Decreased Sleep Spindles and Spindle Activity in Midlife Women with Fibromyalgia and Pain

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Objectives: To compare sleep-spindle incidence (number of spindles per minute of non-rapid eye movement [NREM] stage 2 sleep) and duration, spindle wave time (seconds per epoch in NREM stage 2 sleep), spindle frequency activity, and pain measures (pressure pain threshold, number of tender points, skinfold tenderness) between midlife women with fibromyalgia (FM) and moderate to high levels of pain and fatigue, compared to control women of similar age. These data imply that some aspect of thalamocortical mechanisms of spindle generation might be impaired in FM.

Design: A cross-sectional descriptive study.

Setting: A university-based sleep research laboratory and a referral clinic for chronic fatigue and pain.

Participants: Thirty-seven medication-free women with FM (mean age, 44.9 ± 8 years) and 30 women with reported good sleep and no pain (mean age, 44.1 ± 7.7 years) completed a psychiatric interview and the Beck Depression Inventory prior to 2 consecutive nights of polysomnography, with pain measures obtained in the morning. Time domain analysis of spindle incidence and spectral analysis of spindle frequency activity were conducted on night 2 of polysomnography recordings.

Interventions: NA.

Results: Women with FM had fewer mean spindles per minute of NREM stage 2 sleep and lower mean spindle time per epoch of NREM stage 2 sleep (both \(P < .02\)), but mean spindle duration, although slightly shorter, was not statistically significantly different (\(P < .06\)) compared to control women. Women with FM had a lower mean pressure pain threshold, a higher average number of positive tender points, and higher skinfold tenderness compared to control women (all \(P < .001\)). Group differences in spindle frequency activity were found after controlling for age, depression, and psychiatric diagnosis in a general linear model (\(P < .02\)). One-way analysis of variance revealed significantly lower spindle activity in the 3 frequency bins (12-12.5 Hz, 13-13.5 Hz, 14-14.5 Hz) at C3 (all \(P < .04\)), Fz (all \(P < .02\)), and Cz (all \(P < .02\)). Finally, after controlling for age and depression, pain pressure threshold significantly predicted spindles per minute and spindle time per epoch of NREM stage 2 sleep (\(r^2 = .26; P < .001\)).

Conclusions: Women with FM and pain have fewer sleep spindles and reduced electroencephalogram power in spindle frequency activity compared to control women of similar age. These data imply that some aspect of thalamocortical mechanisms of spindle generation might be impaired in FM.

Key Words: Sleep spindles, spindle activity, fibromyalgia, pain, spectral analysis, chronic fatigue, sleep

Citation: Landis CA; Lentz MJ; Rothermel J et al. Decreased sleep spindles and spindle activity in midlife women with fibromyalgia and pain. SLEEP 2004;27(4):741-50.

INTRODUCTION

FIBROMYALGIA (FM) IS A COMPLEX CHRONIC PAIN CONDITION THAT AFFECTS 2% TO 4% OF THE GENERAL POPULATION AND PREDOMINATELY AFFECTS WOMEN.\(^1\)\(^-\)\(^2\) FM is diagnosed on the basis of widespread pain in 4 body quadrants for at least 3 months’ duration with tenderness detectable by palpation at 11 of 18 discreet musculoskeletal points.\(^1\) Although sleep difficulties are not part of standard diagnostic criteria, insomnia complaints of poor and nonrestorative sleep are common and have been associated with intense pain, fatigue, sleepiness, and cognitive difficulties in FM.\(^1\)\(^-\)\(^3\)\(^,\)\(^7\)

