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Characterization of sleep disturbance in established rheumatoid arthritis patients: exploring the relationship with central nervous system pain regulation

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Abstract

Background To characterize sleep disturbance in patients with established rheumatoid arthritis (RA) and explore the relationship between sleep and mechanisms of central nervous system pain regulation.

Methods Forty-eight RA participants completed wrist-worn actigraphy monitoring and daily sleep diaries for 14 days to assess sleep-wake parameters. Participants underwent quantitative sensory testing to assess pressure pain thresholds, temporal summation, and conditioned pain modulation. Data were analyzed using descriptive statistics, Spearman's correlation, and multivariable median regression analyses.

Results Median actigraphy and sleep diary derived sleep duration was 7.6 h (interquartile range (IQR) 7.0, 8.2) and 7.1 h (IQR 6.7, 7.6), respectively. Actigraphy based sleep fragmentation (rho = 0.34), wake after sleep onset (rho = 0.36), and sleep efficiency (rho = -0.32) were each related to higher temporal summation values in unadjusted analyses, but these relationships did not persist after controlling for age, body mass index, disease duration, and swollen joint count. No significant relationships were observed between sleep with pressure pain thresholds and conditioned pain modulation.

Conclusion Actigraphy and sleep diary monitoring are well tolerated in established RA patients. Future investigations should include both subjective and objective assessments, as they may provide information relating to different components and mechanisms.

Keywords Actigraphy, Sleep, Pain, Rheumatoid arthritis

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Introduction

Over half of patients with rheumatoid arthritis (RA) report sleep disturbances [1–4]. Investigations examining sleep disturbances in patients with RA typically utilize questionnaires that ask individuals to report perceptions of sleep quality, restoration and/or depth, yielding a self-reported score that summarizes sleep disturbances over a specific period of time (e.g., past 7 days) [3, 5, 6]. However, these questionnaires usually do not collect data with sufficient granularity to enable identification and quantification of specific types of sleep disturbances (e.g., low duration, high fragmentation, long onset latency) [7].

Historically, sleep disturbances have been objectively assessed using polysomnography. Polysomnography, however, may not accurately reflect day-to-day real world sleep disturbances, given that it is usually performed in a controlled laboratory setting over a short period of time [8–11]. To assess sleep in a real-world setting, daily self-reported measures (e.g., sleep logs/diaries) and/or real-time objective tools (e.g., actigraphy) are needed, but few studies have used these methods in patients with RA [6, 8–10, 12].

Comprehensively phenotyping sleep disturbances is important because associations with clinical outcomes (e.g., pain) may differ, depending on the type of sleep disturbance. Our prior observational studies have linked self-reported sleep disturbance to dysregulated pain-related sensory pathways assessed by quantitative sensory testing (QST) in patients with RA [13–15]. Specifically, greater sleep disturbance was related to enhanced pain sensitivity assessed by pressure pain thresholds [13], inefficient descending analgesia assessed by conditioned pain modulation [14], and higher pain facilitation assessed by temporal summation [15]. One experimental investigation demonstrated that sleep restriction to 4 h a night led to increases in next-day pain severity and number of painful joints in patients with RA [8]. To our knowledge, no studies have examined the association between specific types of sleep disturbances (e.g., sleep duration, sleep fragmentation, sleep onset latency) and mechanisms of pain regulation in RA.

The purpose of this investigation was to (i) characterize sleep disturbance (derived by actigraphy and sleep diary) in patients with RA and, (ii) examine the associations between sleep measures and QST paradigms of pain regulation. Furthering our understanding of sleep disturbances and their relationship to CNS pain regulatory pathways may aid in identifying sleep related intervention targets, to improve sleep and minimize pain.

Methods

Forty-eight participants were included in the Sleep, Pain, and AutoNomic function in RA (SPAN-RA) study. The primary aim was to determine the association between actigraphy-based measures of sleep and QST measures of pain regulation. A secondary aim was to determine associations between autonomic function and pain regulation. All participants were recruited from a single academic rheumatology practice located in Chicago from March 2021 to May 2022. Inclusion criteria were meeting the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for RA and being at least 18 years old. Exclusion criteria included night shift work and use of the following medications: prednisone at a dose greater than 10 mg/day, chronic opioids (more than once a week), or central-acting pain medications (e.g., amitriptyline, duloxetine, milnacipran, gabapentin, pregabalin). In addition, participants with obstructive sleep apnea (OSA), cardiac arrhythmias and other heart conditions, as well as participants routinely taking sedatives or beta-blockers, were excluded because these factors affect heart rate variability (secondary aim of the parent study). Ethics approval was obtained from the Institutional Review Board of Northwestern University. All participants provided written informed consent.

