INTRODUCTION

Chronic fatigue syndrome (CFS) is a medically unexplained condition characterized by persistent or relapsing fatigue lasting at least 6 months, which substantially reduces normal activity. In addition to severe fatigue, one of the symptoms used for diagnosing CFS is “unrefreshing sleep,” and this sleep-related problem is the most common complaint among patients with CFS. Fibromyalgia (FM) is a medically unexplained illness characterized by 4-quadrant pain and multiple tender points and frequently occurs in conjunction with CFS. In fact, CFS and FM often have similar symptoms, including sleep-related complaints; this has led some researchers to suggest that they are essentially the same illness. Therefore, rather than focus on similarities between the 2 disorders, it seems more appropriate to focus on differences between them. Finding differences would suggest that the pathophysiologic processes responsible for the 2 illnesses could differ.

Polysomnographic studies have shown that sleep problems in patients with CFS and FM are quite similar (e.g., alpha-delta sleep, more arousals, reduced sleep efficiency, prolonged sleep onset, increased stage 1 sleep [S1], reduced slow-wave sleep [SWS]). However, these observations are not consistent between studies for both CFS and FM, and there are even studies reporting no statistical differences in traditional sleep parameters between healthy humans and those with CFS or FM or between patients with CFS, with or without FM. Historically, most sleep studies have been performed based upon sleep staging according to the traditional standardized scoring criteria established by Rechtschaffen and Kales in 1968. While this methodology has been extremely useful, sleep-stage analysis has been limited to simple descriptive statistics (e.g., total sleep time, sleep efficiency, and total duration of each sleep stage), providing static information about overnight sleep. Recently, we investigated dynamic aspects of sleep for patients with CFS and revealed that they had altered patterns of sleep-stage transitions, compared with healthy control subjects. This kind of information could not be obtained using the traditional analysis based on Rechtschaffen and Kales criteria; moreover, the pattern of sleep-stage transitions across a night of sleep could be a novel way of determining the quality of sleep.

Therefore, we hypothesized that dynamic aspects of sleep, a new focus of sleep researchers, would be different between the 2 groups of patients. We thus studied transition probabilities between sleep stages and duration distributions of each sleep stage of patients with CFS, with or without FM.

Methods

Subjects
The subjects were 52 women—26 healthy control subjects (age: 38 ± 8 years; mean ± SD), 14 patients with CFS without fibromyalgia, and 12 patients with fibromyalgia. The subjects were 26 healthy control subjects (age: 38 ± 8 years; mean ± SD), 14 patients with CFS without fibromyalgia, and 12 patients with fibromyalgia.
FM (CFS alone; age: 37 ± 9 years), and 12 patients with CFS and FM (CFS+FM; age: 41 ± 6 years). None of these subjects had clinically evident sleep disorders in the form of restless leg syndrome or obstructive sleep apnea (see next subsection). An extensive health screening was used to exclude patients taking antidepressants, opiates, steroids, hypnotics, and other sedatives, including benzodiazepines. The patients all fulfilled the 1994 case definition for CFS and thus had neither any medical explanation for their symptoms based on history, physical examination, and blood tests to rule out other disorders nor did they have any serious psychiatric diagnoses, including schizophrenia, eating disorders, substance abuse or bipolar disorder, as determined by using the computerized version of the Diagnostic Interview Schedule (DIS-IV)\textsuperscript{26}; of these patients, 14 also fulfilled the American College of Rheumatology criteria (1990) for FM. Controls all reported their health to be excellent or good and had normal findings upon examination and normal results from blood tests. Because sleep-electroencephalographic changes are frequent symptoms of major depressive disorder, we also used the psychiatric diagnostic interview to confirm that no subject with major depressive disorder was included. To further reduce variability, menstruating subjects were all studied in the follicular phase of their menstrual cycles.