Polysomnography (PSG) has been used extensively to monitor sleep physiology in FM, but controversy surrounds its clinical significance and diagnostic value. Compared to control subjects of similar age, the most consistent findings from PSG studies show slightly longer sleep latencies, more wakefulness, and more non-rapid eye movement (NREM) stage 1 sleep with reduced sleep efficiency in FM.\(^8\)\(^-\)\(^11\) However, total sleep time and the percentage of other sleep stages are similar in FM patients, even with moderate to high levels of pain and fatigue,\(^13\)\(^-\)\(^14\) compared to patients with other types of chronic pain.\(^15\) An alpha electroencephalographic (EEG) anomaly during NREM sleep has been considered a biologic correlate of chronic pain and a possible basis for nonrestorative sleep complaints in FM.\(^16\)\(^-\)\(^20\) Since its initial description in patients with ‘fibrositis’ and in healthy individuals deprived of stage 4 sleep in 1 laboratory,\(^16\)\(^-\)\(^17\) a few other investigators, by visual inspection and spectral analysis, have described increased alpha activity in NREM sleep in patients with FM.\(^19\)\(^,\)\(^20\) However, others have revealed that increased alpha activity is not present in a majority of FM patients with considerable pain,\(^14\)\(^,\)\(^15\) or in patients with other chronic pain conditions.\(^21\)\(^-\)\(^23\) Clearly, alpha activity during NREM sleep is not specific to FM,\(^24\)\(^-\)\(^26\) and the neuronal substrate and mechanisms underlying this presumed pain-related ‘arousal’ pattern in NREM sleep are not known.\(^27\)

In contrast to alpha activity, the neuronal basis of sleep spindles, an easily identified EEG marker of NREM sleep, has been studied extensively and well described.\(^27\)\(^-\)\(^30\) Sleep spindles from 12 to 14 Hz represent unambiguous EEG evidence of sleep onset, occur every 3 to 10 seconds throughout NREM stage 2 sleep,\(^31\)\(^,\)\(^32\) and are considered important for the induction and maintenance of NREM sleep.\(^27\) Moreover, they are a critical component of thalamocortical mechanisms of spindle generation.\(^27\)

Disclosure Statement
No significant financial interest/other relationship to disclose.

Submitted for publication October 2002
Accepted for publication December 2003

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SLEEP, Vol. 27, No. 4, 2004 741
lamic gating mechanisms through which the transmission of and cortical responses to internal and external stimuli are attenuated during sleep.\textsuperscript{25-30,33} Cerebral blood flow in the thalamus is reduced in conjunction with EEG spindle activity during NREM sleep, possibly reflecting disfacilitation (modulation of excitatory inputs) and hyperpolarization of neurons involved in spindles.\textsuperscript{34}

Sleep spindle incidence in NREM stage 2 sleep is affected by age, varies between subjects, shows considerable individual stability from night to night, and is altered in various clinical conditions and after experimental manipulations. Compared to the incidence in normal subjects, spindle incidence is augmented in patients with hypersomnia,\textsuperscript{35} neurologic movement disorders,\textsuperscript{31} and conditions associated with somatosensory deficits\textsuperscript{36} and after learning a new task\textsuperscript{37} and administration of hypnotic medications.\textsuperscript{31} Conversely, spindle incidence is reduced in older adults;\textsuperscript{38} in various central nervous system diseases, including brain tumors, stroke, infection,\textsuperscript{31} depression,\textsuperscript{39} insomnia\textsuperscript{40}; and with experimental auditory stimulation in NREM stage 2 sleep.\textsuperscript{41} Reports of spindle incidence relative to pain are sparse. However, investigators recently described reduced spindle activity (sigma power) in nondepressed patients with chronic low back pain compared to healthy controls.\textsuperscript{23}