Sleep variables

Participants wore an actigraphy monitor (Actiwatch Spectrum; Phillips Respironics) on their nondominant wrist for 14 consecutive days and maintained a daily Karolinska Sleep Diary [16]. Actigraphy data were sampled at 30 s epochs. Data were processed and scored using the manufacturer's proprietary software (Actiware, version 6.0). The main rest intervals were manually scored [17]. Any 24-hour period of recording with >4 h of non-wear period was excluded.

Actigraphy based sleep measures of interest included: sleep fragmentation index, wake after sleep onset (WASO), sleep duration, sleep onset latency, sleep efficiency, and the number of wake bouts (awakenings). The sleep fragmentation index assesses restlessness during the sleep interval and was calculated as the sum of percent mobile bouts and percent one-minute immobile bouts divided by the number of immobile bouts for the main rest interval. WASO was defined as the time (mins) spent awake after the onset of sleep and was calculated as total time of the epochs scored as wake between sleep onset and sleep offset in the sleep interval. Sleep duration, defined as the time (mins) spent asleep, was calculated as total time of the epochs scored as sleep in the main rest interval. Sleep efficiency reflects the percentage of time spent asleep while in bed and was calculated as 100% x scored total sleep time/the time spent in bed. Sleep onset latency was defined as the time (mins) it takes to fall asleep and was calculated as the time between the start of the main rest interval and the sleep onset time. The number of wake bouts was defined as the number of

5-minute periods of continuous wakefulness separated by at least 15 min of sleep before and after the episode of awakening. All sleep measures were averaged across all valid days in the recording period.

Sleep measures derived from the Karolinska sleep diary entries included: sleep duration (subjective sleep length in hours and mins), sleep onset (subjective hours and mins to fall asleep), sleep efficiency (derived from sleep length/time spent in bed), subjective number of awakenings during sleep, and WASO (derived from number of awakenings/sleep duration). For descriptive purposes, select items from the sleep diary that inquire about rating (Likert scale) specific aspects of sleep (i.e., feeling refreshed after awakening, ease of falling asleep) were assessed.

Pain evaluations

Participants underwent quantitative sensory testing (QST) to assess pressure pain thresholds (PPTs), temporal summation (TS), and conditioned pain modulation (CPM), using previously described methods [18]. PPTs indicate overall pain sensitization, whereas TS and CPM reflect ascending pain facilitation and descending pain inhibition, respectively. PPTs at joint (wrists) and non-joint sites (trapezius muscles) were assessed using an algometer (Wagner Force 10 FDX; Greenwich, CT). Pressure was increased until participants indicated that the stimulus was "first perceived as painful," terminating the stimulus. Mechanical TS was tested using a pinprick stimulator, with a weighted, 0.25 mm diameter, flat-end wire tip (MRC Systems, Heidelberg, Germany). The probe was tapped against the skin 10 times, and each participant rated their pain on a 0–10 numeric rating scale after the first and tenth taps. TS was defined as the difference between pain levels at the 10th and 1st taps. CPM was assessed using a paradigm that includes a noxious conditioning stimulus (hand in cold water at 10 °C) and a test stimulus to assess the analgesic response to the conditioning stimulus (PPT at the trapezius).

Table 1 Demographic and clinical characteristics of the 48 RA participants

	Value
Demographics	
Age, *years*	55.0 [41.5, 64.8]
Female, *%*	95.8
BMI, kg/m^2	26.6 [22.4, 32.8]
Race and ethnicity, *%*	
White	52.1
Black or African American	12.5
Asian	6.3
Hispanic or Latino	25.0
Other	4.2
RA-related Factors	
Clinical Disease Activity Index (CDAI)[a]	5.0 [2.0, 12.0]
RA Duration, *years*	9.8 [4.0, 16.2]
Tender joint count [a]	1.0 [0, 4.5]
Swollen joint count [a]	0 [0, 2.0]
Seropositivity, *%*	70.8
Medication use, *%*	
Biologic & targeted synthetic DMARDs	54.2
Conventional DMARDs	62.5
Steroids [b]	12.5

Note Value is median [Q1, Q3], unless noted otherwise. [a] $n=47$. [b] Dose ≤ 10 mg

