fragmented rhythms, low daily activity) were associated with increased psychotic symptom severity among CHR participants at baseline. Circadian disruptions (lower daily activity, rhythms that were more fragmented and/or desynchronized with the light/dark cycle) also predicted severity of psychosis symptoms and psychosocial impairment at 1-year follow-up among CHR youth.

Conclusions—Circadian rhythm disturbances may represent a potential vulnerability marker for emergence of psychosis, and thus, rest/activity rhythm stabilization has promise to inform early-identification and prevention/intervention strategies for CHR youth. Future studies with longer study designs are necessary to further examine circadian rhythms in the prodromal period and rates of conversion to psychosis among CHR teens.

Keywords

Circadian Rhythm; Actigraphy; Prodromal; Clinical High-Risk; Psychosis; Schizophrenia

1. Introduction

Psychotic disorders are debilitating illnesses associated with marked distress and functional impairment, which often results in a significant socioeconomic burden (e.g., greater healthcare utilization, reduced occupational productivity; Jin and Mosweu, 2016). Thus, a critical programmatic priority has focused on elucidating risk factors for psychosis onset with the purpose of enhancing early identification and prevention/intervention approaches that reduce the rates of conversion (Cannon et al., 2008). Longitudinal investigations with adolescents with clinical-high risk (CHR) syndromes (e.g., subthreshold symptoms of psychosis, reduced psychosocial functioning) is a promising approach to identify etiological mechanisms implicated in disorder onset (Addington and Heinssen, 2012), as a high proportion (up to 36%) of CHR adolescents convert to psychosis within a two-year period (Fusar-Poli et al., 2012).

The sleep/wake cycle, which is comprised of two interacting processes (i.e., homeostatic *sleep* “Process S” and *circadian* pacemaker “Process C”; Borbely et al., 2016), is frequently disturbed in adults with psychotic disorders, including both medicated and medication-naïve individuals (Chan et al., 2016) and those with and without comorbid mood symptoms (Wulff et al., 2012). Specifically, disrupted sleep/wake cycles increase the severity of psychosis (Cohrs, 2008) and precede relapse of psychotic episodes (Benson, 2015), and interestingly, when addressed therapeutically, reduce psychotic symptom severity (Kantrowitz et al., 2010). While sleep/wake cycle disturbances have been documented and investigated since the earliest conceptions of psychosis (Kraepelin et al., 1919), related clinical features have also recently garnered interest as potential biomarkers for CHR individuals (Lunsford-Avery and Mittal, 2013; Zanini et al., 2013).

To date, investigations with at-risk adolescents have largely focused on the *sleep* component of the sleep/wake cycle with results showing increased self-reported, actigraphic-measured, and polysomnographic-measured (PSG) sleep disturbances among at-risk participants compared to healthy controls (HC) (Brietzke et al., 2015; Castro et al., 2015; Castro et al.,

2012; Keshavan et al., 2004; Lunsford-Avery et al., 2015; Lunsford-Avery et al., 2013; Poe et al., In Press; Zanini et al., 2015). These disturbances in sleep are related to increased concurrent psychosis symptoms, poorer psychosocial functioning, cognitive deficits (i.e., impaired procedural learning), and sleep-related neural abnormalities (i.e., thalamus reductions) (Lunsford-Avery et al., Under Review; Lunsford-Avery et al., 2015; Lunsford-Avery et al., 2013; Poe et al., In Press). Perhaps most importantly, self-reported and actigraphic-measured sleep disturbances at clinical intake predict increased positive symptom severity over a 1-year period among CHR adolescents (Lunsford-Avery et al., 2015), suggesting potential risk markers for psychosis onset. Indeed, prior work has revealed self-reported sleep disturbances as an important factor in predicting transition to psychosis among CHR youth (Ruhrmann et al., 2010).

