INTRODUCTION

WHILE BOTH NONPHARMACOLOGIC AND MEDICATION THERAPIES HAVE BEEN DEVELOPED FOR THE MANAGEMENT OF PERSISTENT PRIMARY INSOMNIA (PPI), these treatments are associated with significant limitations. An important factor limiting the development of improved treatments for PPI is that the pathophysiology remains unknown. As a result, it has not been possible to develop treatments targeted to the specific physiologic abnormality responsible for the sleep complaints in PPI. The standard for studying the physiology of sleep has long been the polysomnogram (PSG). Since the 1960s, PSG has been applied to study insomnia. A number of studies have found evidence for a difference in the PSG between PPI subjects and those without a sleep complaint; however, many studies have not found any difference in the PSG. Overall the evidence suggests that many people with PPI appear to have sleep complaints in the absence of any PSG deviation from normal that might account for their sleep disturbance (subjective insomnia sufferers). This has been referred to as a split between objective (PSG) and subjective (complaints) indicators of sleep disturbance and may reflect heightened arousal during sleep. These differences are reflected in the diagnostic schema of the ASDA which includes 3 subtypes of PPI in the International Classification of Sleep Disorders (ICSD). These include 2 diagnostic entities: psychophysio logic insomnia and idiopathic insomnia, which are associated with PSG abnormalities, and a third, sleep-state misperception, which is characterized by a normal PSG.

This subtyping has been controversial primarily because of concerns about the sleep-state-misperception criteria in the ICSD. It has been argued that the sleep-state-misperception criteria would include fewer than 5% of PPI patients and that sleep-time misperceptions are too universal in PPI to serve as a basis for subtyping, such that those diagnosed with sleep-state misperception would simply be at the end of a meaningless continuum.

Despite these criticisms, a number of studies have been carried out that sub-categorize PPI patients on the basis of the ICSD schema or other strategies, based on whether there are PSG deviations from normal controls. Although these studies do not resolve the issue of how to optimally categorize PPI patients, they indicate that the prevalence of those with PSG deviations from normal controls in the PPI population is 15% to 50%. Several problems plague any attempt to develop a criterion for PSG normality. One is that individuals may differ in the degree of objective sleep disturbance that they must sustain before they will complain about their sleep. This makes it more difficult to determine a PSG difference between noncomplaining individuals and PPI patients. Another is the well-known fact that sleep requirements vary a great deal across individuals, and there is presently no way to assess these differences accurately.

Despite these difficulties, there is evidence that PSG measures do appear to deviate from normals in some individuals with PPI, suggesting that a PSG deviation either explains or is associated with insomnia complaints in a subset of those with PPI. For the remainder of those with PPI, the conventionally scored PSG provides no physiologic explanation for the sleep difficulties. It would be expected that their complaints will relate more strongly to factors other than traditional PSG measures. A number of studies have been carried out examining the physiology...
of PPI using measures other than traditional PSG measures. These studies suggest that PPI patients may have physiologic evidence of hyperarousal and a hypermetabolic state. Several studies indicate that PPI sufferers have greater body temperature, body movements, heart rate, basal skin resistance, 24-hour urinary cortisol and catecholamine metabolites, anxiety levels, metabolic rate, and sleep-onset latencies (SOL) on the multiple sleep latency test (MSLT). Thus, further, there is some preliminary evidence that the apparent hyperarousal is not a secondary effect of sleep disruption or deprivation but appears to reflect a primary central nervous system hyperarousal. This hyperaroused state seems to characterize PPI subjects with and without PSG abnormality and has been found to relate to sleep complaints in those with normal PSGs. Yet, there are no neurophysiologic alterations that are known to mediate or that reflect the associated sleep complaints.

A number of studies employing sleep EEG spectral analysis have been carried out as a means to study the neurophysiology of PPI in more depth. Three studies have reported evidence of elevated NREM sleep EEG high-frequency activity in PPI compared to normals. These studies examined EEG frequency content in data recorded during NREM sleep after carefully removing segments contaminated with artifacts and arousals.

Merica and Gaillard focused on the sleep-onset period. They noted that 14.7-30 Hz activity recorded from temporal and central EEG leads dropped more slowly and to a lesser extent following sleep onset in 26 individuals with PPI versus 28 normal controls. They also reported that there was less 4 Hz activity in the PPI group. In a subsequent study, this group compared EEG frequency for the first 4 REM and NREM periods in 19 PPI and 20 control subjects. They found lower activity for all frequencies below 14.75 Hz and found greater 14.75-30 Hz activity in NREM sleep in the PPI group.

A study by Perlis and coworkers compared 9 PPI subjects with 9 controls and 9 with major depression. They analyzed data from the first 3 NREM periods and found evidence for greater relative power (power within a frequency band divided by the sum of power in all bands) of high-frequency activity (14-45 Hz) in the PPI group than the other two groups.

Whereas these studies are suggestive of greater high-frequency EEG activity in NREM sleep in PPI compared with normal controls, one study only found greater high-frequency EEG activity in the sleep-onset period and another did not find elevated high-frequency activity in NREM sleep in PPI compared with controls. Like Merica and Gaillard, Freedman studied insomnia sufferers with sleep-onset difficulties and found greater high-frequency activity (18-30 Hz) during waking and stage 1 patients in PPI but did not find any differences from normals in Stage 2 or SWS. A study by Nofzinger and colleagues indicated that there was no difference in high-frequency NREM EEG activity between 15 PPI subjects and 15 controls but found greater 0.5-8 Hz activity in the PPI group.