Central nervous system mechanisms involved in pain processing are thought to be abnormal in FM. Common manifestations are consistent with a phenomenon called central sensitization that is associated with heightened pain perception reported in response to light touch (allodynia) and with reduced pressure pain threshold (hyperalgesia).\textsuperscript{42-49} Patients with FM consistently report higher levels of pain in response to pressure applied to specific tender points (as designated by the American College of Rheumatology criteria) compared to patients with chronic back pain, headache, and rheumatoid arthritis.\textsuperscript{49} They also show evidence of hyperalgesia regardless of whether the pressure stimulus is presented randomly or in a predictable manner (as with systematic tender point assessment by dolorimetry).\textsuperscript{50} The assessment of the number of painful tender points is commonly used as an indicator of symptom severity in FM. Further, in a recent study, considerably more brain areas were activated, as shown by functional magnetic resonance images, and perceptions of pain intensity were increased in response to light pressure in patients with FM compared to controls.\textsuperscript{51} These findings were interpreted as evidence of cortical and subcortical augmented pain processing indicative of a chronic hyperalgesic state. Imaging studies in FM have shown reduced resting blood-flow patterns in the cerebrocortical and thalamus that are consistent with imaging evidence of cortical and subcortical augmented pain processing and conditions associated with somatosensory deficits and after learning a new task and administration of hypnotic medications. Conversely, spindle incidence is reduced in older adults; in various central nervous system diseases, including brain tumors, stroke, infection, depression, insomnia; and with experimental auditory stimulation in NREM stage 2 sleep. Reports of spindle incidence relative to pain are sparse. However, investigators recently described reduced spindle activity (sigma power) in nondepressed patients with chronic low back pain compared to healthy controls.

Our main goal was to select women with painful manifestations of FM and control women with minimal or no pain. A standard verbal-descriptor pain scale (1 = “no muscle aches and pain” to 10 = “worst muscle aches and pain you can imagine”) was used to measure pain intensity during the initial screening interview via telephone. Women with FM were excluded if they (1) were < 25 or > 60 years old; (2) had a body mass index > 35 kg/m\textsuperscript{2}; (3) did shift work; (4) had a history of major physical or psychiatric illness or sleep disorder; (5) had any substance abuse within the last year; and (6) were unable or unwilling to discontinue all hypnotic, sedative, or psychotropic prescription medications and herbal supplements for at least 2 weeks prior to and during the sleep study. Subjects were further screened for pain, physical activity, and medications as described below.

### Pain

Women previously diagnosed with FM (based on widely accepted and published criteria\textsuperscript{1}) were recruited from an academic referral clinic devoted to the evaluation of fatigue; they were identified from the clinic database, contacted by telephone, and invited to participate in the study. Control women from the local community were recruited from advertisements placed on bulletin boards and in neighborhood newspapers. For all women, information on age, height, weight, and medical history were obtained during an initial screening interview via telephone. Women were excluded if they (1) were < 25 or > 60 years old; (2) had a body mass index > 35 kg/m\textsuperscript{2}; (3) did shift work; (4) had a history of major physical or psychiatric illness or sleep disorder; (5) had any substance abuse within the last year; and (6) were unable or unwilling to discontinue all hypnotic, sedative, or psychotropic prescription medications and herbal supplements for at least 2 weeks prior to and during the sleep study. Subjects were further screened for pain, physical activity, and medications as described below.

### Subjects and Screening Procedures

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Physical Activity

Because women with FM report low levels of physical activity,56 we selected control women with relatively low levels of physical activity. Three items from the Paffenbarger Physical Activity Questionnaire (number of stairs climbed, blocks walked, and time spent in vigorous activities)57,58 were administered during the initial telephone interview to obtain information on usual weekly physical activities. Using a locally developed computer program, energy expenditure was calculated as the kilocalories expended weekly from the self-reported physical-activity responses and published estimates of kcal per activity.57 Control women with a calculated energy expenditure of at least 1500 kcal per week were excluded from the study. This cutoff level of energy expenditure was based on an average score of 1408 kcal per week derived from the Paffenbarger Physical Activity Questionnaire that was reported in a sample of 541 women similar in age to the women in this study.59 Activity data for comparisons were not obtained on 6 FM patients. One FM subject was omitted from the analysis because she had started an intensive exercise program and her estimated kcal per week was 3 SD above the FM group mean.

Medications

All women were excluded from the study if they were taking steroids (except birth control pills or menopausal or controlled thyroid hormone replacement therapy). Women with FM were first weaned from all antidepressant, hypnotic, or psychotropic medications using individualized protocols and then were drug free for at least 2 weeks (based on daily diary reports) prior to the laboratory study.60 Medications such as nonsteroidal anti-inflammatory drugs, antihistamines, and herbal preparations were permitted until a time corresponding to 5.5 half-lives prior to the first night of the sleep study.