However, less is known about disruptions to the *circadian* process of the sleep/wake cycle (24-hour, time-dependent, light-dependent, oscillatory variation in sleep propensity; Borbely et al., 2016) among at-risk adolescents or how circadian disturbances may contribute to worsened clinical outcomes for affected youth. Although sleep and circadian processes are closely interrelated, they are also separate processes with distinct biological markers, neural underpinnings, and implications for treatment (Borbely et al., 2016). Thus, clarifying a role of circadian disruptions in addition to sleep problems in the development of psychosis has important implications for understanding the etiology of the illness as well as developing interventions. In a recent study, Castro and colleagues (2015) investigated circadian rest/activity rhythms in teens displaying At Risk Mental States (i.e., ARMS; risk of psychosis and/or bipolar disorder) and found rhythms to be more irregular, fragmented, and desynchronized with the light/dark cycle among at-risk youth compared to HC. In a follow-up case study of three youth from the ARMS project, there was evidence of irregular rest/activity rhythms in the period directly prior to psychosis conversion (Goncalves et al., 2016), suggesting that circadian disturbances may play a role in psychosis development. However, given the small sample size, this issue warrants further attention.

This study had three principal objectives. First, we aimed to replicate Castro and colleagues' (2015) findings and hypothesized that CHR adolescents would display disrupted circadian rhythms compared to HC youth. Second, to extend this work, we tested whether circadian rhythm disturbances relate to concurrent psychosis symptom severity and psychosocial impairment among CHR youth. Finally, among CHR youth, we investigated whether circadian rhythm disturbances at intake predicted psychosis symptom severity and worsened psychosocial functioning at the 1-year follow-up assessment. Evidence linking circadian disturbances and worsened prognosis for CHR youth would support a possible role of rest/activity disruptions in psychosis pathophysiology as well as inform potentially beneficial prevention/intervention efforts for individuals at risk for psychosis.

2. Method

2.1 Procedure

Participants were recruited via internet and print advertisements and physician referrals as part of the Adolescent Development and Preventative Treatment (ADAPT) program's ongoing longitudinal study of CHR youth. At the intake evaluation (time 1; T1), informed

consent and assent were obtained and adolescents participated in clinical interviews to determine eligibility, and if deemed eligible, completed self-report forms as well as 5 days of actigraphy and a sleep/activity diary (described below). Participants returned for a 1-year follow-up (time 2; T2), at which time clinical interviews were repeated to assess for changes in symptom severity and psychosocial functioning during the follow-up period.

2.2 Participants

Participants (CHR = 45, HC = 42) included youth aged 12–21 years. Several adolescents in each group (CHR = 11, HC = 10) were excluded after the intake evaluation due to deficient data regarding rest/activity patterns (less than 5 days of registration or removing the actigraph for more than 3 hours), and only the final sample (CHR = 34, HC = 32) were included in T1 analyses. Participants who were excluded based on insufficient actigraphy data did not differ from included adolescents on any demographic or clinical variables. Inclusion criteria for the CHR group included: 1) attenuated positive psychosis symptoms (moderate severity) *or* 2) global functioning declines accompanied by family history of psychosis *or* schizotypal personality disorder (Miller et al., 1999). Histories of head injury/loss of consciousness, intellectual disability, and neurological disorder were exclusionary for both groups. Formal psychotic disorder was a further exclusionary criterion for CHR youth as was Axis I disorder and family history of psychosis for HC. Twenty-nine of 34 CHR participants had returned for the 1 year follow-up at the time T2 analyses were completed.

2.3 Clinical Assessments

The Structured Interview for Prodromal Symptoms (i.e., SIPS; McGlashan et al., 2001; Miller et al., 2003; Rosen et al., 2006), Structured Clinical Interview for DSM-IV (i.e., SCID, Research Version; First et al., 1995), and Global Assessment of Functioning (i.e., GAF; Jones et al., 1995) assessed CHR syndromes, Axis I disorders, and psychosocial functioning respectively at both time points (interrater reliability Kappa >.80). As depression is common in CHR youth (Rosen et al., 2006; Salokangas et al., 2012; Shioiri et al., 2007; Svirskis et al., 2005) and related to circadian rhythms among adolescents (Robillard et al., 2013), youth completed the 21-item Beck Depression Inventory-II at T1 (BDI-II; Beck et al., 1996) which served as a covariate in statistical analyses.

2.4 Actigraphic Measurement of Circadian Rhythms

Circadian rhythms were measured at T1 via an ActiSleep wrist monitor (approximate cost = \$225; ActiGraph; Pensacola, FL), which was continuously worn by participants over a 5 day period. Participants concurrently completed a daily sleep/activity diary, which required participants to record bedtimes, wake times, and nap times, as well as information about activity participation, school attendance, and any medical concerns (Acebo and LeBourgeois, 2006; Ancoli-Israel et al., 2003). Participants were also asked to record any times they removed the actigraph (e.g., bathing), which was confirmed by ActiLife validation scoring (version 5.10.0).