Thus, elevated higher-frequency activity was reported in the NREM sleep EEG in PPI in 3 of 5 studies. Diminished low-frequency EEG content in PPI was also reported in several studies. Methodologic differences exist between these studies, such as the use of relative versus absolute power, recording from different locations, different criteria for subject selection, and the use of data from portions of the night versus the whole night which may account for some of the difference. We hypothesize that, while these aspects of methodology contribute to the differences in results, the factor most responsible for the inability to consistently find greater high-frequency EEG content in PPI is that alterations in NREM EEG frequency spectra are present only for the subjective subgroup of patients with primary insomnia.

We formulated this hypothesis based on evidence that the observed alterations in NREM frequency content (diminished low-frequency and elevated high-frequency activity) are associated with relatively elevated regional brain activity during NREM sleep that would be expected to lead to relatively heightened awareness during NREM sleep. Also, studies in both humans and animals provide a basis for the idea that EEG frequency content might be a useful measure of the degree of arousal. Brainstem reticular electrical stimulation leads to behavioral arousal in animals, which is accompanied by the appearance of fast rhythms in the EEG. Also, recordings from many cortical regions have demonstrated an increase in higher frequency content in conditions of increased alertness. These observations led us to hypothesize that altered NREM EEG spectral content might be a physiologic correlate for the sleep complaints of those with PPI who do not have a deviation evident in the PSG from that of normal subjects, which includes those with a "misperception" of wakefulness with respect to traditional PSG indexes.

We sought to test these hypotheses by studying the relationship of NREM frequency spectral indexes with the degree of underestimation of sleep time and by comparing these indexes in normal controls and a group of PPI patients classified into subjective and objective subtypes. This classification was intended to generate a group of subjects with subjective insomnia who had "normal" PSGs according to traditional scoring methodology and who, therefore, did not have a traditional PSG basis for their sleep complaints. We determined whether the subjective-insomnia sufferers had elevated high frequency and diminished low-frequency NREM EEG spectral activity compared with the other groups and whether such alterations were associated with the sleep complaints. Because of the controversy associated with classifying subjects in this manner and the absence of a currently accepted standard for how to define a "normal" PSG, we carried out an analysis to determine how robust the results were to changes in the categorization criteria.

**METHODS**

**Subjects**

Subjects with PPI. Subjects with insomnia were a subset of those involved in a double-blind, placebo-controlled study of the efficacy of cognitive behavioral therapy. The 30 subjects included in the present study were those for whom PSG data was suitable for computer spectral analysis.

Subjects were 40 to 80 years old with primary sleep-maintenance insomnia who were thoroughly screened via structured psychiatric and sleep interviews, 1 night of ambulatory PSG, medical examination, thyroid testing, and sleep-log monitoring. This age range is wider than that used in prior studies of sleep EEG frequency spectral content in PPI. While this might lead to different results than those previously reported, it also enhanced our ability to study the effects of age on sleep EEG spectral content and differences found in subtypes of PPI. All subjects (1) met diagnostic criteria for PPI (2) had fewer than 15 apneas or hypopneas or periodic limb movement-related arousals per hour of sleep (these limits were based on our prior work with subjects in this age range), (3) had no significant medical disorder that confounded their sleep and (4) had a mean WASO > 60 minutes per night during 1 week of screening with sleep-log monitoring. The PPI subjects had a mean age of 54.9 (SD=10.4) and comprised 18 women and 12 men.

Subjects with sleep-maintenance insomnia were studied rather than those with sleep-onset problems because the analysis of EEG data around sleep onset is problematic because of the extreme variability of the EEG in drowsiness, the presence of slow-eye movements, and the absence of artifact-free, waking, eyes-closed, nondrowsy data in a large number of subjects.

**Normal controls.** The normal controls were 20 subjects from a prior study of a comparison of sleep at home versus in the lab. Like the insomnia subjects, the controls were 40 to 80 years of age and were thoroughly screened via structured psychiatric and sleep interviews, medical examination, thyroid testing and sleep-log monitoring. Individuals were excluded if they had a medical illness affecting sleep, a psychiatric illness, substance abuse, and PSG evidence of more than 15
Table 1—Subject Characteristics by Group