All the subjects gave their informed consent, approved by the New Jersey Medical School’s Institutional Review Board, to participate in this research. Following instructions to refrain from alcohol and caffeine ingestion and avoid engaging in prolonged and/or strenuous exercise in the daytime before study nights, the subjects underwent 1 night of polysomnographic recording in a quiet, darkened, hospital room. The subjects went to bed at their usual bedtime and awoke the next morning between 07:15 and 08:00.

**Polysomnography**

Subjects underwent full nocturnal polysomnography consisting of electroencephalogram (C3/A2, O1/A2 and FZ/A2), electrooculogram, submental electromyogram, anterior tibialis electromyography, a lead II electrocardiogram, thoracic and abdominal motion, airflow using a nasal cannula/pressure transducer and an oral thermistor, and pulse oximetry.

Sleep was scored every 30 seconds by a single scorer according to standard criteria of Rechtschaffen and Kales.\textsuperscript{24} Sleep stages were scored by dividing a sleep recording into nonoverlapping epochs of 30 sec duration, and a single stage assigned to each epoch. If more than 1 sleep stage occurred within an epoch, the sleep stage that occupied the greatest portion of the epoch was scored as the stage of the whole epoch. An arousal was defined according to standard American Academy of Sleep Medicine criteria\textsuperscript{31} as a return to alpha or fast-frequency electroencephalographic activity, well differentiated from the background, lasting at least 3 seconds but no more than 15 seconds. If alpha or fast-frequency electroencephalographic activity lasted at least 15 seconds within an epoch, the stage of the epoch was scored as awake.

Respiratory events were defined as any combination of apneas and hypopneas lasting at least 10 seconds or airflow suggesting flow limitation\textsuperscript{32} lasting at least 10 seconds associated with an arousal. Apnea was defined as a reduction in airflow to less than 10% of waking level in the nasal cannula and absent airflow in the oral thermistor, and hypopnea was defined as a decrease in inspiratory airflow to less than 50% of waking levels. Flow limitation was considered to occur when there were 2 or more consecutive breaths (for an event duration generally ≥ 10 sec) that had a flattened or nonsinusoidal appearance but had peak inspiratory amplitudes that did not meet the more than 50% reduction requirement of a hypopnea. These events were required to end abruptly, with a return to breaths with a sinusoidal shape. The respiratory disturbance index (RDI) was defined as the total number of apneas, hypopneas, and flow-limitation events per hour of sleep.\textsuperscript{32} The RDI including the flow limitation events terminated by arousal has been previously shown to be essentially identical to the number of the esophageal manometry events terminated by arousal, which have been called respiratory effort-related arousals.\textsuperscript{32} Our RDI is functionally equivalent to the “alternative definition” of the apnea-hypopnea index (AHI) proposed by the American Academy of Sleep Medicine in 2007.\textsuperscript{33} Based on results by Ayappa et al.,\textsuperscript{32} it was assumed that an RDI of at least 18 events per hour was sufficient to account for excessive daytime sleepiness on the basis of sleep disordered breathing, and the diagnosis of sleep disturbed breathing was then made for patients and healthy control subjects with this finding. Periodic leg movements were defined as 4 or more consecutive, involuntary leg movements per hour during sleep, lasting 0.5 to 5.0 seconds, with an intermovement interval of 5 to 90 seconds. Patients were labeled as having periodic leg movements in sleep syndrome when the number of periodic limb movements per hour of sleep was greater than 5 per hour. Using these criteria, we confirmed that none of the subjects in this study had either an RDI of 18 or greater or periodic leg movements in sleep syndrome.

**Data Analysis**

The dynamic aspects of sleep are composed of probabilities of sequential transitions of sleep stages and statistical distributions of duration of each stage. These 2 features are considered sufficient in describing the “path” to specific episodes that might lead to, for example, poor sleep quality, and are useful in studying underlying mechanisms responsible for their occurrences.

