ARTICLE

Shared and distinct abnormalities in sleep-wake patterns and their relationship with the negative symptoms of Schizophrenia Spectrum Disorder patients

Ahmad Mayeli[1,12], Alice D. LaGoy[1,12], Stephen F. Smagula[1], James D. Wilson[1], Cristina Zarbo[2], Matteo Rocchetti[3], Fabrizio Starace[4], Manuel Zamparini[2], Letizia Casiraghi[3], Stefano Calza[5], Matteo Rota[5], Armando D'Agostino[6], Giovanni de Girolamo[2], DiAPAson Consortium* and Fabio Ferrarelli[1]✉

Sleep and rest-activity-rhythm (RAR) abnormalities are commonly reported in schizophrenia spectrum disorder (SSD) patients. However, an in-depth characterization of sleep/RAR alterations in SSD, including patients in different treatment settings, and the relationship between these alterations and SSD clinical features (e.g., negative symptoms) is lacking. SSD ($N = 137$ altogether, $N = 79$ residential and $N = 58$ outpatients) and healthy control (HC) subjects ($N = 113$) were recruited for the DiAPAson project. Participants wore an ActiGraph for seven consecutive days to monitor habitual sleep-RAR patterns. Sleep/rest duration, activity (i.e., M10, calculated on the 10 most active hours), rhythm fragmentation within days (i.e., intra-daily variability, IV; beta, steepness of rest-active changes), and rhythm regularity across days (i.e., inter-daily stability, IS) were computed in each study participant. Negative symptoms were assessed in SSD patients with the Brief Negative Symptom Scale (BNSS). Both SSD groups showed lower M10 and longer sleep/rest duration vs. HC, while only residential patients had more fragmented and irregular rhythms than HC. Compared to outpatients, residential patients had lower M10 and higher beta, IV and IS. Furthermore, residential patients had worse BNSS scores relative to outpatients, and higher IS contributed to between-group differences in BNSS score severity. Altogether, residentials and outpatients SSD had both shared and unique abnormalities in Sleep/RAR measures vs. HC and relative to one another, which also contributed to the patients' negative symptom severity. Future work will help establish whether improving some of these measures may ameliorate the quality of life and clinical symptoms of SSD patients.

Molecular Psychiatry; https://doi.org/10.1038/s41380-023-02050-x

INTRODUCTION

Schizophrenia Spectrum Disorders (SSD) have an enormous impact in terms of suffering, disability, and health care costs worldwide [1]. While the diagnosis of SSD is based on the presence of positive (i.e., hallucinations, delusions) and negative (i.e., apathy, anhedonia) symptoms [2], disturbed sleep and activity patterns have been consistently observed since the earliest clinical descriptions of SSD and are commonly reported by these patients [3, 4]. Disturbed sleep and rest-activity rhythm (RAR) patterns in SSD patients can also have implications for certain aspects of health. For example, sedentary lifestyles (i.e., less daytime activity and longer/more frequent rest periods) may contribute to an increased risk of suicide, metabolic disorder, and cardiovascular disease and consequently to the shorter lifespan observed in SSD patients [5–9]. Characterization of sleep/RAR disturbances and their relationships with clinical symptoms may therefore help to establish the implication of these disturbances in the pathophysiology of SSD, which in turn could improve prognosis and treatment outcomes in these patients.

Actigraphy can be employed to quantify disturbances in RAR and sleep parameters (Box 1) objectively and non-invasively. Sleep and circadian abnormalities in patients with SSD have been reported, regardless of the phase of the disorder (i.e., prodromal phase and early course or chronic stages) [10–12]. A significant increase in total sleep time and a reduction in motor activity are some of the most consistently reported findings in SSD patients relative to control groups [4]. Furthermore, SSD patients often present with irregular rest-activity patterns [13], reduced daytime activity [14], and fragmented sleep periods [15]. However, previous studies assessing sleep and RAR alterations in SSD patients via actigraphy have mostly focused on a subset of these parameters and suffered from relatively small sample sizes; [14, 16–21] thus, an extensive characterization of sleep/RAR alterations in a large cohort of patients with SSD relative to healthy control (HC) subjects is currently lacking. Further, to our knowledge, only one study compared RAR parameters between a small group of inpatients ($n = 10$; mean age: 58.9 years) and

[1]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA. [2]Unit of Epidemiological Psychiatry and Evaluation, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. [3]Department of Mental Health and Dependence, ASST of Pavia, Pavia, Italy. [4]Department of Mental Health and Dependence, AUSL of Modena, Modena, Italy. [5]Unit of Biostatistics and Bioinformatics, Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy. [6]Department of Health Sciences, University of Milan, Milan, Italy. [12]These authors contributed equally: Ahmad Mayeli, Alice D. LaGoy. *A list of authors and their affiliations appears at the end of the paper. ✉email: ferrarellif@upmc.edu

Received: 15 November 2022 Revised: 21 March 2023 Accepted: 23 March 2023
Published online: 14 April 2023

Box 1. Sleep/rest-activity measures assess by actigraphy

Sleep Outcomes

Estimated from Cole-Kripke sleep scoring algorithm

Total Sleep Time (TST): Total minutes scored as sleep

Wake After Sleep Onset (WASO): Minutes of wakefulness after sleep onset until final awakening for the day; higher values reflect more fragmented sleep

Rest-Activity Rhythm (RAR) Parameters

Estimated using nparACT to calculate nonparametric and cosinor RAR measures

M10: Average activity level during the most active 10 h of the day

L5: Average activity level during the least active 5 h of the day

Relative Amplitude (RA): Standardized measure of rhythm strength calculated from M10 and L5

Intra-daily Variability (IV): Measure of rhythm fragmentation within days; higher values reflect more variable rest and activity patterns within an average day (e.g., more transitions between periods of rest and activity within a day)

Inter-daily Stability (IS): Measure of rhythm stability/consistency across days; higher values reflect more consistent rest and activity patterns across different days

Rest Length: Duration of the main (longest) rest period of the day estimated based on an extended cosine model

Beta: Steepness/abruptness of transitions between primary rest and activity periods

Activity Offset: Time of activity offset

Activity Onset: Time of activity onset

F-stat: Measure of overall rhythm strength

outpatients ($n = 10$; mean age: 54.3 years) with chronic schizophrenia and found a higher IS and lower physical activity combined with lower IV in inpatients compared to outpatients [21]. Thus, differences in RAR parameters between residential and outpatient SSD patients, especially in a large group of patients, which could help to disentangle disease- and environment-driven abnormalities, have not been thoroughly examined [4].

Altered sleep and RAR parameters have been found to be related to the clinical symptoms of SSD. Among those, negative symptoms, which contribute significantly to reduced social and psychosocial functioning, less working capacity, decreased goal-oriented activities, and ultimately a lower quality of life in schizophrenia [22–24], have been associated with longer total sleep time and lower motor activity patterns in these patients [25, 26]. Furthermore, the negative symptom dimension confers a significant disease burden, yet it is unresponsive to current treatments. Collectively, such findings highlight the importance of negative symptoms for the prognosis and ultimate clinical outcome in SSD patients and illustrate that some aspects of sleep-wake patterns may relate to these symptoms. Nonetheless, establishing the relationships between sleep-wake parameters and negative symptoms in SSD in the context of different treatment settings remains under-investigated [27].