<table>
<thead>
<tr>
<th></th>
<th>Normals (N=20)</th>
<th>Subjective Insomnia (N=12)</th>
<th>Objective Insomnia (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53.5 (10.4)</td>
<td>56.1 (11.7)</td>
<td>54.3 (9.9)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>12/8</td>
<td>8/4</td>
<td>11/7</td>
</tr>
<tr>
<td>BDI score</td>
<td>4.8 (4.1)</td>
<td>5.3 (2.6)</td>
<td>4.8 (3.4)</td>
</tr>
<tr>
<td>STAI score</td>
<td>30.5 (7.1)</td>
<td>34.5 (9.6)</td>
<td>33.9 (7.7)</td>
</tr>
<tr>
<td>PPI duration (years)</td>
<td>-</td>
<td>12.6 (7.8)</td>
<td>16.2 (14.4)</td>
</tr>
<tr>
<td>Onset latency (min)</td>
<td>15.9 (16.7)</td>
<td>11.6 (5.9)</td>
<td>19.5 (15.0)</td>
</tr>
<tr>
<td>TST (min)</td>
<td>* 394.8 (47.0)</td>
<td># 427.7 (51.4)</td>
<td>+ 303.8 (56.4)</td>
</tr>
<tr>
<td>WASO (min)</td>
<td>* 45.4 (31.0)</td>
<td>* 67.9 (40.9)</td>
<td>+ 114.8 (43.8)</td>
</tr>
<tr>
<td>SE%</td>
<td>* 88.1 (5.8)</td>
<td># 85.3 (6.7)</td>
<td>+ 68.8 (10.6)</td>
</tr>
<tr>
<td>Stage 1 time (min)</td>
<td>17.8 (16.5)</td>
<td>25.8 (17.3)</td>
<td>18.1 (10.0)</td>
</tr>
<tr>
<td>Stage 2 time (min)</td>
<td>+ 209.6 (43.1)</td>
<td># 205.8 (36.6)</td>
<td>+ 145.9 (28.8)</td>
</tr>
<tr>
<td>SWS time (min)</td>
<td># 83.1 (30.4)</td>
<td># 84.1 (39.3)</td>
<td>+ 77.1 (22.7)</td>
</tr>
<tr>
<td>REM time (min)</td>
<td>+ 84.3 (20.8)</td>
<td>&amp; # 112.1 (35.9)</td>
<td>+ 62.7 (214)</td>
</tr>
<tr>
<td>%TST underestimate</td>
<td>* -4.3 (9.4)</td>
<td># 15.0 (22.2)</td>
<td>+ 7.5 (28.4)</td>
</tr>
</tbody>
</table>

* indicates significant difference between the 3 groups (p<.05).
& indicates significant difference between normal and subjective insomnia subjects (p<.05).
# indicates significant difference between normal and objective insomnia subjects (p<.05).
+ indicates significant difference between objective and subjective insomnia subjects (p<.05).

Standard deviations appear in parentheses

BDI= Beck Depression Inventory; STAI=State-Trait Anxiety Inventory.

Note: %TST Underestimate = The percentage difference between PSG TST and Sleep Log TST estimates for the same night.

Criterion for Subtyping Subjects

The criteria employed for subgrouping PPI subjects were those employed in a prior study in which subjective sleep ratings were compared with objective PSG measures of sleep.18 The goal was to identify a subset of the insomnia subjects who had sleep complaints for which there was no evidence for a basis for these complaints in the traditionally scored PSG. Defining criteria for PSG normality with which to group subjects is hindered by the fact that there are no agreed-upon criteria for PSG normality and there is individual variability in sleep requirements; however, we developed criteria to define a subgroup wherein, on the average, the PSG would not be expected to be associated with sleep complaints.18,44,45 Due to the lack of definitive criteria, we also carried out an analysis to determine how robust the results were to changes in these criteria for differentiating the subjects.

Because prior work indicates that the 3 criterion below tend to identify subjects with an absence of sleep complaints,18,44,45 we defined a PSG as “normal” when any one of the following 3 findings were true:

1. TST >= 6.5 hours
2. Age < 60 and TST from 6-6.5 hours and SE% > 85%;
3. Age >= 60 and TST from 6-6.5 hours and SE% > 80%

On this basis, PPI subjects were classified as follows:

1. Subjective insomnia (N=12): Met PPI criteria and had a normal single night PSG
2. Objective insomnia (N=18): Met PPI criteria and had an abnormal single-night PSG

The normals (N=20) were identified from a separate population who were without sleep complaints.18 Because it was our intent to employ a control group that could clearly be characterized as both free of sleep complaints and having a “normal” PSG, we also required the normal subjects to meet the above PSG normality criteria based on an average of data from 6 nights (3 home and 3 in lab studies).18 The demographic characteristics and traditional PSG indexes for the 3 subject groups appear in Table 1. There were no significant differences between these groups in terms of age, sex, duration of insomnia, depression symptoms as assessed with the Beck Depression Inventory (BDI) (see below), or anxiety symptoms assessed with the State-Trait Anxiety Inventory (STAI) (see below). As expected, based on the classification criteria employed, the objective-insomnia group had significantly less TST (F=27.2, p<.0001), SE (F=32.4, p<.0001), Stage 2 sleep (F=19.1, p<.0001), and REM sleep (F=15.3, p<.0001) and greater WASO (F=17.2, p<.0001) than the normals and patients with subjective insomnia. Also, as an indication that the criteria employed achieved the desired aim, the patients with subjective insomnia had a greater percentage subjective underestimation of TST compared with PSG TST (both pertaining to the same night) than did the patients with objective insomnia and normal subjects (F=3.8, P<.03; mean % underestimation of TST for the 3 groups: subjective insomnia, 15.0%; objective insomnia, -7.5%; normals, -4.3% ) (see Table 1).

Polysomnography

The controls underwent 6 PSGs (3 at home and 3 in the lab with order randomized) and their first study carried out at home was used in analysis.18 Those with PPI underwent a single night of ambulatory PSG in their homes.3 PSGs were performed using a standard monitoring montage including 2 EEG channels (C3—A2, Oz—Cz), 1 chin EMG channel, 2 channels of EOG (left eye—A1, right eye—A2), 1 channel of airflow (nasal-oral thermistor), and 2 channels of anterior tibialis EMG (right and left legs). All were conducted using Oxford 9000 series recorders (Oxford Medical, Inc., Tampa, FL).57,58 Comparisons of subjective and PSG assessments of sleep always involved the subjective ratings made for the single night for which PSG data was included in analysis.