We used normalized transitions to characterize sleep-stage transitions. Each normalized transition probability between wake, rapid eye movement (REM), S1, stage 2 (S2), and SWS (stages 3 and 4) was calculated by dividing the number of transitions from a specific stage to one of the other stages by the total number of the transitions from that specific stage to another stage. For instance, when calculating the normalized probability of transition from S1 to S2, we divided the number of transitions from S1 to S2 by the sum of the number of transitions from S1 to wake, those from S1 to S2, those from S1 to SWS, and those from S1 to REM, and multiplied it by 100. In our previous paper,\textsuperscript{25} we used both global and normalized transition probabilities; the global transition probability was calculated by dividing the number of transitions between stages by the total number of all transitions. As this global probability can be obtained by calculating the product of the normalized transition probability and the number of continuous runs for each sleep stage (i.e., 1 of the traditional descriptive statistics), probabilities of global transitions will not be reported in this paper. In fact, results with global-transition probabilities were qualitatively the same as...
those with normalized data except for 1 occasion, which we do cite because the difference seemed to have an important implication. The mean ± SD of the number of continuous runs of each sleep stage analyzed per subject and group is shown in Table 1.

Normalization sometimes makes it difficult to interpret the results, mostly because the probability does not provide information about the number of transitions. In the present paper, we supplied the “transition rate” per minute, which was calculated by dividing the number of transitions between sleep stages by the total duration (minutes) of the origin stage of that transition, to complement the interpretation of the result of differences between groups.

Our previous paper reported that duration distributions take a different form for each sleep stage: duration distributions for S1 and REM sleep follow an exponential function \( p(t) \sim e^{-t/\tau} \), where the \( p(t) \) is a probability distribution of durations \( t \) of a stage and the \( \tau \) is a constant (i.e., linear on the log-lin plots); duration distributions for S2 sleep follow a stretched exponential function \( p(t) \sim e^{-t/\tau^\beta} \), where \( \beta \) is a constant (i.e., linear on the log-log-log plots); and duration distributions for wake and SWS follow a power-law \( p(t) \sim t^{-\alpha} \), where the \( \alpha \) is a constant (i.e., linear on the log-log plots). Longer durations, that is, heavy-tailed distributions, we also used the Kolmogorov-Smirnov test. Differences of duration distributions for each sleep stage were assessed using Kolmogorov-Smirnov tests, with statistical significance level adjusted using Bonferroni corrections. To assess interindividual differences in distributions, we used the Kolmogorov-Smirnov test for all the pairs of individuals. Statistical significance was accepted when \( P \) was less than 0.05.

Results

Descriptive Statistics of Traditional Sleep Variables

Comparisons of traditional sleep variables among the 3 groups (healthy control subjects, CFS alone, and CFS+FM) are shown in Table 2. Total sleep time and total duration of REM sleep were significantly longer in healthy control subjects than in subjects with CFS alone. Total durations of S1 and S2 were significantly longer in healthy control subjects than in subjects with CFS+FM, and, conversely, the total duration of SWS was significantly longer in subjects with CFS+FM than in healthy control subjects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy</th>
<th>CFS alone</th>
<th>CFS+FM</th>
<th>Tukey-Kramer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>26</td>
<td>14</td>
<td>12</td>
<td>n.s.</td>
</tr>
<tr>
<td>Time in bed (min)</td>
<td>453.0 ± 32.5</td>
<td>440.0 ± 40.0</td>
<td>435.9 ± 46.4</td>
<td>Healthy &gt; CFS alone (*)</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>385.0 ± 38.1</td>
<td>345.9 ± 60.1</td>
<td>357.6 ± 49.0</td>
<td>Healthy &gt; CFS alone (*)</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>85.1 ± 8.2</td>
<td>78.4 ± 10.2</td>
<td>82.3 ± 9.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Wakefulness (min)</td>
<td>51.7 ± 38.3</td>
<td>63.0 ± 27.1</td>
<td>58.7 ± 39.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>S1 (min)</td>
<td>44.8 ± 18.7</td>
<td>38.3 ± 20.3</td>
<td>27.3 ± 10.5</td>
<td>Healthy &gt; CFS+FM (*)</td>
</tr>
<tr>
<td>S2 (min)</td>
<td>222.4 ± 34.5</td>
<td>203.4 ± 35.1</td>
<td>191.2 ± 30.4</td>
<td>Healthy &gt; CFS+FM (*)</td>
</tr>
<tr>
<td>SWS (min)</td>
<td>35.0 ± 26.2</td>
<td>44.6 ± 34.5</td>
<td>68.9 ± 28.1</td>
<td>CFS+FM &gt; Healthy (*)</td>
</tr>
<tr>
<td>REM sleep (min)</td>
<td>82.8 ± 24.2</td>
<td>59.6 ± 22.2</td>
<td>68.7 ± 30.0</td>
<td>Healthy &gt; CFS alone (*)</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>16.3 ± 18.6</td>
<td>31.2 ± 27.3</td>
<td>19.5 ± 24.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>107.3 ± 49.1</td>
<td>149.2 ± 76.5</td>
<td>101.3 ± 37.3</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Values of traditional sleep variables for healthy controls, CFS alone, CFS+FM are presented as means ± SD.