Circadian rhythms variables were derived from the actigraphy data using the method described by Castro and colleagues (2015), including: autocorrelation function (Ac; slope of the time correlation line (log-transformed); indicative of rhythm fragmentation; lower values

represent less fragmented rhythms), interdaily stability (IS; value for 1440 min provided by Sokolove–Bushell periodogram analysis; denotes synchronization of circadian rhythms with the light/dark cycle), intradaily variability (IV; mean of the first derivative of the actigraphy data normalized by the total variance; a measure of rest–activity rhythm fragmentation), M10 (mean activity level during the most active 10 hours of the day; higher values are indicative of a more active lifestyle), F10 (onset of M10), L5 (sum activity during the least active 5 hours of the day), F5 (onset of the least active 5 hour period/nocturnal activity), and relative amplitude ($RA = (M10-L5)/(M10+L5)$); measures the relationship between diurnal amplitude and night amplitude, the maximum value of 1 occurs when there is no movement during the night) (Chiesa et al., 2010; Eke et al., 2002; Goncalves et al., 2015; Goncalves et al., 2014; Richman and Moorman, 2000; van Beek et al., 1989).

2.5 Statistical Analyses

Independent t-tests and chi-square tests evaluated group differences in demographic variables. Group differences in circadian rest/activity variables at T1 were assessed using linear regressions. Within the CHR group, partial Pearson correlations assessed associations between rest/activity measures and SIPS symptoms (positive, negative) and psychosocial functioning at T1. Lastly, linear regressions covarying for T1 SIPS symptoms (positive, negative) or T1 psychosocial functioning evaluated the extent to which T1 circadian rest/activity disturbances predicted increases in psychosis symptom severity (positive, negative) and psychosocial impairment among CHR youth at T2. Age, sex, and depression were included as covariates in all analyses based on prior literature indicating the impact of these characteristics on circadian rhythms in adolescence (Mateo et al., 2012; Robillard et al., 2013).

3. Results

3.1 Sample Characteristics

Thirty-four CHR and 32 HC youth participated in the T1 assessment and actigraphy study. HC adolescents were slightly younger (trend level) and displayed significantly lower levels of T1 psychosis (positive, negative) and depressive symptoms and higher T1 psychosocial functioning compared to CHR. Groups did not differ by sex or parental education status. Anti-psychotic medication use was somewhat higher among CHR than HC adolescents at T1 (trend level); however, no HC and only 3 CHR (9%) adolescents were taking anti-psychotic medication. Four CHR participants (14%) were taking anti-psychotic medication at 1-year follow-up: 2 participants medicated at T1 continued antipsychotic use, 2 adolescents had initiated an anti-psychotic regimen during the follow-up period, and 1 participant previously medicated at T1 had suspended use. See Table 1.

3.2 Differences in T1 Circadian Rhythms among CHR and HC Youth

At T1, CHR adolescents displayed significantly lower autocorrelation (Ac) function and later onset of nocturnal rest (F5) compared to HC after accounting for age, sex, and depression. CHR and HC youth did not significantly differ on any other circadian measure (see Table 2 and Figure 1).

3.3 T1 Associations between Circadian Rhythm Disruptions and Psychosis Symptoms, Psychosocial Functioning among CHR Youth

Lower autocorrelation function (Ac), lower diurnal activity (M10), and increased intradaily variability (IV) were significantly associated with T1 positive symptom severity (all p values $<.05$) after accounting for age, sex, and depression. Lower relative amplitude (RA) and later onset of nocturnal rest (F5) were related to increased T1 positive symptoms at a trend level ($p < .10$). Decreased activity during the most and least active periods of the day (M10 and L5) was correlated with increased T1 negative symptoms over and above age, sex and depression ($p < .05$). Decreased activity during the most active period of the day was associated with reduced T1 psychosocial functioning at the trend level ($p < .10$). No additional circadian variables were associated with negative symptoms or psychosocial functioning at T1 among CHR youth (See Table 3).