The EEG data were digitized at 128 Hz with 8-bit accuracy with filter settings of 0.5 and 64 Hz (with -3 dB roll off at both ends and a 3rd order Butterworth anti-aliasing filter at 64 Hz) using an Oxford Vision System (Oxford Instruments Inc., Oxford, UK). The digitized data were scored, blind to subject group, in 30-second epochs by ADK, an experienced, board-certified polysomnographer using standard scoring criteria.59 Standard methods were also used to identify apneas, hypopneas, and periodic limb movements, which were utilized to determine whether subjects qualified to participate.50,52 The results of this scoring was used to determine whether each subject met criterion for PSG normality and to generate indexes that were used in analysis TST, WASO, SOL, SE(100.x total sleep time/time in bed), number of awakenings, number of arousals, and the time spent in each sleep stage. Fourteen PSGs (13 subjects) were excluded from analysis because of the absence of calibration data (N=2) or pervasive artifacts in the C3—A2 lead, which did not preclude traditional PSG scoring but would have led to spurious calculation of frequency spectra.

EEG Analysis

A single C3—A2 (left central to right mastoid) channel was used for spectral analysis. Epochs were only included in spectral analysis if they

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were free of movements (other than eye movements in REM), artifacts, arousals, or transitions between sleep stages. Selection of these “uncontaminated” epochs was carried out by ADK in all cases and allowed us to determine the frequency content of each of the sleep stages without influence of arousals, transitions, and contamination by artifacts. Because of a report of elevated high-frequency and diminished low-frequency spectral content during REM in PPI subjects compared to controls, we studied REM sleep as well as NREM sleep. As described above, it was not possible to carry out analysis of data from waking and Stage 1 sleep because of the relative lack of artifact-free data from these periods. Because this was the first time this type of analysis has been performed, we also analyzed the NREM data separated into Stage 2 and slow-wave sleep (SWS). We found the same results for Stage 2 and SWS as for NREM and, therefore, only NREM results are reported below.

These data underwent autoregressive high-pass filtering and Hanning windowing followed by fast Fourier transformation in 2-second epochs, averaging over both time and frequency, yielding spectral estimates in 6 bands: delta (0.5-3.5 Hz), theta (4.0-8.0 Hz), alpha (8.5-12 Hz), sigma (12.5-16 Hz), beta (16.5-30 Hz), and gamma (30.5-60 Hz). This analysis was carried out using custom software written in Visual C++ by ADK, which employed the commercial technical software package, MATLAB (The MathWorks, Inc. Natick MA) for computing fast Fourier transforms. The results of this analysis were verified against results generated by the commercial EEG analysis and acquisition system, EEGRYS (Friends of Medical Science, Inc.). The frequency bands were chosen based on the work of Armitage and coworkers and are comparable to those used by others studying sleep EEG frequency spectra. Both absolute (in µV/Hz) and relative spectral power were computed for each sleep stage over the entire night. Relative spectral power was studied because of its use in prior studies of EEG spectra in PPI and was derived by dividing the power in each band by the sum of the power across all bands. Because activity in more than one frequency band contributes to relative power, absolute power was also employed to aid in the interpretation of results in terms of the contributions of data in each frequency band.

We studied the probability distributions of both the absolute and relative spectral power indexes using the Shapiro-Wilk test. We found that neither the relative nor absolute data approximated the normal distribution, indicating the need for a normalizing transformation. We found that among a number of transforms studied, the distributions of both the absolute and relative power best approximated a normal distribution with a logarithmic transformation as has been previously reported. As a result, the logarithm of the absolute and relative power were utilized in analysis.

**Assessment Tools**

**Sleep History Questionnaire:** A ten-page sleep-history questionnaire was completed by all subjects during screening. This instrument contains questions that elicit demographic information, current and past sleep complaints, medical and psychiatric history, and previous treatment history.

**Sleep Logs:** Subjective estimates of nocturnal sleep were obtained from sleep logs maintained by subjects after arising in the morning for a two-week baseline period. These logs were used to derive the primary subjective measures of sleep used: WASO, TST, SE, sleep quality, and how rested they felt upon arising (quality and restedness were 5-point scales).

**State-Trait Anxiety Inventory:** Because a number of studies have shown that insomniacs display relatively high levels of anxiety, the STAI was administered during screening to assess the level of anxiety.

**Beck Depression Inventory:** Various studies have shown that insomniacs display complaints of mood disturbance in addition to reports of poor sleep. The 21-item BDI was administered during screening to assess mood complaints.
Table 2—Mean and standard deviation of relative spectral power as a function of subject group for NREM Sleep

<table>
<thead>
<tr>
<th>Group</th>
<th>Delta **</th>
<th>Theta</th>
<th>Alpha *</th>
<th>Sigma ****</th>
<th>Beta ***</th>
<th>Gamma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normals</td>
<td>73.6 (6) #</td>
<td>14.1 (2)</td>
<td>6.8 (3)#</td>
<td>3.4 (1.5)##</td>
<td>1.7 (0.6)##</td>
<td>0.40 (0.4)</td>
</tr>
<tr>
<td>Subjects</td>
<td>66.7 (7)</td>
<td>15.8 (3)</td>
<td>9.1 (4)</td>
<td>5.6 (2.4)</td>
<td>2.4 (0.8)</td>
<td>0.41 (0.1)</td>
</tr>
<tr>
<td>Objectives</td>
<td>70.5 (6)#</td>
<td>14.6 (3)</td>
<td>8.0 (3)</td>
<td>4.5 (1.3)##</td>
<td>1.9 (0.7)##</td>
<td>0.43 (0.2)</td>
</tr>
</tbody>
</table>

*p<.10; **p<.05; ***p<.01 difference between the 3 groups;
# p<.10 different than patients with subjective insomnia; ## p<.05, different than patients with subjective insomnia.