In this study, we examined whether sleep and RAR parameters differed in residential and outpatient patients with SSD relative to HC and to each other. We also assessed whether negative symptoms differed between residential and outpatient groups and whether the severity of negative symptoms was linked with sleep-wake pattern disruptions. We hypothesized that: (1) there would be shared and unique alterations in sleep and RAR parameters in residential patients and outpatients relative to HC. (2) Specific sleep and RAR parameters, including total sleep time, physical activity, and rhythm fragmentation and regularity would be more altered in residential compared to outpatient groups. (3) Negative symptoms would be worse in residential vs. outpatient individuals, and some sleep/RAR parameters that differed across SSD groups would be associated with between-group differences in negative symptom severity.

MATERIALS/SUBJECTS AND METHODS

Eligibility and recruitment

The inclusion criteria for all study participants were to be between 18 and 56 years of age and have a good knowledge of the Italian language. Additional inclusion criteria for patients were SSD diagnosis according to the DSM-5 criteria [28] and being in treatment at residential facilities or as outpatients at Department of Mental Health (DMH) facilities. Furthermore, the following exclusion criteria were applied to all participants: inability to provide informed consent (e.g., because of a low level of education); significant cognitive deficit (i.e., assessed with a Mini-Mental State Examination [MMSE], with a corrected score ≤24.0); recent (in the last six months) diagnosis of substance use disorder according to the DSM-5 criteria; [28] history of a clinically significant head injury; and cerebrovascular diseases. All participants provided informed consent.

From October 2020 to October 2021, patients with a diagnosis of SSD were evaluated at ten participating centers. Outpatients were community-dwelling patients with SSD who were approached consecutively at the outpatient units of local Departments of Mental Health for potential participation until the recruitment target was achieved. At residential facilities, the local heads prepared an alphabetical list of patients with SSD present on an index-day; based on this list, residential patients were consecutively invited to participate in the study until the recruitment target was achieved. Additional information about residential facilities is provided in the supplementary materials.

The psychiatric history of patients was assessed using a structured ad hoc survey based on the DSM-5 conducted by a psychiatrist or a psychologist and aimed at collecting information on the current diagnosis, illness duration, and lifetime duration of psychiatric hospitalizations. For each recruited participant, socio-demographic details were gathered. The Charlson Comorbidity Index [29] was used for the assessment of the physical comorbidities of participants. The 24-item Brief Psychiatric Rating Scale (BPRS) [30, 31] was used for the assessment of the severity of psychopathology. The 43-item Specific Levels of Functioning Scale (SLOF) [32, 33] was used for the assessment of psychosocial functioning.

Regarding healthy comparison subjects, a negative psychiatric history, along with the no current treatment with psychoactive medications, was confirmed during a clinical interview conducted by a psychiatrist or a psychologist. Furthermore, shift workers and \or individuals who recently traveled to a different time zone were excluded. Healthy controls were recruited by public advertisements and snowball sampling procedures and were matched by gender and age group (i.e., 18–24, 25–29, 30–34, 35–39, 40–44, 45–49, and 50–56) with the SSD clinical sample.

Detailed information about the study was provided to all participants. The actigraphy monitoring was preceded by a briefing session in which research staff gave instructions about the study procedures and how to effectively perform such procedures; this was followed by a debriefing session in which the same research staff member collected information on study acceptability and feasibility. Clinician-administered and self-report surveys were completed by each study participant. During the debriefing session, SSD outpatients and HC participants received € 25,00 for travel expense reimbursement. For additional information about the study protocol, please refer to De Girolamo et al. 2020 [34].

Assessment of negative symptoms

Negative symptoms severity was assessed with the Brief Negative Symptom Scale (BNSS) [35, 36], a 13-item instrument designed for the evaluation of blunted affect, alogia, asociality, anhedonia, and avolition (from 0—not present- to 6—severe deficit). Higher total scores correspond to more severe negative symptoms.

Assessment of rest-activity rhythms and sleep

Each study participant was instructed to wear an ActiGraph GT9X Link (manufactured by ActiGraph, Pensacola, FL 3250, USA) on the non-dominant wrist for seven consecutive days to monitor

habitual sleep-wake patterns. The wearable accelerometer-based biosensor Actigraph GT9X Link is a validated triaxial accelerometer that includes a gyroscope, magnetometer, accelerometer, and Bluetooth capability manufactured by ActiGraph, LLC (https://actigraphcorp.com/actigraph-link).

Data analysis

A non-parametric approach implemented with the package nparACT [37, 38] in the R Statistical Software was utilized to estimate several rest-activity rhythm (RAR) and sleep parameters. RAR measures included: M10, the average activity level during the participant's most active 10 h; L5, the average activity level during the participant's least active 5 h; relative amplitude (RA), a standardized measure of rhythm strength; intra-daily variability (IV), a measure of rhythm fragmentation within days; inter-daily stability (IS), a measure of rhythm stability or consistency across days; rest length: duration of the main (longest) rest period of the day estimated based on an extended cosine model; beta, steepness of rest-active changes; the approximate times of activity onset and offset; and F-statistic (F-stat), a measure of overall circadian rhythmicity of rest and activity. Sleep parameters were computed with the ActiLife software using the Cole–Kripke sleep scoring algorithm [39]. The following sleep parameters were assessed: total sleep time (TST), defined as the number of minutes scored as sleep (primary/night period), and wake after sleep onset (WASO), defined as the minutes of wakefulness observed after sleep onset.

Statistical analyses

The minimum sample size of 50 participants for each group was chosen based on a recent study assessing physical activities and clinical measures in bipolar disorder [40] (please refer to study 3 design section in [34] for further information) and our final sample exceeded that number (i.e., 50 participants) in each group.

Before running any statistical analyses, we removed data from participants with less than 3 days of actigraphy valid data or if any of the sleep/RAR values were outside the mean ±3 standard deviations. Group differences in demographic variables were examined using analysis of variance (ANOVA) and Chi-squared test. Analysis of covariance (ANCOVA) was performed to identify differences in RAR and sleep parameters between HC, outpatient SSD, and residential SSD groups after controlling for covariates (i.e., age, sex, total number of antipsychotic medications, and total number of non-antipsychotic medications). We applied two-sample *t* tests that accounted for unequal variance for pairwise comparisons when the ANCOVA global F-tests showed significant differences across the three study groups.

Differences in negative symptoms, assessed with BNSS scores, between residential and outpatient SSD groups were first examined by performing Student *t* tests for a two-sample mean comparison. We also tested for an interaction effect for each RAR parameter that differed between SSD residentials and outpatients and group on BNSS using a linear regression model, while controlling for age, sex, the total number of antipsychotic medications, and the total number of non-antipsychotic medications as covariates. A Kolmogorov-Smirnov test was used to verify normality of the residuals of the regression model. We ran a correlation between the RAR parameter, which showed significant interaction, and BNSS. Correlation analyses were also performed to assess the relationship between sleep/RAR parameters and age. Finally, we ran several exploratory correlation analyses to investigate the relationship between sleep/RAR measures and clinical measurements, including BPRS, MMSE, and SLOF total scores. Partial correlations were applied to examine associations between different measurements across groups while controlling for the groups. For all correlation analyses, we applied Pearson correlation.