Psychiatric Illness

The Diagnostic Interview Schedule (C-DISR version, C-DIS group, Ottawa; sections on panic, generalized anxiety, posttraumatic stress, mania or bipolar disorder, alcohol, drug abuse or dependence, and depression) was administered to all women by 2 nurses trained to conduct telephone interviews.61 In addition to completing the psychiatric interview via telephone, women completed the Beck Depression Inventory (BDI) at the time of the laboratory study. The original BDI is a 21-item questionnaire designed to assess affective, cognitive, motivational, vegetative, and psychomotor aspects of depressed mood.62,63 The response choices for each item range from “neutral or not present” (0) to “maximal severity” (3) graded for the past week, including the day of administration. We used the 13-item short form of the BDI because it reflected psychological aspects of depressed mood after somatic symptom items were removed.64 The maximum possible score on BDI short form is 39. Scores of 0 to 4 indicated none or minimal depression; 5 to 7, mild; 8 to 15, moderate, and 16 or greater, severe depression.

Pain Measures

Tender Points and Pressure Pain Threshold

During a laboratory orientation session and the morning and evening of the second sleep-recording night, tender points were assessed by research trained assistants (intrarater agreement > 95%) according to methods previously described.64,65 A standard dolorimeter was held perpendicular to the body, and pressure was applied to 9 bilateral anatomic sites at an approximate rate of 1 kg/1.54 cm² per second. A paired site on the left and right forearm was used as control. The dolorimeter was withdrawn when either the subject verbally indicated a ‘painful’ sensation or a maximum preset pressure (8 kg) was reached. The point on the pressure gauge (recorded to the nearest one-tenth kg) at the time the dolorimeter was withdrawn or the preset maximum was used as the indicator of pain threshold. A mean score of the pressure pain threshold for each subject was calculated for the 18 FM criteria points and also for the 2 control sites tested at each time point. The number of positive tender points (ie, reported pain with < 4 kg pressure), excluding the 2 control sites, was summed for each woman.

Skinfold Tenderness

Skinfold tenderness (an indicator of skin pain) was assessed by research-trained assistants (intrarater agreement > 95%).65 Skinfold tenderness was rated from “no pain” (0) to “severe pain” (3) after the skin over the upper border of the trapezius muscle was rolled between the thumb and fingers of the research assistant.

The scores for pressure pain threshold and skinfold tenderness reported in this study represent those obtained the morning after the second night in the sleep laboratory.

Sleep Laboratory Procedures and Recordings

All women carried out their usual daytime activities but were requested to not take naps. They maintained daily diary reports of symptoms, sleep onset and offset times, estimates of number of awakenings, and how rested they felt on awakening. Each night, approximately 2 hours before their usual bedtime, they reported to the sleep laboratory and then slept in the School of Nursing Sleep Research Laboratory in temperature-controlled sound-attenuated rooms for 3 consecutive nights. Women went to bed at their usual time (as established by previous daily diary entries) and were awakened at 7:00 AM. They were permitted to consume beverages and foods containing caffeine in usual amounts but were asked to refrain from consuming them and to abstain from drinking beverages containing alcohol during the afternoon and evening prior to the sleep laboratory study. Based on daily diary reports of caffeine and alcohol consumed, the women did not consume more than their usual amount of caffeine and did not have any beverages containing alcohol during the sleep study. Women with menstrual cycles were scheduled for laboratory study during the 5 to 10 days following menses. The first night was considered as adaptation to the laboratory, and the data were used for PSG screening of all subjects for sleep apnea (index of ≥ 5 events per hour).66 During the second night, data were collected to describe sleep parameters, quantitative EEG waveform, and spectral analysis and to score periodic leg movements (index of ≥ 5 events per hour).67,68 Blood samples were obtained during night 3, and findings have been reported previously.69
Electrodes for recording the EEG, the electrooculogram, and the electromyogram were placed according to standards. Transducers to measure airflow (Easyflow, Sleepmate, Newlife Technologies, Midlothian, Virg) and upper-airway obstruction (Opti-Flex, Sleepmate) were placed under the nose and at the sternal notch, respectively. Electrodes to measure leg movements were placed on the tibialis anterior muscle of 1 leg. The standard C3 EEG lead was placed on all subjects and referenced to A2 (mastoid bone). Additional midline EEG electrodes were placed at Fz and Cz based on the International 10-20 system. The midline EEG electrodes were referenced to linked A1-A2 lead connected to a 10-kOhm resistor. Electrophysiologic signals were amplified and conditioned on a Grass model 7 polygraph (Grass Instruments, Co., Quincy, Mass). All PSG data were recorded and digitized with the Oxford Sleep Acquisition Computer system (SACS, version 847 model 700 board, Clearwater, Fla) on a desktop computer. The EEG channels were sampled at 250-Hz 8-bit resolution. Prior to each recording session, channels on both the polygraph and the SACS for EEG, electrooculogram, and electromyogram were calibrated. The SACS (software version 10) was used to first score sleep and wake stages in 30-second epochs followed by rescoring by a sleep technologist according to standard criteria. An overall interrater agreement > 90% was maintained for all scored records in this study.