Statistical analysis

Descriptive statistics were summarized using percentages for categorical variables and medians and interquartile ranges (IQR) for continuous variables. We performed Spearman's correlation (*rho*) analyses to determine the strength of bivariate correlations between (i) actigraphy-based and the corresponding sleep diary derived sleep measures, and (ii) each QST measure (PPT, TS, CPM) and each sleep parameter (sleep fragmentation index, WASO, sleep duration, sleep onset latency, sleep efficiency, number of awakenings). Only sleep parameters that demonstrated significant bivariate associations with any QST measure were included in multivariable median regression analyses adjusted for age, body mass index (BMI), disease duration, and swollen joint count (28 total joint count). Separate adjusted models were constructed to avoid multicollinearity between actigraphy-based sleep parameters that were treated as independent variables in each model with a significant QST measure as the outcome. The strength and direction of associations was determined using regression coefficients (β) with 95% confidence intervals. All data analyses were performed using R (version 4.3.2). Alpha level was set at $p<.05$ for all analyses. A post-hoc analysis was performed, indicating that a sample size of 48 provided 80% power to detect a Spearman's correlation of 0.42 at an alpha level of 0.05.

Results

Sample characteristics

Forty-eight patients with RA participated in this study (Table 1). The sample had a mean ± SD age of 53.4 ± 14.7 years, BMI of 28.4 ± 7.8 kg/m^2, and disease duration of 11.5 ± 9.4 years. Mean clinical disease activity index (CDAI) score was 9.6 ± 11.0, indicating low disease activity. Of the 48 participants, 62.5% were taking a conventional disease modifying anti-rheumatic drug (DMARD), 54.2% were taking a biologic or targeted synthetic DMARD, and 12.5% reported taking steroids (prednisone ≤ 10 mg/day). The mean ± SD PROMIS sleep disturbance t-score was 50.7 ± 8.4, and the sleep-related impairment t-score was 48.8 ± 11.4.

Actigraphy and diary derived sleep characteristics

The mean±SD duration of valid actigraphy recording was 14.1±1.2 days, and the number of completed daily Karolinska Sleep Diary entries was 13.4±1.1 days. Mean daily total sleep duration was 7.7±0.8 h based on actigraphy, compared to 7.1±0.8 h based on self-reported sleep diaries (Table 2). Actigraphy-based WASO was 38.9±15.9 min, compared to 20.0±18.4 min based on sleep diaries. Estimations of sleep onset latency were 13.1±8.4 min based on actigraphy versus 21.7±17.9 min based on sleep diaries, and estimates of sleep efficiency were 86.4±3.5% based on actigraphy versus 89.4±6.0% based on sleep diaries. Positive bivariate correlations were observed between actigraphy-based and the equivalent sleep diary derived total sleep duration (rho=0.64, $p<.01$), sleep onset latency (rho=0.45, $p<.01$), and WASO (rho=0.30, $p=.04$). Actigraphy-based sleep efficiency was not strongly related to the sleep diary derived measure (rho=0.16, $p=.28$).

Table 2 QST pain and sleep characteristics of the 48 RA participants

	Median [Q1, Q3]
Pain characteristics	
Quantitative Sensory Testing (QST)	
PPT (trapezius), *kgf*	2.3 [1.8, 3.2]
PPT (wrist), *kgf*	2.6 [1.7, 3.1]
TS	1. 7 [0.7, 3.3]
CPM	0.9 [0.7, 1.1]
Sleep characteristics	
Actigraphy	
Sleep duration, *hours*	7.6 [7.0, 8.2]
Sleep Fragmentation Index, %	16.2 [12.6, 20.8]
Sleep Efficiency, *%*	86.4 [84.2, 89.0]
Wake after sleep onset, *minutes*	36.5 [26.8, 48.0]
Sleep Onset Latency, *minutes*	11.1 [7.0, 17.3]
Number of wake bouts	30.3 [26.3, 37.2]
Karolinska Sleep Diary	
Sleep duration, *hours*	7.1 [6.7, 7.6]
Sleep Efficiency, *%*	89.9 [86.0, 94.0]
Wake after sleep onset, *minutes*	11.9 [6.5, 30.1]
Sleep Onset Latency, *minutes*	18.0 [10.5, 25.9]
Number of awakenings	1.8 [1.0, 2.5]
*Likert scale questions**	
Quality of sleep	3.6 [3.1, 4.0]
Feeling refreshed in the morning	3.4 [2.8, 3.9]
Slept soundly	3.6 [3.1, 4.1]
Slept throughout night	3.6 [2.7, 4.2]
Ease of waking up	3.4 [3.1, 4.1]
Ease of falling asleep	3.8 [3.3, 4.1]
Amount of dreaming	2.0 [1.4, 2.5]