All *p* values comparing different sleep/RAR variables, as well as the pairwise comparisons among groups, were adjusted for multiple testing using Bonferroni correction. All statistical analyses were performed using R (version 3.6.3). All statistical tests were two-sided and assumed a 5% significance level.

RESULTS

Demographic and clinical characteristics

Two hundred and fifty participants, including one hundred and thirty-seven individuals with SSD (i.e., $N = 79$ residential patients and $N = 58$ outpatients) and one hundred and thirteen HC subjects, were recruited [34]. Eleven participants ($N = 8$ residential patients and $N = 3$ HC subjects) were excluded from the analyses due to having less than 3 days of actigraphy valid data. Nine additional subjects ($N = 3$ residential patients, $N = 4$ outpatients, and $N = 2$ HC subjects) were removed based on our outlier detection criteria (i.e., being outside the mean ± 3 standard deviations for at least one RAR or sleep parameter). Therefore, 68 residential patients, 54 outpatients, and 108 HC individuals were included in all further analyses (Table 1). Additional clinical characterizations of the patients, including Brief Psychiatric Rating Scale (BPRS), are reported in the supplementary Table S1.

There were no sex differences across the three groups, while we observed a significant across-group difference in age ($F(2,227) = 3.44$, $p = 0.034$). Specifically, the post-hoc analysis revealed significant age differences between SSD residential patients and outpatients (*mean diff* $= 4.93$, $t(120) = 2.56$, $p_{adj} = 0.035$) but not between each of the SSD groups and HC (Outpatients vs. HC: *mean diff* $= -2.77$, $t(160) = -1.56$, $p_{adj} = 0.368$; Residential vs. HC: *mean diff* $= 2.16$, $t(174) = 1.38$, $p_{adj} = 0.507$). The age range of SSD outpatients was between 18 and 55, whereas HCs and SSD inpatients had an age range of 21 to 56 years. Additional across-group differences in sociodemographic parameters and number of medications prescribed to patients are presented in Table 1. Please refer to the supplementary Table S2 for additional information about the medications that the SSD patients were taking.

ACROSS GROUP DIFFERENCES IN ANCOVA ANALYSIS

One-way ANCOVAs were performed for each sleep and RAR parameter across the three groups (i.e., independent variable), using age, sex, and total numbers of antipsychotic and non-antipsychotic medications as covariates. Among sleep parameters, TST (F (2, 223) $= 19.28$, $p < 0.001$), but not WASO, was different between groups (Table 2). Furthermore, several RAR measures, including IV (F (2, 223) $= 6.45$, $p_{adj} = 0.023$), IS (F (2, 223) $= 6.51$, $p_{adj} = 0.021$), M10 (F(2, 223) $= 8.72$, $p_{adj} = 0.003$), rest length (F(2, 223) $= 13.89$, $p_{adj} < 0.001$), and beta (F(2, 223) $= 16.74$, $p_{adj} < 0.001$) were significantly different across the three groups after Bonferroni's correction (i.e., corrected for 12 sleep/RAR parameters; Table 2), while no significant across group differences were found for RA, activity offset, activity onset, F-stat, and L5.

SHARED AND DISTINCT DIFFERENCES IN SLEEP/RAR PARAMETERS BETWEEN SSD GROUPS AND HC

TST was higher in both SSD groups compared to HC ($t(174) = 11.50$, $p_{adj} < 0.001$, Cohen's d effect size (ES) $= 1.84$; and $t(160) = 8.43$, $p_{adj} < 0.001$, $ES = 1.50$; for residential and outpatients SSD vs. HC, respectively) (Fig. 1, Table S3). Regarding RAR parameters, both SSD groups showed higher rest length (residential vs. HC: $t(174) = 8.04$, $p_{adj} < 0.001$, and $ES = 1.30$; outpatients vs. HC: $t(160) = 6.59$, $p_{adj} < 0.001$, and $ES = 1.21$) along with lower M10 (residential vs. HC: $t(174) = -8.41$, $p_{adj} < 0.001$, and $ES = -1.31$; outpatients vs. HC: $t(160) = -3.58$, $p_{adj} = 0.002$, and $ES = -0.62$, Fig. 1, Table S3). Furthermore, when compared to HC, SSD residential patients showed higher IV ($t(174) = 2.53$, $p_{adj} = 0.038$, and $ES = 0.40$), IS ($t(174) = 5.29$, $p_{adj} < 0.001$, and $ES = 0.82$), and beta (residential vs. HC: $t(174) = 5.44$, $p_{adj} < 0.001$, and $ES = 0.92$).

Table 1. Demographic and clinical variables of the study groups.

VARIABLES	Healthy control $N = 108$	Outpatient $N = 54$	Residential patient $N = 68$	*p* value
Sex, *n* (%)				0.293[a]
Male	66 (61%)	30 (55.5%)	47 (69.1%)	
Age (mean, sd)	41.5 (10.1)	38.8 (10.9)	43.7 (10.1)	**0.034**[b]
Illness duration (mean, sd)	NA	15.5 (9.2)	20.1 (10.1)	**0.010**[c]
Education years (mean, sd)	16.7 (4.9)	12.2 (2.4)	11.7 (3.3)	**<0.001**[b]
Working status, n (employed, student, neither)	99 employed; 8 students; 1 neither	27 employed; 6 students; 21 neither	12 employed; 2 students; 54 neither	**<0.001**[a]
Charlson Comorbidity Index (mean, sd)	0.49 (0.80)	0.31 (0.67)	1.12 (1.53)	**<0.001**[b]
Brief Negative Symptom Scale (BNSS)	NA	17.2 (13.9)	24.1 (14.9)	**0.009**[c]
Total number of non-antipsychotic medications	0	0.89 (0.84)	1.56 (1.14)	**<0.001**[c,d]
Total number of antipsychotic medications	0	1.39 (0.63)	1.63 (0.77)	0.057[c,d]

BOLD = Statistically significant, $p < 0.05$.
sd standard deviation.
[a]Pearson Chi-Square *p* value computed with Monte Carlo simulation (B = 2000).
[b]Analysis of variance (ANOVA) *p* value.
[c]Unequal variance *t* test.
[d]The comparison was made only between SSD patient groups.

Table 2. Group differences in sleep and rest-activity-rhythm parameters.