Spindle Incidence, Time Domain Analysis

Spindle waveforms were identified by the SACS automated computer software, a system that uses zero crossing combined with period amplitude and pattern recognition. In this system, individual detection of spindle waveform frequency is defined as 6 consecutive waves, each from 11.4 to 16.7 Hz (SACS Manual, version 10). Spindles in NREM stage 2 sleep were quantified according to incidence (number of spindles per minute of stage 2 sleep) and duration (in seconds). Spindle wave time (in seconds) also was expressed per epoch during NREM stage 2 sleep to control for individual differences in the total amount of NREM stage 2 sleep.

Power Spectral Analyses

Each epoch of data from 3 EEG electrode sites (C3, Fz, Cz) was screened for observable artifact (eg, temporary disconnect spikes, sweating, body movements) and removed from further analysis. The remaining data from each EEG electrode were extracted from the scored sleep data file by a locally developed software program and stored in separate binary data files. Spectral analysis was performed on 2-second windows with a frequency resolution of 0.5 Hz using a discrete Fourier transform algorithm. Fifteen power spectra (range 0-30 Hz) were computed per 30-second epoch for each EEG electrode for the entire recording period. These spectra were later matched with the scored sleep data by stage and converted to an SPSS (version 9.0; SPSS, Inc., Chicago, Ill) data file for statistical analysis. To compensate for variability among subjects and across the night in EEG power, the spectra were normalized (value in each frequency bin divided by the total power) and log transformed to correct for nonlinear error.

Data Analysis

Given the different types of variables measured in this study, data analyses were carried out in predetermined blocks by variable type (eg, demographic, clinical features, pain measures, spindle incidence, and spindle frequency activity). Each block was considered a separate analysis with significance set at $P < .05$. The Bonferroni correction was applied for multiple comparisons within blocks. The $\chi^2$ test was used to test differences on race (demographic block), menses status, and hormone replacement (clinical features block). The $t$ test was used to test differences between groups on age (demographic) and on spindle incidence (spindle number, duration, and time per epoch of NREM stage 2 sleep). The Mann-Whitney U test was used to test differences between groups on body mass index, pain measures (pressure pain thresholds, number of tender points, and skinfold thickness) and depression because the distributions of these variables did not meet the assumptions required for parametric statistical tests. Because age and psychiatric illness (eg, depression) potentially affect EEG spindle frequency activity, we used a general linear model for the multivariate analysis of spindle frequency activity at 3 electrode sites (C3, Fz, Cz) and 3 frequency bins (12-12.5, 13-13.5, 14-14.5Hz) with age, depression, and psychiatric diagnosis as covariates. Even though the groups were similar in age, using age as a covariate reduced error variance. Subsequently, 1-way analysis of variance (ANOVA) was used to test group differences in spindle frequency activity at each electrode site in each frequency bin. Finally, separate stepwise regression models with backward deletion were used to predict spindle incidence (spindle number and duration and time per epoch of NREM stage 2 sleep) on the basis of pain pressure threshold after controlling for age and depression.