3.4 Disrupted T1 Circadian Rhythms Predict Increased Psychosis Symptom Severity and Psychosocial Impairment at 1-Year Follow-up

Reduced diurnal activity (M10), relative amplitude (RA), interdaily stability (IS), and autocorrelation function (Ac) and increased intradaily variability (IV) were associated with greater positive symptom severity at the 1-year follow-up after covarying for age, sex, depression, and T1 positive symptom severity. Decreased T1 diurnal activity (M10) also was predictive of greater negative symptom severity at 1-year follow-up after accounting for age, sex, depression, and T1 negative symptom severity. Finally, reduced diurnal activity (M10), relative amplitude (RA), and autocorrelation function (Ac), greater intradaily variability (IV), and later onset of the most active period of the day (F10) at T1 were related to poorer psychosocial functioning at T2 above and beyond age, sex, depression, and T1 psychosocial functioning. See Table 4.

4. Discussion

The current study tested whether circadian rhythms are disturbed in CHR adolescents in comparison to healthy peers. In addition, we examined how disturbed rest/activity rhythms may relate to concurrent psychosis symptoms and psychosocial functioning as well as prognosis over a 1-year period. First, consistent with prior research (Castro et al., 2015), CHR individuals displayed more fragmented circadian rhythms and later onset of nocturnal rest relative to HC youth. Notably, later onset of nocturnal rest may suggest increased alertness and reduced readiness to sleep at bedtime (Gradisar and Crowley, 2013), which may contribute to the longer sleep latencies (and REM-latencies) observed in prior CHR studies as measured by PSG (Zanini et al., 2015) and self-report (Lunsford-Avery et al., 2013). Second, among CHR youth, more fragmented circadian rhythms and lower daily activity were cross-sectionally associated with increased positive symptom severity, and lower daily activity was related to negative symptoms at T1. Last, after controlling for T1 symptoms, greater fragmentation of rhythms, desynchronization of circadian rhythms with the light/dark cycle, and decreased daily activity at T1 were predictive of increased positive symptoms one year later, while lower T1 daily activity levels were associated increased negative symptoms at follow-up among CHR youth. Lower activity level and more

fragmented/less regular circadian rhythms at intake were further associated with poorer functioning at follow-up for CHR adolescents.

In previous research, we proposed a neurodevelopmental diathesis-stress model of psychosis wherein sleep/wake disturbances are hypothesized to reflect both an underlying biological vulnerability as well as a stressor in adolescence (through its impact on neuromaturation, endocrine, biological, and psychological factors) that interact to drive psychosis onset (Lunsford-Avery and Mittal, 2013). The current findings that rest/activity disturbances are predictive of worsened prognosis suggest that in addition to disturbances to the *sleep* component of the sleep/wake cycle (Lunsford-Avery et al., 2015), *circadian* pacemaker disruptions may also contribute to psychosis development. This is an important addition to the model, as it suggests that the distinct but interactive biological processes underlying nighttime sleep and daytime rest/activity rhythms may each contribute to mechanisms underlying psychosis etiology as well as inform interventions with this population.

For example, while it is not possible to disentangle the direction of causality in the current study (circadian rhythm disruptions may contribute to or result from emerging psychosis), results suggest a potential mechanism by which circadian disruptions may result in psychosis onset. Specifically, among vulnerable individuals, disturbances in daily rhythm synchronizers (e.g., exposure to light, food intake, amount and timing of social interaction and exercise; Golombek and Rosenstein, 2010) may result in disruptions to the circadian clock, which in turn, may interact with other genetic (e.g., genes supporting brain development) and environmental (e.g., social/academic/occupational stress) vulnerabilities to drive psychosis emergence (see Figure 2).

Future longitudinal research utilizing longer study designs and investigating a range of potential mechanisms through which sleep/wake disturbances may result in illness onset (e.g., through changes in cortisol response, neurodevelopment, or cognition) is essential for informing our understanding of the possible contribution of sleep/wake abnormalities to psychosis etiology. Experimental designs using PSG sleep/wake assessment, cortisol sampling, and next-day measures of neurocognitive functioning (e.g., memory impairment; Keshavan et al., 2010; Li et al., 2016) may also be useful for clarifying risk factors and mediators of relationships between specific sleep/wake disturbances and clinical and functional outcomes in CHR youth. In addition, research has suggested an influence of circadian phase on cortical excitability (i.e., neural reactivity), which in turn impacts cognitive performance (Ly et al., 2016). Cortical excitability, as measured by scalp EEG responses to transcranial magnetic stimulation, may represent another potential mediator of sleep/wake-cognition relationships for future study with CHR adolescents.