Note: Relative power was computed as the power within a frequency band (in µV²/Hz) divided by the power across all frequencies (0.5-60 Hz) (also in µV²/Hz) and is therefore dimensionless. In this table the values are multiplied by 100, indicating the percentage of power in the frequency band of interest.

Statistical Analysis

Analysis was carried out using the SAS statistical software (SAS Institute, Inc. Cary, NC) using two-tailed tests of significance. Age was used as a covariate or included in regression analyses because of evidence that low-frequency EEG spectral amplitude decreases with age. Because sex may affect this phenomenon, such that changes with age have been reported to be more pronounced in men than in women, sex was also included in analyses. All statistical analysis was carried out in two stages with an omnibus, multivariate test employed in the first stage to protect against Type I error with subsequent follow-up testing if significant results were found. The omnibus test was either a multivariate analysis of covariance (MANCOVA) or regression analysis. The regression analyses included multiple dependent variables and because of multicollinearity (all of the spectral indexes were significantly correlated with each other (p<.05), the predictor (independent) variables were added individually to the model using forward selection. Only variables that contributed at least a trend to prediction of the dependent variables were retained.

RESULTS

Differences in Sleep EEG power spectra among subjective insomnia, objective insomnia, and normal subjects

We compared relative spectral power in each frequency band for NREM and REM among subjective insomnia sufferers, objective insomnia sufferers, and normal control subjects. The NREM results appear in Table 2 for relative spectral power. First, MANCOVA was carried out in which subject group (subjective insomnia, vs. objective insomnia, vs. normal) was the independent variable, spectral power measures were the dependent variables, and age and sex served as covariates. This analysis indicated significant effects for subject group (F=5.6, p<.007), the interaction of subject group and sleep stage (F=6.7, p<.003), the interaction of subject group and frequency band (F=2.2, p<.03), and the 3-way interaction among subject group, sleep stage, and frequency band (F=2.5, p<.02).

In order to assess the differences between the subject groups as a function of frequency band and sleep stage, we then carried out profile analysis. Profile analysis is an application of MANCOVA developed to compare the configuration (profile) of multiple assessments in two or more groups of subjects. In this application, the profile of relative spectral power across the 6 bands was compared in the 3 subject groups. This was done separately for REM and NREM data. We found that for NREM sleep the relative spectral amplitude profile differed significantly across the 3 subject groups (F=7.0, p<.003) (see Table 2 and Figure 1). No difference in the REM-sleep frequency spectral profile across groups was found.

This analysis was followed by ANCOVA to delineate the significant effects. We found that for NREM, the patients with subjective insomnia had significantly lower delta relative power than did the normals (F=8.2, p<.003), and there was a trend for lower relative power compared with the patients with objective insomnia (F=3.0, p<.09). Patients with subjective insomnia also had greater NREM relative power than did the normals in the alpha (F=3.3, p<.08), sigma (F=16.3, p<.0007), and beta (F=10.1, p<.007) bands, and greater activity than the patients with objective insomnia in the sigma band (F=3.7, p<.08) and beta band (F=5.1, p<.05). The patients with objective insomnia had significantly greater NREM relative power than did the normals only for the sigma band (F=6.0, p<.03). The NREM relative spectral amplitude profiles for the 3 groups appears in Figure 1.

Analysis of absolute power yielded similar results except that no differences in the delta frequency band were found (see Figure 2).

In terms of covariates, across all subject groups, older age was associated with significantly lower sigma relative power NREM (F=4.1, p<.05) and men had greater NREM Beta relative power (F=5.5, p<.03) than women.

In order to determine how dependent these results were on the particular criteria used to subtype PPI subjects, we repeated this analysis iterating over different classification criteria for NREM relative power indexes (See Table 3). Because the primary measure used to categorize PPI subjects was TST, and because we were interested in the degree of underestimation of sleep, we repeated this analysis over a range of TST cutoffs from 280 to 410 minutes and percent underestimation of sleep from -25% to 25%. Beyond these limits, the number of subjects in one of the groups became unreasonably small. In each case, the objective group was defined as the PPI subjects with TST and percent underestimation of sleep below the cutoff, and the subjective group had TST or percent underestimation of sleep greater than or equal to the threshold.

We found that, over the entire range of TST and percent underestimation of sleep cutoffs studied, the subjective insomnia group had significantly (p<.05) less delta relative power and significantly greater sigma and beta (and at least a trend for alpha except for percent underestimation cutoffs of .20 and .25) relative power than the normal group (See Table 3). For TST, over the range of cutoffs from 290 to 360 minutes, the subjective group had significantly less delta and significantly greater beta relative power than had the objective group and at least a trend for greater sigma power. Significant differences between the objective insomnia group and normals were only present for TST cutoffs over 340 minutes and were limited to the sigma band. For percent underestimation of sleep, over the range of cutoffs from 15% to 5% underestimation, the subjective group had at least a trend for less delta and greater beta relative power than the objective group. Significant differences between the objective insomnia group and normals were present for all percent underestimation cutoffs studied for the Sigma band (See Table 3).