	Mean (SD)			Group Difference *	
Variable	**Healthy Control**	**Outpatient**	**Residential**	**F-Stat**	P_{adj}
TST (minutes)	369.30 (60.07)	488.72 (95.07)	500.04 (80.72)	19.28	<0.001
WASO minutes	65.30 (21.95)	71.20 (28.72)	59.03 (26.55)	3.92	0.255
IV	0.77 (0.20)	0.72 (0.19)	0.86 (0.24)	6.45	0.023
IS	0.60 (0.11)	0.63 (0.10)	0.69 (0.12)	6.51	0.021
M10	3039.67 (695.53)	2527.32 (930.91)	2087.38 (753.54)	8.72	0.003
L5	123.61 (71.14)	97.33 (76.52)	82.61 (55.31)	1.79	1.00
RA	0.92 (0.04)	0.92 (0.05)	0.92 (0.06)	0.09	1.00
Rest length (hours)	8.14 (0.94)	10.07 (2.05)	9.69 (1.42)	13.89	<0.001
Beta	10.43 (7.50)	12.16 (13.28)	30.79 (30.30)	16.74	<0.001
Activity offset	23.06 (1.09)	21.63 (2.05)	21.59 (1.51)	2.74	0.803
Activity onset	7.19 (0.92)	7.69 (1.88)	7.28 (1.70)	4.77	0.112
F-stat	2354.25 (985.12)	1816.44 (740.49)	2071.39 (1356.79)	3.57	0.357

The degrees of freedom for Analysis of Covariance (ANCOVA) F-test analysis are numerator = 2, and denominator = 223 for all variables.
*One-way ANCOVA result, group as an independent variable, and age and sex as covariates, and the *p* values are corrected for multiple tests using Bonferroni's correction (12 tests).
SD standard deviation, *TST* total sleep time, minutes, *WASO* wakefulness after sleep onset, minutes, *IV* intra-daily variability, *IS* inter-daily stability, *M10* average activity level during the participant's most active 10 h, *L5* average activity during the participant's least active 5 h, *RA* relative amplitude, *F-stat* F-statistic.

In contrast, SSD outpatients had no differences in either of those measures relative to HC (Fig. 1, Table S3).

DIFFERENCES IN RAR PARAMETERS BETWEEN RESIDENTIAL AND OUTPATIENT SSD GROUPS

We also observed that some RAR measures differed between residential and outpatient participants. We found that M10 was lower in residential compared to outpatient SSD ($t(120) = -2.82$, $p_{adj} = 0.018$, and $ES = 0.52$), whereas IV ($t(120) = 3.53$, $p_{adj} = 0.002$, and $ES = 0.63$), IS ($t(120) = 3.37$, $p_{adj} = 0.003$, and $ES = 0.61$), and beta ($t(120) = 4.55$, $p_{adj} < 0.001$, and $ES = 0.80$) were higher in residentials subjects compared to outpatients (Fig. 1, Table S3).

To specifically assess the effects of negative symptoms, sleep and RAR parameter comparisons between SSD residentials and outpatients were repeated by adding BNSS total score as a covariate along with age, sex, and the total number of medications, As shown in Supplementary Table S4, findings from this analysis were comparable to those obtained excluding BNSS.

To further assess the potential effects of mood stabilizer medications, first, we repeated the across-group sleep and RAR parameter comparisons by removing SSD patients taking those medications (Table S5). Findings from this analysis were similar to the findings from the original analysis, as shown in Table 2. Second, for the residential group that included most of the patients on mood stabilizer medications, we compared residential SSD taking mood stabilizers vs. those not taking such medications (please see Supplementary Table S6). We found no difference in any of the sleep and RAR parameters between these two groups.

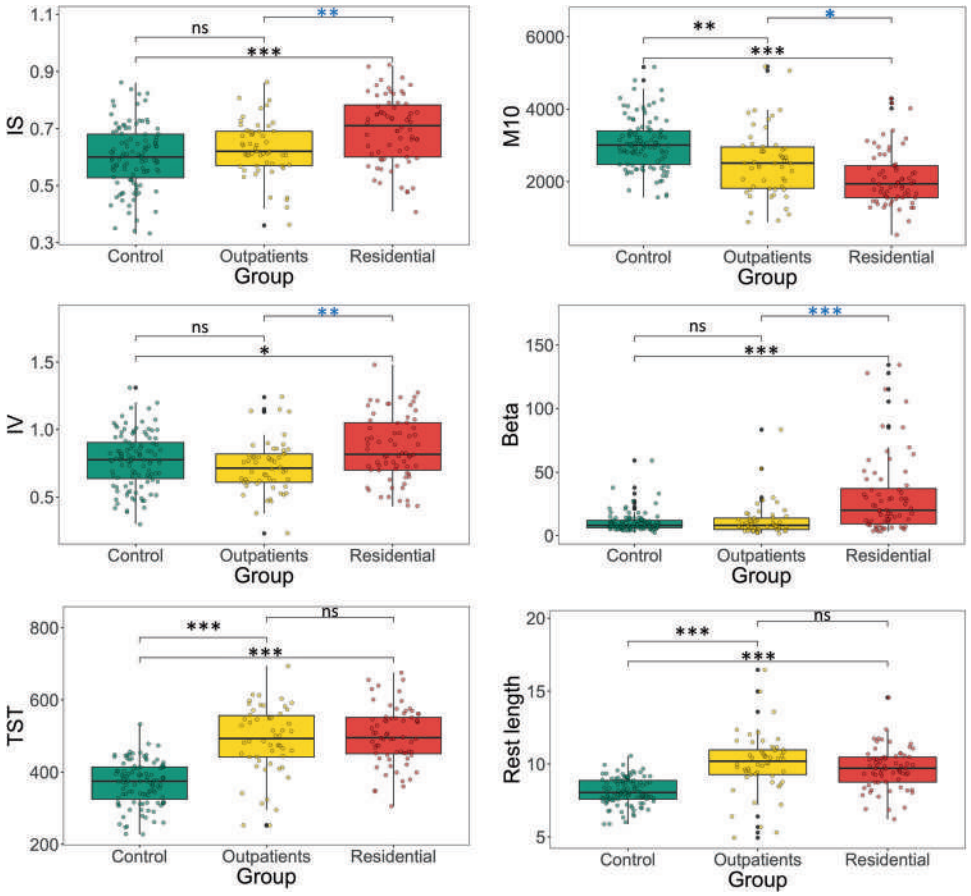

Fig. 1 Sleep and rest-activity rhythm (RAR) parameters that differed across control (green), schizophrenia spectrum disorder (SSD) outpatients (yellow), and SSD residential patients (red). The following parameters differed between groups: inter-daily stability (IS; top left), average activity level during the participant's most active 10 h (M10; top right), intra-daily variability (IV; middle left), beta (middle right), total sleep time (TST, bottom left), and rest length (bottom right). *P* values were corrected for multiple comparisons using Bonferroni's correction. (*0.01< p_{adj} < 0.05, **0.001 ≤ p_{adj} ≤ 0.01, *** p_{adj} < 0.001). Blue asterisks indicate parameters that differed between SSD groups. IV intra-daily variability, IS inter-daily stability, M10 average activity level during the participant's most active 10 h, TST total sleep time.