These results also open an opportunity to intervene with this population by modifying daily rhythm synchronizers. For example, increasing social routine regularity (e.g., bedtime, wake time, meals) and improving light/dark synchronization (e.g., increasing daytime light exposure, decreasing nighttime light exposure from electronic devices such as television, smartphones, and computers) may improve interdaily stability and reduce positive symptoms in CHR youth. Additionally, increasing daytime physical activity may enhance several

circadian stability and activity measures (IS, RA, M10) and reduce intradaily variability, which may attenuate both positive and negative symptoms and improve functioning.

Recent evidence suggests that treatments such as Interpersonal and Social Rhythm Therapy (i.e., IPSRT), which targets circadian rhythm stabilization, result in improved clinical outcomes for teens diagnosed with or at risk for severe mental illnesses such as bipolar disorder (Goldstein et al., 2014; Inder et al., 2015). In addition, treatments focused on increasing physical activity through exercise are associated with clinical, functional, and neurocognitive improvements among individuals with schizophrenia (Firth et al., 2015). Such interventions may also reduce current CHR symptom severity, enhance functioning, and prevent or delay psychosis onset, and future studies should examine this possibility. Technological innovations (e.g., smart phone applications that assess circadian/activity patterns and provide real-time feedback to patients) could be considered an additional tool of interest to augment and increase access to circadian/activity interventions for CHR youth.

Noninvasive brain stimulation (NIBS) techniques during sleep, such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS), have been successfully employed to improve sleep/wake functioning in individuals with severe mental illnesses, such as bipolar disorder (Minichino et al., 2014), and appear to have a positive impact on neurocognitive functioning in individuals with psychosis (e.g., memory; Goder et al., 2013). In addition, given our prior finding of relationships between sleep disturbances and bilateral thalamic volume reductions in CHR youth (Lunsford-Avery et al., 2013), it is important to consider that supplements that enhance GABA_B, such as gamma hydroxybutyric acid (GHB), have been shown to improve sleep in adults with schizophrenia (Kantrowitz et al., 2010) and may be useful for targeting sleep and related impairments in CHR teens. However, potential complications and issues associated with use of NIBS and GHB with youth are currently unclear (Davis, 2014; Kamal et al., 2016). Future studies may assess the utility, tolerability, and feasibility of incorporating these treatments into preventative and intervention work with CHR youth.

This study is subject to several limitations. First, our current analysis only includes two time points. Only a portion of CHR youth (~36%) develop psychosis and identifying those most likely to convert is vital to the development of targeted prevention strategies (Cannon et al., 2008). Given the relatively few conversions in our sample during the follow up period (N = 2 at T2), our investigation was limited to relationships between circadian disruptions and symptom and functional prognosis. Second, our sample was relatively small and may have been underpowered to detect the full range of circadian disturbances experienced by CHR youth. Third, our study was only 5 days in duration. Although this duration is consistent with prior studies of circadian rhythms in youth with severe mental illness (e.g., Faedda et al., 2016), longer studies would optimize consistency of sampling across participants (e.g., equal proportion of weekend/weekdays assessed). Future studies using larger samples, multiple time points (i.e., past the typical window for conversion), and longer circadian rhythm assessments (7+ days) will further clarify the sleep/wake disturbances experienced by CHR youth and their role in the emergence of psychosis. Finally, several CHR youth (9%) were medicated during the actigraphy assessment; however, the direction and

magnitude of effects did not differ when medicated individuals were removed from analyses (data not shown).

In conclusion, results suggest that CHR youth display circadian rhythm disturbances that are associated with clinical presentation and prognosis. Paired with prior research investigating sleep disturbances in at-risk samples, findings support a potential role of both sleep and circadian processes of the sleep/wake cycle in psychosis etiology and suggest that interventions targeting these phenomena may have utility in improving the clinical course of illness for adolescents at-risk for severe psychopathology.