These results indicate that the finding of diminished delta and greater higher-frequency amplitude in patients with subjective insomnia is not limited to the particular criteria that we used to define PSG normality. Further, a TST cutoff of 300 to 370 minutes (the criterion we defined for this study was essentially a TST cutoff of 360 minutes and, therefore, falls in this range) or a percent underestimation of cutoff of -15% to 5% defines a subjective insomnia group with diminished delta and elevated high-frequency relative power compared to both normal and objective insomnia subjects.

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We carried out further analysis to determine if NREM EEG spectral content might be related to the subjective complaints of insomnia in patients with subjective insomnia, and whether this relationship was stronger than in patients with objective insomnia where their complaints...
of insomnia were hypothesized to relate more strongly to their stage-scored PSG aberrations or other factors.

**Relative Spectral Power**—First, multivariate regression analysis was carried out in which subjective sleep-log ratings (TST, sleep quality, restedness, WASO, and SE ratings derived from 2 weeks of sleep logs) served as dependent measures. The independent predictor variables were subject group (normal, subjective insomnia, or objective insomnia), relative spectral power measures, and group by relative spectral power interactions. Age and sex were included as covariates. The BDI score and STAI were also included as covariates because these symptoms have been commonly reported in those with PPI and the possibility that such symptoms might explain the effects.60-66

We found that, for the subjective insomnia group, relative spectral power measures contributed at least a trend for prediction of sleep ratings of quality, restedness, TST, and SE ratings (see Table 4) after controlling for age, sex, BDI, and STAI. For TST, greater relative NREM alpha power was predictive of less TST (R²=0.41, F=6.5, p<.04). Greater NREM delta relative power was associated with higher sleep-quality ratings (R²=0.34, F=5.2, p<.05). There were also trends for greater NREM delta relative power to predict greater Restedness (R²=0.32, F=4.8, p<.10) and SE (R²=0.17, F=3.5, p<.10) ratings. There were no significant relative spectral power relationships found for patients with objective insomnia.

**Traditional PSG Ratings**—This same analysis was repeated using traditional PSG measures as predictor variables. The PSG predictors were TST, WASO, SE, number of awakenings and the amount of stage 1, stage 2, SWS, and REM sleep.

In contrast to the relative spectral power analysis, relationships with sleep ratings were only found for the patients with objective insomnia (see Table 4). In this group, greater PSG-derived TST was positively related to subjective TST ratings (R²=0.30, F=10.3, p<.004). There was also a trend for greater REM time to be negatively related to sleep-log TST ratings (R²=0.11, F=4.3, p<.06). The PSG-derived TST was also a significant predictor of greater sleep-log SE ratings (R²=0.15, F=4.7, p<.05) and a trend for lower sleep-log subjective ratings of WASO (R²=0.13, F=3.5, p<.10).

**Conclusion**

This study provides evidence that diminished delta and greater alpha, sigma, and beta EEG relative spectral power in NREM sleep may be an objective physiologic correlate of subjective sleep complaints in individuals with chronic PPI who have sleep complaints despite conventional PSG measures that do not differ from normal subjects (subjective insomnia subjects). This conclusion is supported in several ways by the present study. Firstly, diminished delta and greater alpha, sigma, and

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**Figure 2**—NREM absolute power profiles. Absolute amplitude is depicted in z-scores, which are the degree of deviation from the mean over all subjects normalized by the standard deviation of all subjects. This figure illustrates that the patients with subjective insomnia have greater alpha, sigma, and beta amplitude compared to the other 2 groups.
beta NREM EEG relative spectral power was seen in patients with subjective insomnia compared to normals and compared to patients with objective insomnia for some indexes. Secondly, diminished delta and greater alpha, sigma, and beta relative spectral power were significantly related to sleep complaints in subjective but not patients with objective insomnia for whom sleep complaints tended to relate to traditional PSG measures. This suggests that not only does altered NREM physiology characterize the subjective subgroup of PPI but that these alterations appear to be related to the sleep complaints of these individuals. The specificity of these findings for subjects who have sleep complaints in the absence of aberrations in their traditionally scored PSG suggests that diminished delta and greater alpha, sigma, and beta relative EEG power in NREM sleep might be related to sleep complaints and also may be associated with a mismatch of sleep complaints and traditional PSG findings that has been described as sleep "misperception." The latter conclusion is further supported by our finding that a greater degree of subjective underestimate of sleep time compared with PSG estimates of sleep were found in those with lower delta NREM relative EEG power.

It is important to note that these findings are not due to micro arousals or movements, which might be manifest as changes in EEG activity in these frequency ranges, because epochs with these events were carefully eliminated from the analysis. Instead, the results point to a specific physiologic difference between subjective insomnia, objective insomnia, and normal subjects that are related to their sleep complaints. We now discuss these findings in greater depth.

**Differences in Sleep EEG Spectral Content Among Subjective Insomnia, Objective Insomnia, and Normal Subjects**

The finding of greater NREM EEG sigma and beta in patients with subjective insomnia is in agreement with prior reports of greater 14.7-30 Hz and 14-45 Hz NREM EEG activity in chronic insomnia patients compared with normals except that we did not find elevated relative power in the greater than 30-Hz range as reported by Perlis et al. The trend we observed for greater NREM Alpha activity in patients with subjective insomnia has not been previously reported. Also, diminished EEG delta relative power in NREM sleep agrees with the report of Merica and coworkers in NREM sleep who found diminished NREM EEG activity in primary insomniacs compared with controls for frequencies below 14 Hz; however, we did not find evidence for diminished theta (4.0-8.0 Hz) or alpha (8.5-12 Hz) activity.