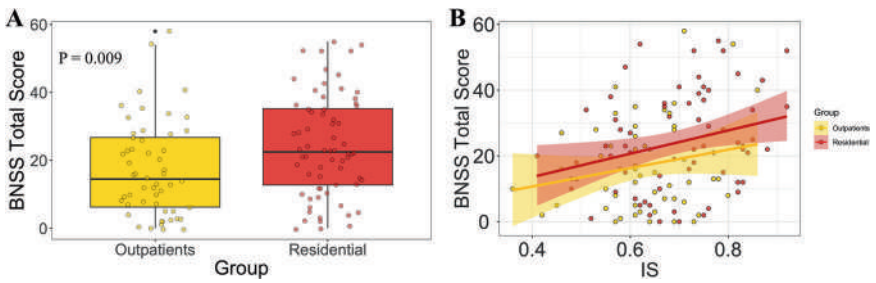

Fig. 2 Brief Negative Symptom Scale (BNSS) comparison between SSD groups and BNSS relationship with inter-daily stability (IS) across groups. A BNSS total scores were different between SSD groups ($p = 0.009$). **B** The scatter plots with the regression lines for the association between interdaily stability (IS) and BNSS total score in outpatients and residential SSD.

RELATIONSHIP BETWEEN NEGATIVE SYMPTOM DIFFERENCES BETWEEN SSD GROUPS AND ALTERED RAR PARAMETERS

Residential patients and outpatients also differed in the severity of negative symptoms assessed with the BNSS. Specifically, residential patients had higher BNSS scores (24.1 ± 14.9) compared to outpatients (17.2 ± 13.9, *t(120)* = 2.65, $p = 0.009$, and *ES* = 0.48; Fig. 2A). We then applied a single linear model of BNSS with all RAR parameters that differed between SSD groups (i.e., IS, M10, IV, and beta) and group to assess the interaction effects of RAR parameters and group on BNSS. After controlling for covariates, we observed a significant interaction between IS and residential SSD patients (*standardized coefficient* = 1.28 and $p_{adj} = 0.004$, after correcting for multiple comparisons). The standardized coefficients for all interactions and the full model are shown in Table S7. By using the Kolmogorov-Smirnov test, we confirmed the residual of the regression model was consistent with a normal distribution ($p = 0.912$; Fig. S1). Furthermore, we established that the positive correlation between negative symptom score and IS was significant in residential patients ($R = 0.280$, $p = 0.021$) but not in outpatients ($R = 0.196$; $p = 0.156$, Fig. 2B).

EXPLORATORY CORRELATION ANALYSIS BETWEEN RAR/SLEEP MEASURES AND AGE AND CLINICAL MEASUREMENTS

We found significant partial correlations between age and IS ($R = 0.238$, $p < 0.001$), rest length ($R = -0.180$, $p = 0.006$), activity offset ($R = -0.217$, $p < 0.001$), activity onset ($R = -0.410$, $p < 0.001$) across 3 groups after controlling for groups. By running correlations for each group separately, we found a significant correlation between age and IS ($R = 0.249$, $p_{adj} = 0.028$; adjusted for 3 groups), activity offset ($R = -0.368$, $p_{adj} < 0.001$), and activity onset ($R = -0.500$, $p < 0.001$) in HC, as well as significant correlations between age and activity onset in both outpatients ($R = -0.369$, $p = 0.018$) and residential patients ($R = -0.384$, $p_{adj} = 0.004$). No other significant correlations were found between age and sleep/RAR parameters in outpatients and residential patients (Supplementary Table S8).

Correlation analyses between sleep/RAR variables and Brief Psychiatric Rating Scale (BPRS) total score and positive symptoms scores yielded no significant results (Table S9–10). Similarly, no significant associations were found between sleep/RAR parameters and MMSE scores (Table S11). Furthermore, while no partial correlations across groups or correlations in individual groups, between sleep/rest parameters and SLOF total scores (Supplementary Table S12) were established, we found significant partial correlations between Charlson comorbidity index and TST ($R = -0.221$, $p < 0.001$), rest length ($R = -0.181$, $p = 0.006$), RA ($R = -0.177$, $p = 0.007$), activity offset ($R = -0.130$, $p = 0.0497$), and activity onset ($R = -0.321$, $p < 0.001$) (Table S13). Correlations for individual groups also showed stronger associations in residential patients than in HC and outpatients, likely due to the higher comorbidity in residential SSD patients (Table S13).

DISCUSSION

In this study, we found that residential patients and outpatients with SSD had longer rest periods (i.e., TST and rest length) and lower activity levels (i.e., M10) compared to HC. Furthermore, residential patients had more fragmented rhythms (i.e., higher IV) that were stable across days (i.e., higher IS) and showed an even more reduced activity (i.e., lower M10) relative to outpatients. Residential patients also had more severe negative symptoms than outpatients, and higher IS was associated with between-group differences in negative symptom severity.

Consistent with prior literature, some sleep and RAR parameters were altered in patients with SSD relative to HC. A recent meta-analysis that included fifteen sleep studies in schizophrenia found greater TST, time in bed, and sleep latency along with reduced motor activity in these patients compared to HC subjects [4]. Here, we reported that SSD patients had longer sleep and rest periods combined with lower daily activity, as reflected by reduced M10. These findings confirm that individuals with SSD tend to sleep more and are overall less active than HC subjects. We also established that such alterations were observed in both residential asnd outpatient groups. The presence of sleep and RAR abnormalities in different settings indicates that they are likely reflective of the pathophysiology of SSD rather than a byproduct of environmental factors. It is, however, important to point out that almost all HC subjects enrolled in our study were either employed or students, whereas most of the SSD patients were neither. These sociodemographic differences may have contributed to the lower levels of motor activity observed in our patients. Further characterization of behavioral factors contributing to lower activity and more sedentary behavior in SSD is therefore needed to ascertain the interaction and directionality of these sleep and RAR parameters in SSD. Furthermore, we did not establish any relative amplitude alterations in either group of SSD patients compared to HC individuals, in line with findings from a recent meta-analysis [4].

In addition to sleep and RAR disturbances shared across both SSD groups relative to HC, we found that residential patients had distinct alterations relative to HC, which included higher IV, beta, and IS. While the first two parameters have not been compared between residentials and other groups, a couple of studies have assessed IS in inpatient SSD vs. clinical or non-clinical groups. One study with a small group of inpatients ($n = 10$; mean age: 58.9 years) and outpatients ($n = 10$; mean age: 54.3 years) with chronic schizophrenia found a higher IS in inpatients compared to outpatients [21], and another study including patients on a long–stay open ward, which can be considered akin to our residential facilities, reported higher IS in inpatients with SSD compared to HC subjects [14], although it did not assess SSD outpatients. Thus, the present study is the first to compare these RAR parameters in large samples of SSD residentials, SSD outpatients, and HC individuals.