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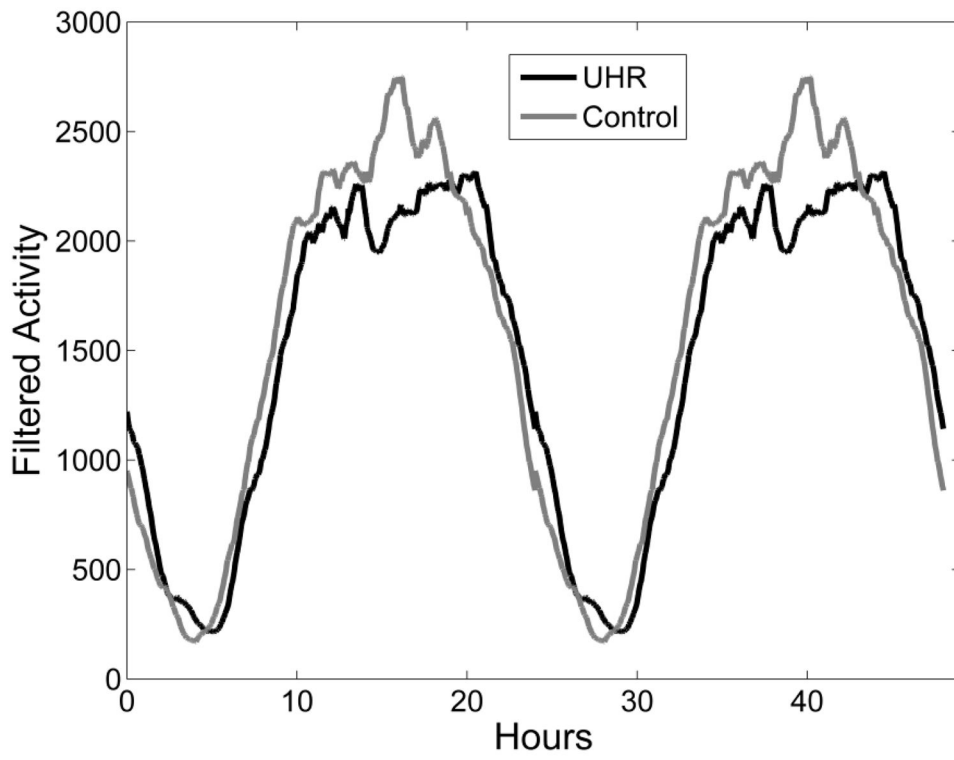


Figure 1. Graphic depiction of group differences in T1 circadian rest/activity rhythms over 48 hour period

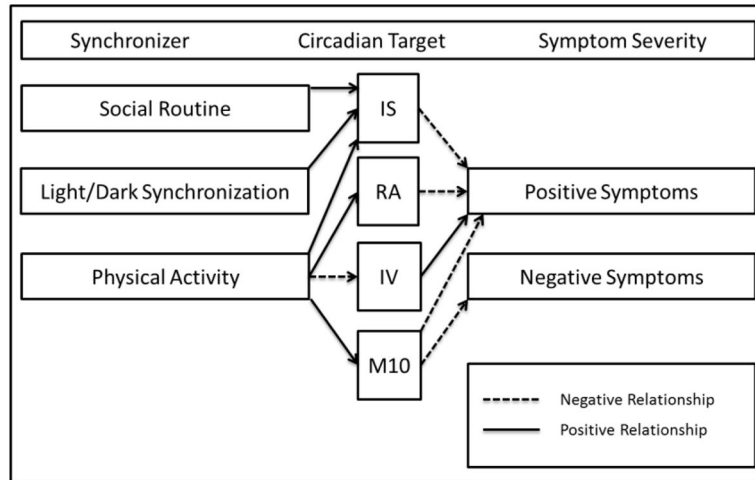


Figure 2. Hypothesized mechanisms by which circadian synchronizers may impact psychosis symptoms in CHR youth