*P < 0.05 by Tukey-Kramer procedure for multiple comparisons.
Although the normalized transition probability from S2 to SWS (S2 → SWS) did not differ significantly between subjects with CFS+FM and control subjects, a significant increase in the global-transition probability was found (12.4% for control subjects and 18.5% for subjects with CFS+FM; \( P < 0.05 \)); these results indicate that the CFS+FM group shows a tendency for higher likelihood of transitions from S2 to SWS (S2 → SWS) than does the control group.

The actual rates of transition between stages are shown in Figure 2 and indicate that subjects with CFS+FM had an increased rate of transition from wake/S1 to deeper sleep and a decreased rate of transition from REM to S1; these results suggest that sleep pressure is greater in subjects with CFS+FM than in normal control subjects and those with CFS alone.

Although subjects with CFS+FM showed less total S2 sleep than did the healthy control subjects or those with CFS alone, neither the actual rate of transitions (Figure 2) nor the normalized probability of transition (Figure 1) out of S2 was significantly altered; this result suggests that the reduction in total duration of S2 is not abnormal and may simply be a consequence of the increased amount of SWS.

Given the greater total time in SWS in subjects with CFS+FM, it is noteworthy that transition probabilities from SWS to wake (SWS → W) did not differ significantly between subjects with CFS+FM and control subjects, a significant increase in the global-transition probability was found (12.4% for control subjects and 18.5% for subjects with CFS+FM; \( P < 0.05 \)); these results indicate that the CFS+FM group shows a tendency for higher likelihood of transitions from S2 to SWS (S2 → SWS) than does the control group.

Figure 1—Normalized transition probabilities between wake (W), rapid eye movement sleep (R), stage 1 sleep (S1), stage 2 sleep (S2), and slow-wave sleep (SWS) for healthy control subjects (white), those with chronic fatigue syndrome (CFS) alone (gray), and subjects with CFS+fibromyalgia (FM) (black). **\( P < 0.01 \) and *\( P < 0.05 \) by Mann-Whitney \( U \) test with Bonferroni corrections.

Transition Probabilities
Normalized probabilities of transitions among the 5 sleep stages (wake, REM, S1, S2, and SWS) of healthy control subjects, those with CFS alone and those with CFS+FM are shown in Figure 1.

Transitions that were greater for healthy control subjects
Both transition probabilities from S1 to REM sleep (S1 → R) and REM sleep to S1 (R → S1) were significantly greater for healthy control subjects than for those with CFS alone or for subjects with CFS+FM.

Transitions that were greater for subjects with CFS alone
The transition probability from REM sleep to wake (R → W) was significantly greater for subjects with CFS alone than for healthy control subjects.