A possible explanation for higher IS in the residential SSD relative to the other two populations is that residential settings provide a more stable, consistent environment that may lead to higher inter-daily stability. However, previous work reported higher IS in residential SSD patients when compared to other psychiatric patients (i.e., major depressive disorder individuals) in the same environment [14], therefore further suggesting that the present findings are unlikely to be significantly affected by the setting. Moreover, the fact that SSD residential had higher beta and IV, both of which reflect RAR fragmentation, further suggests that these findings are unlikely related to the environment and determined by a more structured schedule. Thus, an alternative, intriguing explanation for increased inter-daily stability combined with higher daily fragmentation is a more pronounced neurodegeneration occurring in inpatients relative to outpatients and control individuals. Traditionally, IS has been considered a readout of the overall greater robustness of circadian rhythmicity, and higher IS levels usually indicate a better quality of life due to the good synchronization of external timing signals, so-called zeitgeber's 24 h cycle, along with the good operation of the circadian timing system [41]. However, some studies have shown abnormally elevated IS values in clinical populations, including patients with schizophrenia [14, 21]. Furthermore, previous actigraphy studies in elderly HC participants have reported progressively stable, albeit more fragmented, rhythms as age increases [21, 42]. One study investigating age-related changes in daily activity rhythms concluded that, with older age, the 24-h activity rhythm becomes more rigid, as reflected by higher IS [42], and another pilot study showed that individuals with chronic schizophrenia who were inpatients had higher IS relative to both outpatients and HC, and this increase in IS was associated with poorer functioning [21]. Therefore, higher IS in our residential patients with SSD could reflect excessive rhythm regularity in the context of premature aging due to the neurodegenerative processes occurring in schizophrenia. Finally, although we found that IS was positively associated with age across the three groups ($R = 0.238$ $p < 0.001$, Table S8), post-hoc analyses established that this association was significant only for HC. Furthermore, we used age as a covariate for all our statistical analysis; thus, differences in age are unlikely to have affected higher IS levels in SSD patients vs. HC groups.

We also established that residential SSD had higher negative symptoms compared to outpatients. Negative symptoms are core features of schizophrenia that are often persistent, treatment-resistant, and lead to worse clinical outcomes and poorer quality of life in individuals with schizophrenia. One of the main challenges to developing novel, better treatment interventions for the symptoms is the identification of reliable biological markers of symptom severity, which could be used to monitor the efficacy of such interventions. In this regard, IS in residential SSD patients may reflect premature aging and/or neurodegenerative processes occurring in patients with more severe forms of schizophrenia which, in turn, could contribute to the worse

negative symptoms. Alternatively, individuals in the residential setting tend to have more negative symptoms, which lead to higher IS due to the inability to "get out of their routine" or do anything novel/exploratory outside of the residential environment. Consistent with this interpretation is the observation that individuals in residential settings tend to be more ill and chronically impaired compared to outpatients SSD. Thus, to further examine these different interpretations, longitudinal studies are warranted. Furthermore, future examinations into the length of residential stay may provide additional insight into changes in sleep and RAR parameters within such settings. It is also important to point out that IS, and BNSS may measure related aspects of the pathophysiological processes occurring in SSD.

We also demonstrated that, of all RAR parameters that were significantly different across the three cohorts, a decrease in activity (i.e., reduced M10) was the only one that was significantly lower in both SSD groups vs. HC, and that this decrease in activity was more pronounced in residential relative to outpatients SSD. Overall, this suggests that reduced activity is a shared feature of SSD patients vs. non-clinical groups, which is especially altered in residential patients. This finding also indicates that decreased activity is a pervasive problem affecting SSD individuals, which could be targeted (i.e., by promoting an increase in physical activity in SSD patients, particularly during the most active hours of the day) to improve the quality of life of these patients, as it has been recently shown [43].

Building on the present findings, future work is needed to address some of the current study's limitations and unanswered questions. First, data were collected during the COVID-19 period, which may have impacted the sleep and RAR measures collected. Second, we did not collect information about antipsychotic doses as well as about recent changes in the dosage of antipsychotic medications and potential over the counter/prescribed sleep aids. Future work is therefore needed to assess the effect of antipsychotic doses and these related parameters on sleep/RAR measures. Nonetheless, in this study, we collected and utilized the number of antipsychotic and non-antipsychotic medications as covariates in all statistical analyses and found that it did not affect the between-group reported alterations in these measures. Third, future studies combining wearable biosensors with EEG/polysomnography recordings will allow us to investigate further the objective sleep/RAR disturbances and underlying neural and molecular mechanisms. Fourth, studies in at-risk/early-course patients with schizophrenia are needed to determine when sleep/RAR abnormalities first occur, while longitudinal studies with repeated assessments in SSD patients will contribute to characterize in greater detail the relationship between reduced activity, high IS, and negative symptoms. Lastly, experimental studies that, for example, focus on increasing physical activity and reducing IS in SSD patients may help to understand if altered sleep-wake patterns can be modified and if doing so, to establish whether this approach can lead to better clinical outcomes. Finally, while in this study, we excluded shift worker participants and\or individuals who recently traveled to a different time zone, the employment status of three groups of participants were different (Table 1). Because of the potential impact of employment status on sleep and circadian rhythm, future studies should try to match the working status of HCs with patients.

CONCLUSION

Altogether, this is the first study comparing both sleep and RAR parameters in a large cohort of inpatient and outpatient SSD with each other and with control participants and examining the relationships between sleep and RAR parameters and the negative symptoms of the SSD patients. Our findings demonstrated that residential and outpatient SSD had both shared and unique abnormalities in Sleep/RAR measures vs. HC and relative to one another, which also contributed to the patients' negative symptom severity. Building on these findings, future work will help establish whether improving some of these measures may ameliorate the quality of life and clinical symptoms of SSD patients.