Note *Likert scale with 1–5 response options, where 5 is the more positive option (e.g., very well, very easy)

Abbreviations PPT, pressure pain threshold. TS, temporal summation. CPM, conditioned pain modulation

Associations between sleep parameters and QST

Spearman's correlation analyses revealed significant correlations between certain actigraphy-based sleep measures and pain facilitation assessed by TS (Table 3). Participants with a higher sleep fragmentation index had higher values of TS (rho=0.34, $p=.02$). Similarly, participants with longer WASO (rho=0.36, $p=.01$) had higher TS, and participants with lower sleep efficiency also had higher TS (rho = -0.32, $p=.03$). Sleep duration (rho = -0.02, $p=.87$), sleep onset latency (rho=0.12, $p=.41$), and the number of awakenings (rho=0.26 $p=.07$) were not significantly associated with TS. There were also no significant bivariate correlations between any of the actigraphy-based measures and either PPT or CPM (rho = -0.19 to 0.15, $p=.30$ to 0.87). None of the sleep diary derived measures were significantly related to QST measures, except WASO, which was significantly associated with CPM (rho=0.29, $p=.05$); other correlation coefficients ranged from −0.18 to 0.29 ($p=.05$ to 0.97).

Median regression analyses

Separate adjusted multivariable median regression models were conducted for actigraphy-based sleep fragmentation index, WASO, and sleep efficiency with TS as the outcome in each model. The models revealed no significant associations between sleep fragmentation index (β = -0.03, 95% CI -0.10 to 0.04), WASO (β=0.01, 95% CI -0.02 to 0.04), and sleep efficiency index (β = -0.09, 95% CI -0.24 to 0.05) with TS, when accounting for the covariates age, BMI, disease duration, and swollen joint count. A separate adjusted multivariable median regression model was also conducted for sleep diary derived WASO with CPM as the outcome. Sleep diary derived WASO time remained statistically significantly associated with CPM values after accounting for age, BMI, disease duration, and swollen joint count (β=0.01, 95% CI 0.00 to 0.01).

Discussion

In this study of patients with established RA and low average disease activity, the average sleep duration, measured by both actigraphy and sleep diaries, was similar to the general population norm of about 7 to 8 h per night [19]. This is also within the range (7–9 h) that is suggested to promote optimal health in the general adult population [20]. Correlations between actigraphy and sleep diary-derived measures ranged from weak (sleep efficiency) to moderate (sleep duration). While higher sleep fragmentation, more minutes of WASO, and lower sleep efficiency were each related to facilitated pain processing (higher TS) in bivariate analyses, these relationships did not persist after accounting for potential confounders (age, BMI, disease duration, and swollen joint count).

Table 3 The Spearman's (rho) correlations between QST pain outcomes and sleep measures ($n=48$)

	QST			
	PPT_t	PPT_w	TS_t	CPM
Actigraphy				
Sleep fragmentation Index	−0.03	−0.12	**0.34***	−0.11
Sleep efficiency	0.03	0.04	**−0.32***	0.00
WASO	−0.05	−0.07	**0.36***	−0.14
Sleep duration	−0.05	−0.05	−0.02	−0.02
Sleep onset latency	−0.15	−0.05	0.12	0.15
Number of awakenings	−0.11	−0.19	0.26	−0.10
Sleep Diary				
Sleep efficiency	0.13	0.13	0.01	−0.15
WASO	0.04	0.02	−0.11	**0.29***
Sleep duration	0.00	0.00	0.10	−0.06
Sleep onset latency	−0.20	−0.22	−0.04	0.05
Number of awakenings	−0.16	−0.18	0.15	0.02

Note Spearman's correlation coefficients. *$p<.05$

Abbreviations QST, quantitative sensory testing. PPT, pressure pain threshold (t=trapezius, w=wrist). TS, temporal summation (t=trapezius). CPM, conditioned pain modulation. WASO, wake after sleep onset

In comparison to a prior study that described actigraphy and sleep diary derived measures in relation to quality of life in RA [12], participants in this study had similar average sleep durations (7+hours) but less sleep fragmentation, quicker sleep onset, and greater sleep efficiency. A possible reason for these discrepancies is that participants with OSA and/or those taking sedatives on a routine basis were excluded from this study, as one of the main aims of the parent study was to assess heart rate variability, which is altered in these patients. Based on our screening data, 6% of participants were screened out because of a diagnosis of OSA and an additional 7% were screened out because they were regularly taking sedatives. Thus, our population may reflect a group with less severe sleep disturbances than the general RA population.