Table 1

Sample characteristics at T1

Variable	CHR (n = 34)	HC (n = 32)	<i>t</i> value	<i>p</i> value
Mean (SD)				
Age, <i>years</i>	18.79 (1.93)	17.75 (2.79)	1.77	0.08
Parent Education	15.96 (2.22)	15.97 (2.50)	-0.02	0.98
SIPS-Positive	12.35 (4.96)	0.78 (1.52)	12.65	< 0.01
SIPS-Negative	9.56 (6.32)	0.41 (0.84)	8.13	< 0.01
GAF	61.24 (13.08)	85.75 (6.41)	-9.57	< 0.01
BDI	17.50 (11.86)	3.59 (5.13)	6.11	< 0.01
Number (%)			<i>χ</i>² value	
Sex, <i>male</i>	15 (44%)	16 (50%)	0.23	0.63
Anti-Psychotic Use	3 (9%)	0 (0%)	2.96	0.09

Abbreviations: CHR, Clinical High-Risk participants; HC, Healthy Control participants; SIPS, Structured Interview for Prodromal Symptoms (total positive and negative symptoms); GAF, Global Assessment of Functioning; BDI, Beck Depression Inventory

Table 2

Differences in T1 circadian rhythms among CHR and HC youth

	CHR mean (SD)	HC mean (SD)	R ²	df	F	p
Ac	-0.29 (0.11)	-0.26 (0.07)	.05	4, 61	3.18	0.04
IV	0.70 (0.16)	0.65 (0.14)	.02	4, 61	0.93	0.17
IS	0.47 (0.13)	0.46 (0.12)	.00	4, 61	0.03	0.44
RA	0.96 (0.02)	0.97 (0.02)	.01	4, 61	0.77	0.19
M10	1599775.71 (449886.43)	1697687.00 (547432.99)	.02	4, 61	1.09	0.15
F5	1587.35 (108.44)	1542.95 (115.06)	.05	4, 61	3.03	0.04
F10	679.82 (138.28)	654.97 (129.58)	.01	4, 61	0.40	0.27
L5	27732.93 (13892.24)	26016.27 (9157.06)	.00	4, 61	0.20	0.33

Abbreviations: CHR, Clinical High-Risk participants; HC, Healthy Control participants; Ac, Autocorrelation function (log-transformed); IV, Intradaily Variability; IS, Interdaily Stability; RA, Relative Amplitude

Table 3

Associations of T1 circadian rhythms, psychosis symptom severity, and psychosocial impairment in the CHR group

Circadian Variable	T1 Positive Symptoms	T1 Negative Symptoms	T1 GAF
Ac	-0.34*	-0.03	0.05
IV	0.36*	0.07	-0.05
IS	-0.13	-0.04	0.16
RA	-0.29 ⁺	0.19	0.03
M10	-0.32*	-0.35*	0.24 ⁺
F5	0.25 ⁺	0.06	-0.14
F10	-0.04	-0.09	0.03
L5	0.08	-0.34*	0.14

Values represent partial Pearson correlations. Significance:

* indicates $p < .05$,

⁺ indicates $p < .10$

Abbreviations: Ac, Autocorrelation function; IV, Intradaily Variability; IS, Interdaily Stability; RA, Relative Amplitude; GAF, Global Assessment of Functioning

Associations between T1 circadian rhythms and 1-year follow-up psychosis symptoms and psychosocial functioning among CHR adolescents

Table 4

T1 Predictor Variable	T2 Positive Symptoms			T2 Negative Symptoms			T2 GAF		
	df	R ²	F	R ²	F	p	R ²	F	p
Ac	5, 23	.20	5.95	.06	1.44	0.01*	.42	17.15	<0.001**
IV	5, 23	.17	4.84	.04	0.98	0.02*	.37	13.23	<0.001**
IS	5, 23	.13	3.69	.06	1.46	0.03*	.03	0.61	0.22
RA	5, 23	.17	4.88	.04	1.02	0.02*	.21	6.16	0.01*
M10	5, 23	.13	3.35	.18	5.20	0.04*	.33	11.11	0.002**
F5	5, 23	.02	0.61	.06	1.44	0.22	.08	1.94	.09
F10	5, 23	.00	0.12	.00	0.05	0.36	.13	3.43	.04*
L5	5, 23	.04	0.92	.00	0.00	0.17	.03	0.71	.20

Significance:

** indicates $p < .01$,

* indicates $p < .05$

Abbreviations: Global Assessment of Functioning, GAF; Ac, Autocorrelation function; IV, Intradaily Variability; IS, Interdaily Stability; RA, Relative Amplitude