DATA AVAILABILITY

Dataset referring to this manuscript is published with restricted access on Zenodo platform and accessible at this link: https://doi.org/10.5281/zenodo.7738228. The data analysis scripts used in this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Knapp M, Mangalore R, Simon J. The global costs of schizophrenia. Schizophrenia Bull. 2004;30:279–93.
2. First MB. Diagnostic and statistical manual of mental disorders, and clinical utility. LWW; 2013. p. 727–9
3. Ferrarelli F. Sleep abnormalities in schizophrenia: state of the art and next steps. Am J Psychiatry. 2021;178:903–13.
4. Meyer N, Faulkner SM, McCutcheon RA, Pillinger T, Dijk D-J, MacCabe JH. Sleep and circadian rhythm disturbance in remitted schizophrenia and bipolar disorder: a systematic review and meta-analysis. Schizophrenia Bull. 2020;46:1126–43.
5. Laursen TM, Wahlbeck K, Hällgren J, Westman J, Ösby U, Alinaghizadeh H, et al. Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the Nordic countries. PloS One. 2013;8:e67133.
6. Laursen TM, Munk-Olsen T, Vestergaard M. Life expectancy and cardiovascular mortality in persons with schizophrenia. Curr OpinPpsychiatry. 2012;25:83–88.
7. Henderson DC, Vincenzi B, Andrea NV, Ulloa M, Copeland PM. Pathophysiological mechanisms of increased cardiometabolic risk in people with schizophrenia and other severe mental illnesses. Lancet Psychiatry. 2015;2:452–64.
8. Vancampfort D, Probst M, Knapen J, Carraro A, De, Hert M. Associations between sedentary behaviour and metabolic parameters in patients with schizophrenia. Psychiatry Res. 2012;200:73–78.
9. Schmitt A, Maurus I, Rossner MJ, Röh A, Lembeck M, Von Wilmsdorff M, et al. Effects of aerobic exercise on metabolic syndrome, cardiorespiratory fitness, and symptoms in schizophrenia include decreased mortality. Front Psychiatry. 2018;9:690.
10. Pritchett D, Wulff K, Oliver PL, Bannerman DM, Davies KE, Harrison PJ, et al. Evaluating the links between schizophrenia and sleep and circadian rhythm disruption. J Neural Transm. 2012;119:1061–75.
11. LaGoy AD, Mayeli A, Smagula SF, Ferrarelli F. Relationships between rest-activity rhythms, sleep, and clinical symptoms in individuals at clinical high risk for psychosis and healthy comparison subjects. J Psychiatr Res. 2022;155:465–70.
12. Mayeli A, LaGoy A, Donati FL, Kaskie RE, Najibi SM, Ferrarelli F. Sleep abnormalities in individuals at clinical high risk for psychosis. J Psychiatric Res. 2021;137:328–34.
13. Wirz-Justice A, Haug H-J, Cajochen C. Disturbed circadian rest-activity cycles in schizophrenia patients: an effect of drugs? Schizophrenia Bull. 2001;27:497–502.
14. Berle JO, Hauge ER, Oedegaard KJ, Holsten F, Fasmer OB. Actigraphic registration of motor activity reveals a more structured behavioural pattern in schizophrenia than in major depression. BMC Res Notes. 2010;3:149.
15. Bromundt V, Köster M, Georgiev-Kill A, Opwis K, Wirz-Justice A, Stoppe G, et al. Sleep–wake cycles and cognitive functioning in schizophrenia. Br J Psychiatry. 2011;198:269–76.
16. Afonso P, Figueira ML, Paiva T. Sleep–wake patterns in schizophrenia patients compared to healthy controls. World J Biol Psychiatry. 2014;15:517–24.
17. Apiquian R, Fresán A, Muñoz-Delgado J, Kiang M, Ulloa RE, Kapur S. Variations of rest–activity rhythm and sleep–wake in schizophrenic patients versus healthy subjects: An actigraphic comparative study. Biol Rhythm Res. 2008;39:69–78.
18. Docx L, Sabbe B, Provinciael P, Merckx N, Morrens M. Quantitative psychomotor dysfunction in schizophrenia: a loss of drive, impaired movement execution or both? Neuropsychobiology. 2013;68:221–27.
19. Gomes E, Bastos T, Probst M, Ribeiro JC, Silva G, Corredeira R. Quality of life and physical activity levels in outpatients with schizophrenia. Braz J Psychiatry. 2016;38:157–60.
20. Hauge ER, Berle JØ, Oedegaard KJ, Holsten F, Fasmer OB. Nonlinear analysis of motor activity shows differences between schizophrenia and depression: a study using Fourier analysis and sample entropy. PloS One. 2011;6:e16291.
21. Kume Y, Sugita T, Oga K, Kagami K, Igarashi H. A pilot study: comparative research of social functioning, circadian rhythm parameters, and cognitive function among institutional inpatients, and outpatients with chronic schizophrenia and healthy elderly people. Int Psychoger. 2015;27:135–43.
22. Sabe M, Kaiser S, Sentissi O. Physical exercise for negative symptoms of schizophrenia: Systematic review of randomized controlled trials and meta-analysis. Gen Hosp Psychiatry. 2020;62:13–20.

23. Milev P, Ho B-C, Arndt S, Andreasen NC. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. Am J Psychiatry. 2005;162:495–506.
24. Buckley PF, Stahl S. Pharmacological treatment of negative symptoms of schizophrenia: therapeutic opportunity or Cul-de-sac? Acta Psychiatr Scand. 2007;115:93–100.
25. Shin S, Yeom C-W, Shin C, Shin J-H, Jeong JH, Shin JU, et al. Activity monitoring using a mHealth device and correlations with psychopathology in patients with chronic schizophrenia. Psychiatry Res. 2016;246:712–18.
26. Wichniak A, Skowerska A, Chojnacka-Wójtowicz J, Tafliński T, Wierzbicka A, Jernajczyk W, et al. Actigraphic monitoring of activity and rest in schizophrenic patients treated with olanzapine or risperidone. J Psychiatric Res. 2011;45:1381–86.
27. Wee ZY, Yong SWL, Chew QH, Guan C, Lee TS, Sim K. Actigraphy studies and clinical and biobehavioural correlates in schizophrenia: a systematic review. J Neural Transm. 2019;126:531–58.
28. American Psychiatric Association D, Association AP. Diagnostic and statistical manual of mental disorders: DSM-5. American psychiatric association Washington, DC; 2013.
29. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–83.
30. Morosini P, Casacchia M. Traduzione italiana della Brief Psychiatric Rating Scale, versione 4.0 ampliata (BPRS 4.0). Rivista di riabilitazione Psichiatrica e Psicosociale. 1995;3:199–228.
31. Overall JE, Gorham DR. The brief psychiatric rating scale. Psychol Rep. 1962;10:799–812.
32. Schneider LC, Struening EL. in *Social Work Research and Abstracts* 19 9-21 (Oxford University Press, 1983).
33. Mucci A, Rucci P, Rocca P, Bucci P, Gibertoni D, Merlotti E, et al. The Specific Level of Functioning Scale: construct validity, internal consistency and factor structure in a large Italian sample of people with schizophrenia living in the community. Schizophr Res. 2014;159:144–50.
34. De Girolamo G, Rocchetti M, Benzi IMA, Agosta S, Casiraghi L, Ferrari C, et al. DAily time use, Physical Activity, quality of care and interpersonal relationships in patients with Schizophrenia spectrum disorders (DiAPASon): an Italian multicentre study. BMC Psychiatry. 2020;20:1–12.
35. Strauss GP, Keller WR, Buchanan RW, Gold JM, Fischer BA, McMahon RP, et al. Next-generation negative symptom assessment for clinical trials: validation of the Brief Negative Symptom Scale. J Schizophr Res. 2012;142:88–92.
36. Mucci A, Galderisi S, Merlotti E, Rossi A, Rocca P, Bucci P, et al. The Brief Negative Symptom Scale (BNSS): independent validation in a large sample of Italian patients with schizophrenia. J Eur Psychiatry. 2015;30:641–47.
37. Blume C, Santhi N, Schabus M. 'nparACT'package for R: a free software tool for the non-parametric analysis of actigraphy data. MethodsX. 2016;3:430–35.
38. Van Someren EJ, Swaab DF, Colenda CC, Cohen W, McCall WV, Rosenquist PB. Bright light therapy: improved sensitivity to its effects on rest-activity rhythms in Alzheimer patients by application of nonparametric methods. Chronobiol Int. 1999;16:505–18.
39. Cole RJ, Kripke DF, Gruen W, Mullaney DJ, Gillin JC. Automatic sleep/wake identification from wrist activity. Sleep. 1992;15:461–69.
40. Merikangas KR, Swendsen J, Hickie IB, Cui L, Shou H, Merikangas AK, et al. Real-time mobile monitoring of the dynamic associations among motor activity, energy, mood, and sleep in adults with bipolar disorder. JAMA Psychiatry. 2019;76:190–98.
41. Gonçalves BS, Cavalcanti PR, Tavares GR, Campos TF, Araujo JF. Nonparametric methods in actigraphy: an update. Sleep Sci. 2014;7:158–64.
42. Luik AI, Zuurbier LA, Hofman A, Van Someren EJ, Tiemeier H. Stability and fragmentation of the activity rhythm across the sleep-wake cycle: the importance of age, lifestyle, and mental health. Chronobiol Int. 2013;30:1223–30.
43. Fernández-Abascal B, Suárez-Pinilla P, Cobo-Corrales C, Crespo-Facorro B, Suárez-Pinilla M. In-and outpatient lifestyle interventions on diet and exercise and their effect on physical and psychological health: a systematic review and meta-analysis of randomised controlled trials in patients with schizophrenia spectrum disorders and first episode of psychosis. Neurosci Biobehav Rev. 2021;125:535–68.