Transitions that differed for subjects with CFS+FM
Several of the transition probabilities for CFS+FM suggested increased sleep pressure and supported the finding of increased total time in SWS found in subjects with CFS+FM: (1) the transition probability from wake to S2 (W → S2) was significantly greater for subjects with CFS+FM than for healthy control subjects or for those with CFS alone, with an almost commensurate decrease in the transition probability from wake to S1, and (2) transition probabilities from S1 to S2 (S1 → S2) and REM sleep to S2 (R → S2) for subjects with CFS+FM were significantly increased compared with those of healthy control subjects.

Although the normalized transition probability from S2 to SWS (S2 → SWS) did not differ significantly between subjects with CFS+FM and control subjects, a significant increase in the global-transition probability was found (12.4% for control subjects and 18.5% for subjects with CFS+FM; \( P < 0.05 \)); these results indicate that the CFS+FM group shows a tendency for higher likelihood of transitions from S2 to SWS (S2 → SWS) than does the control group.

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Given the greater total time in SWS in subjects with CFS+FM, it is noteworthy that transition probabilities from SWS to wake (SWS → W) did not differ significantly between subjects with CFS+FM and control subjects, a significant increase in the global-transition probability was found (12.4% for control subjects and 18.5% for subjects with CFS+FM; \( P < 0.05 \)); these results indicate that the CFS+FM group shows a tendency for higher likelihood of transitions from S2 to SWS (S2 → SWS) than does the control group.

Figure 1—Normalized transition probabilities between wake (W), rapid eye movement sleep (R), stage 1 sleep (S1), stage 2 sleep (S2), and slow-wave sleep (SWS) for healthy control subjects (white), those with chronic fatigue syndrome (CFS) alone (gray), and subjects with CFS+fibromyalgia (FM) (black). **\( P < 0.01 \) and *\( P < 0.05 \) by Mann-Whitney \( U \) test with Bonferroni corrections.
For healthy control subjects, those with CFS alone and the subjects with CFS+FM, the probability densities for each sleep-stage duration exhibited the expected stage-specific behavior, as we previously have reported. Duration distributions for wake and SWS followed a power-law (i.e., linear on the log-log plots; Figure 3A, D, insets); duration distributions for S1 and REM sleep followed an exponential function (i.e., linear on the log-lin plots; Figure 3B, E, insets); and those for S2 sleep obeyed a power-law function.

The percentage of individual pairs for which the null hypothesis is rejected for each stage for healthy controls, CFS alone and CFS+FM.

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Figure 3—Cumulative distributions for durations of sequential runs for wake and slow-wave sleep (SWS) in double logarithmic plots (A and D), and stage 1 sleep (S1), stage 2 sleep (S2), and rapid eye movement sleep (REM) in semilogarithmic plot (B, C, and E) for healthy control subjects (●), subjects with chronic fatigue syndrome (CFS) alone (▲), and those with CFS+ fibromyalgia (FM) (×). Insets: Distributions for durations of sequential runs for wake and SWS in double logarithmic plot (A and D), S1 and REM sleep in semilogarithmic plot (B and C), and S2 in log-log plot (E) for healthy control subjects (●), those with CFS alone (▲), and subjects with CFS+FM (×). Cumulative duration distributions for S2 sleep are presented not in log-log but in log-lin axis because cumulative distribution of stretched exponential function does not follow a straight line in log-log axis. **P < 0.01 and *P < 0.05 by Kolmogorov-Smirnov test with Bonferroni corrections.
previously performed. Illnesses with symptoms that often coexist—have not been compared with healthy control subjects, and studies comparing CFS and FM—have not shown consistency among patients with CFS, patients with FM, and control subjects, and studies comparing CFS and FM—illnesses with symptoms that often coexist—have not been previously performed.