RESULTS

Subjects

Demographic and clinical features of the women in the sample are summarized in Table 1. Most of the women in the study were White, and there were no statistically significant differences in age, body mass index, or calculated energy expenditure as a measure of physical activity levels. Despite the fact that all of the control women reported “good sleep,” had a periodic leg movement index of at least 5 (range, 10.8-29.9) events per hour, which were not associated with evidence of EEG arousal. Among women with FM, 9 had a periodic leg movement index of at least 5 (range, 5.1-7.9) events per hour. Two women with FM had a periodic leg movement arousal index > 5 (7.7 and 10.5) events per hour. In addition, 1 woman with FM and 1 control woman had a respirator disturbance index > 5 events per hour, which were not associated with evidence of EEG arousal.

Psychiatric Illness History and Depression

Twenty-one women in the FM group had a positive history for psychiatric diagnosis, and 3 women met the Diagnostic and Statistical Manual of Mental Disorders, Third Edition criteria for current depression. Three women in the control group had a positive history for psychiatric diagnosis, and 1 woman met Diagnostic and Statistical Manual of Mental Disorders, Third Edition criteria for current hypomania. Compared to control
women, women with FM had higher scores (range, 2.2-12) on the short form of the BDI, indicating minimal to moderate levels of depression (Table 1).

**Pain Measures**

Pain measures also are listed in Table 1. Compared to control women, women with FM had significantly lower mean scores of pressure pain threshold (tolerated less pressure) for all 18 sites and for the 2 forearm control sites, more positive tender points (< 4 kg), and higher skinfold tenderness scores.

**Sleep Spindles**

The EEG data from an epoch of NREM stage 2 sleep for 1 woman with FM and 1 control woman are shown in Figure 1. Altered spindle characteristics are easily recognized in the recording from the woman with FM compared to the control woman. The data on spindle incidence are summarized in Table 2. Although the average spindle duration was similar, women with FM had fewer spindles per minute of NREM stage 2 sleep and lower spindle time per epoch of NREM stage 2 sleep compared to control women.

**Spindle Frequency Activity**

As shown in Figure 2, compared to control women, women with FM showed significantly decreased spindle frequency activity overall at C3, Fz, and Cz and in all 3 frequency bins \((P < .02)\) but there was no effect of age, depression, or psychiatric diagnosis on group differences. Subsequently, a 1-way ANOVA revealed lower spindle activity in all 3 frequency bins at C3 (all \(P\) values < .04), Fz (all \(P\) values < .02), and Cz (all \(P\) values < .02). The results of the regression analysis are summarized in Table 2.

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**Table 1**—Demographic, Clinical Characteristics, Psychiatric Illness, and Pain Measures in Women with Fibromyalgia and Controls*

<table>
<thead>
<tr>
<th></th>
<th>Fibromyalgia</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 37</td>
<td>n = 30</td>
</tr>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y(^\dagger)</td>
<td>44.9 ± 8</td>
<td>44.1 ± 7.7</td>
</tr>
<tr>
<td>Race, % white(^\dagger)</td>
<td>86.5%</td>
<td>93.3%</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>27.2 ± 5.4</td>
<td>24.6 ± 3.6</td>
</tr>
<tr>
<td>Physical activity, kcal/wk</td>
<td>582 ± 617</td>
<td>724 ± 405</td>
</tr>
<tr>
<td>Menses Status, % Yes(^\dagger)</td>
<td>48.6 %</td>
<td>63.3 %</td>
</tr>
<tr>
<td>Hormone Replacement, Birth Control Pills, %(^\dagger)</td>
<td>41.7 %</td>
<td>23.3 %</td>
</tr>
<tr>
<td>Beck Depression Inventory short form(^\dagger)</td>
<td>7.1 ± 4.9</td>
<td>1.1 ± 1.4</td>
</tr>
<tr>
<td>Pain Measures(^\dagger)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure thresholds, 18 sites, kg</td>
<td>1.8 ± 1.0</td>
<td>4.0 ± 1.4</td>
</tr>
<tr>
<td>Pressure thresholds, control sites, kg</td>
<td>2.4 ± 12.6</td>
<td>5.2 ± 1.75</td>
</tr>
<tr>
<td>Positive tender points, no.</td>
<td>17 ± 3.05</td>
<td>10.2 ± 5.6</td>
</tr>
<tr>
<td>Skinfold tenderness, rating</td>
<td>2.4 ± 0.8</td>
<td>1.3 ± 0.4</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated.
\(^\dagger\)Age was not reported by 1 subject in each group.
\(^\dagger\)No statistically significant difference by \(\chi^2\).
\(^\dagger\)P < .001, Mann Whitney U.
\(^\dagger\)Measures obtained the morning after night 2. Pressure thresholds were not obtained from 1 control subject.