ACKNOWLEDGEMENTS

We thank the Italian Ministry of Health for the funding received for this research project. We thank all members of the DiAPAson Consortium who actively worked to make this project possible: DMH, ASL *Ancona* (P. D'Elia, S. Impicci, M. Mari, F.M. Quintieri); RF Passaggi Srl-Oricola, *Aquila* (A. Bellotta, F. Jacoponi, A. Maurizi, L. Tranquilli); DMH, ASL *Bari* (V. Latorre, G. Nappi, D. Semisa); DMH, ASST *Bergamo Ovest* (S. Fenaroli, E. Monzani); DMH, ASST Spedali Civili *Brescia* (S. Barlati, M. Facchi, N. Necchini, A. Vita); IRCCS Fatebenefratelli, *Brescia* (G. de Girolamo, A. Martinelli, G. Tura, M. Zamparini, C. Zarbo); Dept of Molecular and Translational Medicine, University of *Brescia* (S. Calza, M. Rota); RF Centro Ippocrate CRA Macchiareddu, *Cagliari* (C. Lanzi, P. Paribello, B. Piccicacchi, C. Schiavo); Fatebenefratelli Sant'Ambrogio e Sacro Cuore di Gesù, *Cernusco sul Naviglio, Milano* (R. Bussi, D. Di Cosimo, G.M. Giobbio, R. Placenti); DMH, ASST *Cremona* (G. Giordano, C. Greco, I. Rossoni, F. Spinogatti); DMH ASST Rhodense, *Garbagnate* (C. Rovera, M. Toscano); DMH, ASL 3 *Genova* (L. Ghio, L. Lattanzi, D. Malagamba, M. Tosato); RF CREST 'La Perla', *Grumello del Monte, Bergamo* (L. Rancati, S. Zizolfi); DMH, ASST *Lodi* (G. Cerveri, C. Cibra, V. Cuman, E. Pionetti); DMH, ASST Melegnano and Martesana, *Melegnano* (A. Di Gregorio, F. Durbano, L. Fussi, V. Masseroni); Fondazione Castellini ONLUS, *Melegnano* (A. Cicceri, A. de Giovanni); DMH, AUSL *Modena* (S. Agosta, A. de Novellis, F. Starace); DMH, ASST *Monza* (C. Calini, M. Clerici, R. Pessina); DMH, Napoli 2 Nord (A. Cucciniello, C. D'Anna, M.G. Foia, M.C. Miranda); DMH, ASST *Pavia* (L. Casiraghi, P. Politi, M. Rocchetti, A. Silva); RF Fondazione Giuseppe Costantino, *Pavia* (M. Marina, S. Panigada, S. Riavera); DMH, ASL *Pescara* (A. Cirincione, V. Di Michele, F. Paolone); DMH, AUSL *Parma* (E. Leuci, G. Paulillo, L. Pelizza); DMH USL Toscana Centro, *Prato* (A. Baroncelli, G. Cardamone, G. D'Anna, L. Tatini); DMH ASL *Roma1* (G. Ducci, A. Maone, T.A. Poliseno, B. Rufelli); Fatebenefratelli Beata Vergine Consolata, *San Maurizio Canavese* (M.E. Boero, E. Castagno, F. De Dominicis); DMH, ASL *Teramo* (C. Della Croce, P. Giosuè); DMH, ASL Città di *Torino* (F. Facchini, G. Gallino); RF Progetto Du Parc, *Torino* (J. Orticola, N. Rossetto); DMH, APSS *Trento* (M. Goglio, F. Lucchi); DMH, ULSS 2 Marca Trevigiana, *Treviso* (A. Brega, R. De Marchi, P. Di Prisco); RF Le Vele ONLUS, *Trezzo sull'Adda* e *Vaprio d'Adda* (E. Bonetti, L. Colasuonno, A. Pozzi, M. Roncalli); DMH, ASUGI *Trieste* (R. Mezzina, A. Norbedo, A. Rippa); DMH, AOUI *Verona* (E. Canova, E. Dal Corso, C. D'Astore, M. Ruggeri); Dept of Neurosciences, University of *Verona* (D. Bertorelle, S. Pogliaghi); RF CTRP Associazione Don Giuseppe Girelli, *Verona* (G. Ferro, G. Gardelli, S. Pagani, A. Signoretti); DMH ULSS 8 Berica, *Vicenza* (I. Rodolfile, R. Tessari, S. Zanolini); RF CREST, *Vinago* (C.M. Dentali, M. Minotto).

AUTHOR CONTRIBUTIONS

Conceptualized and designed the research: AM, ADL, SFS, GDG, and FF. Data and statistical analyses: AM, ADL, SFS, and JD. Writing the draft: AM, ADL, and FF. Critical revision of the manuscript: SFS, JDW, CZ, MR, FS, MZ, LC, SC, MR, AD, GDG, and FF. Funding resources: GDG and FF. All authors contributed to the interpretation of the results, and all authors read, edited, and approved the draft.

FUNDING

The DiAPAson project was funded by the Italian Ministry of Health (Bando per la Ricerca Finalizzata 2018: RF-2018-12365514). The Ministry of Health has no role in analyzing and interpreting study findings. The corresponding author was supported by the National Institute of Mental Health (NIMH) grant, with the grant number R01 MH113827.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

The study has been approved by the ethical committees (Ecs) of the three main participating centers: EC of IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli (31/07/2019; no. 211/2019), EC of Area Vasta Emilia Nord (25/ 09/2019; no. 0025975/19), and EC of Pavia (02/09/2019, no. 20190075685) and by the Ecs of all participating sites.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41380-023-02050-x.

Correspondence and requests for materials should be addressed to Fabio Ferrarelli.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliation.

DIAPASON CONSORTIUM

Alessandra Martinelli[7], Gabriele Nibbio[8], Lorenzo Pelizza[9], Rodolfo Pessina[10], Roberto Placenti[11], Andrea Silva[3] and Giovanni de Girolamo[2]

[7]IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. [8]Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy. [9]Department of Mental Health and Dependence, AUSL of Parma, Parma, Italy. [10]Department of Mental Health and Dependence, ASST of Monza, Monza, Italy. [11]Centro Sacro Cuore di Gesù, San Colombano al Lambro, Lodi, Italy.