**DISCUSSION**

Conventional methods to characterize human sleep have used simple descriptive statistics of traditional (static) sleep variables. However, those indexes have not shown consistency among patients with CFS, patients with FM and control subjects, and studies comparing CFS and FM—illnesses with symptoms that often coexist—have not been previously performed.

In the present study, we did find some differences between illness groups and control subjects: specifically, the total duration of REM sleep was shorter in subjects with CFS alone than in healthy control subjects. Also, total durations of S1 and of S2 were shorter and, commensurately, that of SWS was longer in patients with CFS+FM than in healthy control subjects. These results might lead to the surprising conclusion that sleep quality in patients with CFS+FM is better than that in healthy control subjects, which is not consistent with the common complaint of patients with CFS+FM of “unrefreshing sleep.” An alternate explanation would be that the increase in deep sleep in patients with CFS+FM may be a response to some process that is generating a greater need to sleep in people with CFS+FM. These changes were not seen in patients with CFS alone.

In addition, our transition analysis of sleep stages and duration distributions for each sleep stage revealed striking differences between patients with CFS alone compared with those with CFS+FM. Figure 4 shows a way of depicting the normalized probability of transitions occurring from each sleep state to all of the other sleep states for the 3 study groups—those with CFS only, those with CFS+FM, and healthy control subjects. The thickness of the arrow represents the probability of that particular transition; the legend provides information to the reader as to significant differences. This analysis showed that subjects with CFS alone (open arrow) had a greater probability of transitioning from REM to wake (R → W) than did healthy control subjects. We have previously reported this sleep disruption as the specific sleep problem for CFS alone. We interpret this result to mean that patients with CFS alone have reduced sleep pressure. Supporting this interpretation is a response...
port that sleep latency of patients with CFS is not shortened by sleep deprivation.36

In contrast, patients with CFS+FM (closed arrows) have higher probabilities of having transitions from waking, REM, and S1 to S2 (W/R/S1 → S2) than do healthy control subjects. Transitions from waking and REM to S2 occur only rarely in healthy humans.25 Thus, the pattern of transition probabilities suggests increased sleep pressure in patients with CFS+FM, and this interpretation was supported by increased rates of those transitions in patients with CFS+FM relative to control subjects. In addition, patients with CFS+FM had greater probabilities of having transitions from SWS to waking and S1 (SWS → W/S1); although this may have been due to the increase in total time spent in SWS, it may also reflect sleep disruption or a specific sleep problem. The latter interpretation was supported by increased rates of those transitions in patients with CFS+FM and is consistent with an earlier report showing that disruption of SWS in healthy control subjects results in feeling “unrefreshed” after awakening and the appearance of FM-like symptoms, such as reduced pain thresholds and subjective reports of musculoskeletal symptoms.37 The combination of increased sleep pressure and sleep disruption leads us to hypothesize that patients with CFS+FM may have a pathologic need for increased sleep as well as an intrinsic sleep-disrupting process.

One prior study investigated the dynamic aspects of sleep in patients with FM. Burns et al.38 studied duration distributions of patients with FM and, similar to our data in patients with CFS+FM, found that durations of S2 were shorter in patients with FM than in healthy control subjects. In contrast to our data, these authors did not find an increase in SWS duration. Although the earlier study provided no information as to whether these findings are specific to patients with FM or are shared with patients with CFS, we found the differences to be specific to patients with CFS+FM and not occurring in patients with CFS alone. Specifically, distributions of durations of S2 in patients with CFS+FM were significantly different from those in healthy control subjects and in patients with CFS alone—being shorter in patients with CFS+FM than in healthy control subjects and in patients with CFS alone (duration t < 25 min).