One methodologic difference between our study and those of Merica and colleagues and Perlis and colleagues might account for some of these differences in results is that those studies only computed...
frequency spectra for the first 4 and 3 NREM periods, respectively, whereas we computed spectra over the entire night. Differences in results might be expected on this basis given evidence that NREM EEG spectral content and the degree of differences in spectral content between primary insomnia and control subjects may differ over the course of the night.34,76 Further, there is some evidence that differences between PPI subjects “in general” and normals may be evident in the beta frequency band in EEG data recorded in the period around sleep onset, which was not analyzed in this study because of the relative absence of artifact data from this period.32,35,76 In addition, our study differed from these two previous studies in the limits of the frequency bands employed, which may have also affected the results.

Another methodologic difference is that in our study PSG was carried out in the subjects’ homes, whereas the studies by Perlis and coworkers and Merica and colleagues employed laboratory-based PSG. Our prior work, in which normal subjects and those with insomnia were compared with home and laboratory PSG, indicates that comparisons of sleep between these two groups may yield different results depending on whether PSG is carried out in the home or laboratory.77,78 While these studies suggest that differences between those with insomnia and normal subjects may be greatest when assessed at home, no EEG spectral analysis was carried out, and it remains unknown how the PSG location might have affected the results. A potential advantage of carrying out PSG studies at home in this study is that data from a single night of recording was analyzed, which would be expected to be subject to a first-night effect if performed in the laboratory. While no evidence exists for EEG spectral indexes, our prior work suggests that there does not appear to be a first-night effect in terms of traditional PSG indexes in insomnia or normal subjects when studied at home.77,78

The fact that we did not find elevated activity in subjects with insomnia in the greater-than-30-Hz frequency range (gamma), as has been reported by Perlis and colleagues, may also be due to the methodologic differences described above.34 Another consideration is that the finding of Perlis and colleagues may reflect a greater degree of muscle activity (which characteristically generates a signal in the greater-than-30-Hz frequency range), which could reflect greater somatic arousal in this group.76,79,80 While it is not possible to determine if this is the case, if it is true, we may not have found elevated gamma activity in insomnia subjects because we excluded the data with myogenic artifact or because this activity may be greater in the sleep-onset period studied by Perlis and coworkers.

Our results also differ from those of Merica and coworkers, who reported that those with insomnia had greater high-frequency and diminished low-frequency EEG content in REM sleep compared with controls.34 We did not find a difference in REM spectral activity between the subject groups. While the reason for this difference is unclear, one contributing factor may be that REM EEG spectral content is affected by the artifact produced by rapid eye movements. It is unclear how this artifact may affect the results of the type of analysis carried out in this report, but it would be expected to substantially alter frequency content across many frequency bands because the eye movements tend to have both slow components as well as higher-frequency components deriving from deep rising and falling edges. While further studies are needed to resolve this issue, our study, in contrast to that of Merica and colleagues, suggests that evidence of altered sleep EEG frequency content is restricted to NREM sleep.

Our results also differ from those of several studies that did not find any NREM EEG spectral alterations in those with PPI compared with normals.32,35,36 Evidence from the present study suggests that prior studies did not detect differences between primary insomnia subjects and normals at least in part because they analyzed the data from all of their primary insomnia subjects as a single group whereas we separated our primary insomniacs on the basis of traditionally scored PSG normality. Evidence in support of this conclusion is that we found significantly greater spectral-content differences between normals and patients with subjective insomnia than between normals and those with objective insomnia. Thus, lumping the two groups together might lead to finding no difference between insomnia and control groups. The present study suggests that there is an alteration in NREM sleep physiology that is manifested in EEG frequency content that appears to particularly characterize the subjective subset of primary insomniacs. This conclusion is further supported by our finding that lower delta relative EEG power in NREM sleep was correlated with the degree of disagreement between subjective and objective measures of sleep across all of the subjects in our study. This finding, however, contrasts with the previous report of Perlis and coworkers,34 who found greater high-frequency NREM relative power in those with a greater subjective/objective difference. The methodologic differences between our study and that of Perlis and colleagues, described above, may have led to the differences in results. Also, given that we found significant negative correlation between delta and high-frequency relative power, these seemingly disparate findings may be related.

In this regard, it is important to note how the high correlation among the spectral indexes and the use of the forward-selection procedure may have affected the results of this analysis and the other regression analyses carried out in this study. This approach was conservative in terms of the reporting of results. For example, in cases where several spectral indexes were significant predictors and there was substantial overlap in the variance that they accounted for in the dependent variable (in this case the degree of mismatch), only the variable that accounted for the most variance was entered into the model. As a result, the other highly correlated variables would appear to have no or relatively less relationship with the dependent variable. It is possible that such an effect might have accounted for our not finding larger relationships with particular spectral indices.