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**Table 2**—Sleep Spindles in NREM Stage 2 Sleep in Women with Fibromyalgia and Controls

<table>
<thead>
<tr>
<th></th>
<th>Fibromyalgia</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Spindle Incidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number per minute in stage 2 sleep(^\ast)</td>
<td>3.8 ± 2.2</td>
<td>5.4 ± 2.9</td>
</tr>
<tr>
<td>Duration, sec(^\dagger)</td>
<td>1.2 ± 0.2</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>Spindle time per epoch in stage 2 sleep, sec(^\dagger)</td>
<td>1.7 ± 1.2</td>
<td>2.7 ± 1.8</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD and are from lead C3 \(t\) test: \(^*P = 0.01; \daggerP = 0.06; \ddaggerP = 0.02\) NREM refers to non-rapid eye movement sleep.

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**Figure 1**—Polygraphic recordings of stage 2 sleep for 1 control and 1 subject with fibromyalgia (FM). Spindles are designated by the black bars below the electroencephalogram tracing (C3/A1-A2). In this 30-second epoch, the total number of spindles was 7 for the control subject and 5 for the FM subject.
3. After controlling for age and depression, pain pressure threshold significantly predicted spindle number per minute and spindle time per epoch of NREM stage 2 sleep. Both age and pain threshold were significantly related to spindle duration.

**DISCUSSION**

Women with FM and moderate to high pain intensity had fewer sleep spindles and reduced spindle frequency activity during NREM stage 2 sleep compared to pain-free women of similar age. To our knowledge, this is the first report of lower spindle incidence and spindle power in FM. Importantly, in our analyses, we controlled for variables such as age and depression, which have been associated with reduced spindle incidence and lower spindle power. We studied women after their menses because spindle activity > 14 Hz is increased in the luteal phase of the menstrual cycle.

In addition, none of the women were taking hypnotic drugs during the study, which have been shown to increase both spindle incidence and spindle frequency activity. The spindle detector used has been validated previously. Pain pressure threshold predicted spindle incidence after controlling for important confounding variables. Our findings suggest that reduced spindle incidence in FM could reflect pain-related impairments in thalamocortical oscillatory networks that are important for sleep induction and maintenance processes.

**Spindle Activity**

Two distinct spindle frequencies can be distinguished in different scalp locations. Slow-frequency spindle activity, clustered from 12 to 13 Hz, is detected best over the frontal cortex; fast-frequency activity, clustered at 13 to 15 Hz, is more prominent over parietal cortical regions. Recordings from leads placed centrally (Cz) reflect EEG activity summed from both frontal and parietal regions and are considered the most sensitive for recording spindle activity. Women with FM had lower spindle activity in all frequency bins from the 3 scalp locations recorded over frontal, central, and parietal cortical regions during NREM stage 2 sleep. Slow spindle frequency is associated with longer hyperpolarization such that more spindles occur. Our observation of a reduction in slow spindle frequency activity in women with FM suggests that the duration of neuronal hyperpolarization necessary to induce spindle oscillations may be insufficient. Although the number of recording sites was limited, the consistent finding of reduced spindle activity at all 3 recording sites indicates a potential generalized phenomenon.
The findings of reduced spindle frequency activity in this study differ from those of a previous study showing an increased percentage of spindle frequency activity from frontal cortex in NREM sleep stage 2 during the first NREM cycle in FM subjects compared to controls. Although the age of the women, the spindle frequency range, and lack of hypnotic drug use at the time of the sleep study were comparable to those in our study, the methods of spindle detection and spectral analysis used were substantially different, making direct comparisons difficult. In a recently reported sleep EEG quantification study of a small group of patients with chronic low back pain (n = 10, 90% men), the most striking findings were reduced spindle activity in recordings from frontal, centroparietal, and occipital cortex in the nondepressed pain patients (n = 6) compared to depressed pain patients (n = 4) and controls (n = 11). In addition, greater spindle power was observed over the occipital cortex in controls relative to patients with chronic back pain with and without depression. These data, coupled with the findings from our study, lend support to a relationship between reduced spindles and spindle power and chronic pain. Clearly, additional studies of spontaneous spindle frequency activity with recordings from multiple cortical sites and for multiple nights are needed to address questions related to stability and reproducibility in patients with FM.