One explanation for this finding may be an impairment in the thalamocortical mechanism for generating sleep spindles in patients with FM, seen characteristically in S2—an effect that could lead to altered sensory processing and vulnerability to external stimuli. Data exist showing that sleep in individuals who generate more sleep spindles is more stable and more resistant to disruptive stimuli.39 Moreover, earlier work reported sleep-spindle density and power to be decreased in patients with FM.40 It is possible that the increase in SWS shown by patients with CFS+FM, which suggests an increased sleep pressure, is, in fact, a result of the decrease in stability of S2. Further research will be needed to confirm this notion and the idea that the thalamocortical mechanism responsible for generating sleep spindles is dysfunctional in patients with FM but not in those with CFS.

For the duration distributions for S2 sleep, the stretching exponent β was estimated at approximately 0.4 for all groups, which is consistent with our previous result25 but somewhat different from the result of Burns et al.38 The stretching exponent β ranges between 0 and 1, where the power-law function is the special case β → 0 and the exponential function is the special case β = 1.35 Therefore, the result of β = 0.4 obtained in this study suggests that the functional form of duration distributions for S2 sleep is different from the simple exponential distribution; this result suggests a multifactorial decay for survival times of S2 sleep durations.35

The tendency for patients with CFS+FM to have a higher probability of having transitions from S2 to SWS (S2 → SWS), as compared with control subjects, is of interest in view of our earlier finding that a central serotonergic and dopaminergic antagonist significantly increases the probability of this transition.41 Therefore, finding such increased transitions might indicate downregulation of central serotonergic systems that, importantly, has been reported in patients with FM.32–43 It is possible, therefore, that the tendency for an increased probability of transitions from S2 to SWS occurring (S2 → SWS) might also be a specific feature for FM. We plan to further evaluate this idea in future research.

One limitation of our work was related to the necessity of pooling the duration-distribution data of all subjects in each group, due to limited sample size at each sleep stage for any given subject. Using such a group analysis means that we are not able to use duration distributions to define norms for clinical application at this time. We are currently working on statistical sampling methods to deal with this problem; another possibility might be to collect data on multiple sleep nights for individual subjects.

Another possible limitation is related to our studying subjects on their first night in the sleep laboratory. If differences in rates of habituation to being in a sleep lab existed among the 3 study groups, that might have had an impact on our results. Our use of 30-second sleep-stage scoring in accordance with Rechtschaffen and Kales criteria is another possible limitation. Although the advantage of doing this is that this scoring regimen is widely and easily applicable to existing sleep-stage data, the time resolution is probably not good enough to capture fine microstructural changes of sleep, such as arousals, K-alpha complexes, and the cyclic alternating pattern. A previous study reported an increase in the cyclic alternating pattern rate, a condition of sleep instability, in patients with FM, with a strong correlation with the severity of clinical symptoms.16 Also, the total number of continuous runs of each sleep stage—that is, the data length—of the subjects studied here might not have been long enough to reliably estimate the transition-probability matrix, given the results of the previous computational study.47

Finally, another limitation has to do with our studying sub-
jects with clinical criteria, leading to a clinically heterogeneous population. We have tried to reduce heterogeneity by studying women only at a fixed time in their menstrual cycle and who did not have evidence of major depressive disorder. These choices obviously limit the generalizability of the data presented. We have also tried to control for pain by further stratifying the sample into those with CFS alone and those with CFS+FM. Despite these efforts, however, it is possible that differences in symptom severity might still be playing a role in producing the differences we found between CFS subgroups.

In conclusion, we have clearly demonstrated that dynamic transition statistics differentiate patients with CFS alone from...
those with CFS+FM. The fact that the coexistence of FM alters the dynamic sleep-stage transitions of patients with CFS suggests that CFS and FM may have different pathophysiologic underpinnings associated with different aspects of sleep regulation. Despite the differences, however, both sets of abnormalities could lead to unrefreshing sleep. Improving sleep quality would be quite important for the patients with FM, particularly because it appears they need more delta sleep. Patients with CFS, on the other hand, require treatments to increase sleep pressure or tactics to maintain REM sleep. We believe that the data reported here could lead to targeted sleep treatments that depend on the specific symptom-based diagnosis for any individual patient.

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