The high degree of correlation among the spectral indexes is worthy of further consideration. These findings indicate that the diminished delta and elevated higher frequency NREM relative power found in the patients with subjective insomnia compared with the other subjects may be linked. This type of effect is inherent in the use of the relative spectral power measure in that the relative frequency in each band reflects a percentage of the total power across all bands. Thus, if the percentage (relative power) in a particular band rises with respect to a comparison group, the percentage in other bands must fall a commensurate amount. The advantages of this approach over absolute power are 1) it controls for differences in total power that exists among individuals; 2) it highlights the degree to which activity is shifted across frequency bands; and 3) it removes effects of total power between groups (eg if one group had twice the power as another group in every frequency band it would not be detected). Taken in this light, our findings suggest that, relative to normal sleepers, patients with subjective insomnia show a shift in activity from lower to higher (alpha, sigma, and beta) frequency bands, and this shift is associated with their sleep complaints and a mismatch between their objective measures of sleep and their subjective sleep appraisals.

**Sleep EEG Spectral Indexes Versus Stage-scored PSG Measures as Correlates of Subjective Sleep Ratings**

This possibility is reinforced by our analysis of the relationship between subjective sleep-log ratings and NREM EEG frequency content. The finding that diminished delta and greater higher-frequency NREM EEG activity is related to greater subjective sleep complaints (lower sleep-log restlessness, TST, and SE ratings and greater WASO) in patients with subjective insomnia but not to the sleep complaints of the objective subgroup of primary insomniacs has not been previously reported. This finding points to a difference in pathophysiologic mechanism of insomnia in the subjective and objective insomnia subtypes. For patients with objective insomnia, there appears to be little deviation from normals in NREM EEG frequency spectral content, but deviations in traditional PSG measures appear to be associated with some of their sleep complaints. In contrast, for patients with subjective insomnia, there are no traditional PSG deviations that are associated with their...
sleep complaints; instead these complaints are associated with alterations in NREM physiology as manifested in greater high-frequency and diminished low-frequency EEG relative power.

These findings further suggest that the terms “subjective” and “objective” insomnia are problematic. This study provides evidence for “objective” findings in the PSG that characterize the group we labeled as “subjective” insomnia. Perhaps a more useful term than “subjective” insomnia might be “altered NREM frequency content” insomnia. Further studies will be needed to determine if this is a clinically relevant designation.

The Neurophysiology of NREM EEG Frequency Content

In terms of the neurophysiologic implications of our findings, several hypotheses have been suggested for the type of NREM EEG spectral findings that were reported in the present study. Elevated NREM EEG high-frequency content has been interpreted as evidence of hyperarousal and heightened awareness during periods of apparent PSG NREM sleep. Our finding of an association between the degree of objective-subjective sleep discrepancy and NREM EEG relative delta activity, and the prior report of an association with elevated high-frequency relative activity, is consistent with the latter. Also, our data are consistent with the hypothesis of Merica and colleagues that elevated high-frequency and diminished low-frequency NREM EEG activity were evidence that NREM sleep is a continuum and not an all-or-none phenomenon. They further hypothesize that in insomnia sufferers there are fewer neuronal groups in the physiologic sleep state. This, they believe, is associated with greater awareness during NREM sleep, leading to underestimation of sleep. Also, they suggest that fewer neuronal groups in the sleep state, which is the state associated with lower-frequency EEG activity, might account for diminished NREM EEG low-frequency activity. Our data are consistent with this hypothesis but do not allow any assessment of its validity.

Studies employing positron emission tomography along with NREM EEG spectral analysis are also pertinent to understanding the neurophysiologic significance of the findings of this study. These studies indicate that in NREM sleep, diminished delta (1.5-4.0 Hz) and greater 20-32 Hz EEG activity may be associated with elevated activity in the thalamus, brainstem reticular formation, cerebellum, anterior cingulate cortex, and orbitofrontal cortex. Some evidence suggests that brainstem reticular formation neurons normally decrease firing with the onset of NREM, which leads to hyperpolarization of thalamocortical projection neurons, which eliminates sensory input to the cortex and leads to the cortical slow-waves that are evident in the EEG. Further, there is a decrease in activity in anterior cingulate and orbitofrontal cortex (which receives dense thalamocortical projections) during NREM sleep, which is thought to reflect the degree of attenuation of cortical arousal and sensory awareness. Taken in this context, it is tempting to speculate that the results of the present study suggest that during NREM, subjective-insomnia sufferers may not diminish their activity in the reticular formation and thalamocortical projection neurons as much as normal subjects do. This may lead to less sensory gating at the thalamic level, leading to greater arousal and awareness during NREM sleep, which is reflected in greater high-frequency and diminished low-frequency EEG activity. Though highly speculative, it will be important for future studies to determine whether such changes in neuronal activity might account for the sleep complaints and apparent misperception of sleep in patients with subjective insomnia.

Limitations

A limitation of the present study is that the results are dependent upon the criteria used for categorizing the PPI subjects into subjective- and objective-insomnia subtypes on the basis of PSG normality. One challenge to this effort is that there is currently no accepted way to subdivide subjects into those with normal and abnormal PSGs on the basis of traditional Rechtschaffen and Kales scoring. Lacking a current standard, we implemented criteria that best reflected the available literature and that we had used in a prior study. We confirmed that patients with subjective insomnia had diminished delta and elevated higher-frequency NREM EEG relative power over a wide range of TST and percentage underestimation of sleep criteria. Yet, the current study does not provide any evidence that there are discrete subjective and objective subtypes of PPI or whether there is a subjective/objective continuum. Further studies will be needed to determine if this is the case. Nonetheless, this study provides evidence that changes in NREM EEG frequency content represent a neurophysiologic correlate of sleep complaints in PPI subjects with greater TST and a greater underestimation of sleep.

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