**Effects of Age on Spindle Incidence and Activity**

Mean spindle incidence for the women in this study fell within the range previously reported for middle-aged adults. Since age, along with pain, was significantly related to spindle duration, an effect of age on spindles cannot be ruled out by the findings reported here. However, spindle frequency activity, which is reduced in older compared to younger adults, was lower in women with FM compared to controls when we controlled for the effect of age in the analysis. Further, the idea that pain affects spindle incidence in FM and that this effect can be distinguished from effects of age is supported by recent observations that spin-dle activity. Further studies that focus on quantification of microstructure EEG elements of sleep, including spindle activity, slow waves, and the relationship to slow oscillations, have the potential to enhance understanding of age-related and pain-related mechanisms involved with decreased spindle incidence and power.

**Limitations**

This study has several limitations. First, the women with FM were highly selected, since they were drawn from an academic referral clinic and willing to discontinue their medications. In addition, the study was restricted in terms of age and sex. As such, our patients might not represent the larger population of community-dwelling individuals of all ages who suffer from FM. Second, despite the fact that the spindle-detection system used in this study has been validated previously, automated systems have the potential to generate false-positive spindle counts and to miss spindles that do not meet specific waveform criteria. Altered morphology of spindles was evident in visual inspection of the EEG in the women with FM compared to control women. Third, although there are no reports of steroid-hormone effects on spindle incidence, more women with FM were on hormone replacement compared to the control women. However, we have previously reported no group differences in plasma levels of estradiol. Lastly, although we obtained daily reports of medication use in the 2 weeks prior to and during the days of the sleep study, we did not do drug toxicology assessments to ensure that our subjects were not taking hypnotic and antidepressant medications. Most reports in the literature show that hypnotics are associated with increased spindle incidence and activity and that low-dose antidepressants that are commonly used to treat symptoms in FM have minimal affect on EEG spectral power. Although a 2-week wash-out period for hypnotic and antidepressant medication, as done for this study, is considered sufficient to obviate the effects prior to visual scoring of sleep architecture, there is a remote possibility that some residual effects of these medications could influence spectral activity.

**Pain and Sleep-State Instability in FM**

Intuitively, it seems obvious that pain, as commonly occurs with acute injury and trauma, ought to lead to central nervous system arousal, as evidenced by the presence of arousal indexes or wakefulness in the EEG, thus interfering with falling and staying asleep. However, chronic pain conditions like FM are quite different and far more complex. In FM, despite self-reports of poor sleep, few changes in sleep-stage amounts or indexes of arousal with evidence of sleep fragmentation or stage instability are observed. Further, clinical pain severity has not been consistently correlated with EEG indicators of arousal during sleep or with typical measures of sleep fragmentation. Investigations using various types of signal analysis have just begun to uncover discrete EEG microstructure abnormalities not observed with conventional visual-scoring techniques of sleep in FM and in other chronic pain conditions, pointing to the need for much more work to gain clarity regarding pain and sleep instability.

In this study we chose to focus on quantification of an EEG “sleep” marker considered important to adequate sleep induction and maintenance rather than markers typically associated with arousal. We based our analysis and interpretation on evidence that FM is considered a chronic hyperalgesic state, and chronic
Sleep Spindles in Fibromyalgia—Landis et al


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