In the present study, there were significant correlations among select actigraphy and sleep diary derived measures, but overall, correlations were low. The highest correlations were observed for sleep duration (rho=0.64) and sleep onset latency (rho=0.45). It is not uncommon for objective (polysomnography and actigraphy) and sleep diary derived parameters to be discrepant [7, 10, 12, 21, 22]. Both actigraphy and sleep diary data require processing, which involves manual screening. This process may differ across studies and can contribute to errors in calculation of both actigraphy and sleep diary derived measures, which may decrease correlations between these measures. In addition, actigraphy-derived measures of sleep and wake are dependent on thresholds based on activity counts. These thresholds likely differ from what individuals perceive to be wake vs. sleep. Neither measure is "better" than the other, but both provide complementary information, which is most valuable when considered together rather than in isolation.

To our knowledge, this is the first study to investigate associations between actigraphy-based sleep disturbance measures and QST-based assessments of pain in RA. Interestingly, bivariate correlations showed a consistent relationship between measures of sleep fragmentation (sleep fragmentation index and WASO) and heightened pain facilitation, assessed by TS. These results are consistent with findings from an experimental study showing that forced awakenings result in greater pain facilitation in healthy women [23]. However, relationships between sleep fragmentation and pain facilitation were not statistically significant in adjusted models. Additionally, we did not observe relationships between the actigraphy-based sleep measures and other QST measures (PPT and CPM). A potential explanation for these findings could be that the sleep disturbances of our study participants were not severe enough to show an association with QST measures of pain perception. The exclusion criteria may have contributed to selection bias towards individuals with less sleep problems (i.e., without OSA and not routinely taking sedatives) and better controlled disease state (i.e., low prednisone dose). Further investigations utilizing actigraphy monitoring in a larger sample with varying disease activity scores, and a wide range of sleep and pain impairment is needed to better characterize the role specific sleep components may play in interfering with pain processing.

Strengths of this study include the comprehensive assessment of sleep and pain, including actigraphy, sleep diaries, and quantitative sensory testing. To our knowledge, these measures have not been described concurrently in an RA population. Limitations include the cross-sectional design, which limits our ability to infer temporality, and the relatively healthy study population, with low disease activity and low levels of sleep disturbance. The small sample size may also limit the statistical power of our findings. However, considering the exploratory nature of our study, the presented findings may provide guidance for future investigations into the longitudinal effects of sleep on pain in a larger sample. In addition, the relationship between sleep and pain processing is complex and multi-factorial, and there may be residual confounding by other factors (e.g., fatigue, depression), which were not accounted for in these analyses.

Conclusion

In summary, our findings highlight the importance of utilizing multiple assessments for quantifying sleep as these factors do not correlate highly with each other and relationships between these factors and pain may differ. Future investigations should include both subjective and objective assessments, as they likely tap into

different concepts, which, taken together, may advance our understanding of sleep disturbances and their impact on patients with RA.

Abbreviations

RA	Rheumatoid arthritis
QST	Quantitative sensory testing
CNS	Central nervous system
ACR	American College of Rheumatology
EULAR	European League Against Rheumatism
OSA	Obstructive sleep apnea
WASO	Wake after sleep onset
PPTs	Pressure pain thresholds
TS	Temporal summation
CPM	Conditioned pain modulation
BMI	Body mass index
CDAI	Clinical disease activity index
DMARD	Disease modifying anti-rheumatic drug
PROMIS	Patient-Reported Outcomes measurement Information System

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Author contributions
The authors confirm contributions to the article as follows: study conception or design: BA, LM, JS, KR, DG, DD, PZ, YL; data acquisition, analysis, or interpretation: BA, LM, JS, KR, AI, KDA, MC, DD, RC, PZ, YL; and drafted the article: BA, YL. All authors were involved in revising the article critically for important intellectual content, approved the final version to be submitted for publication, and agreed to be accountable for the accuracy or integrity of any part of the work.

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Data availability
The processed data set that supports the findings of this study is available from the authors upon reasonable request and completion of a data use agreement.

Declarations

Ethics approval and consent to participate
This study was performed in line with the principles of the Declaration of Helsinki. Ethics approval was granted by the Institutional Review Board of Northwestern University (No. STU00211633), and all participants provided informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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