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Temporal and stagewise distribution of high frequency EEG activity in patients with primary and secondary insomnia and in good sleeper controls

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SUMMARY In the present study, we evaluate the temporal and stagewise distribution of high frequency EEG activity (HFA) in primary and secondary insomnia. Three groups ($n = 9$ per group) were compared: primary insomnia (PI), Insomnia secondary to major depression (MDD), and good sleeper controls (GS). Groups were matched for age, sex and body mass. Average spectral profiles were created for each sleep epoch. Grand averages were created for each NREM cycle and each stage of sleep after removing waking and movement epochs and epochs containing micro or miniarousals. It was found that HFA (in terms of relative power) tends to increase across NREM cycles, occurs maximally during stage 1 and during REM sleep, and that both these effects are exaggerated in patients with PI. In addition, HFA was found to be inversely associated with Delta activity and the three groups in our study appear to exhibit characteristic Delta/Beta patterns. Our data are consistent with the perspective that HFA is related to CNS arousal to the extent that Beta/Gamma activity occurs maximally during shallow stages of sleep and maximally in subjects with PI.

KEYWORDS beta, high frequency EEG, insomnia, power spectral analyses, sleep

INTRODUCTION

Several studies have shown that patients with insomnia exhibit elevated levels of Beta EEG activity (14–35 Hz) at or around sleep onset and during NREM sleep (Freedman 1986; Jacobs *et al*. 1993; Lamarche and Ogilvie 1997; Mercia and Gaillard 1992; Merica *et al*. 1998; Nofzinger and Nowell 1999; Perlis *et al*. 2001). There is also limited evidence to suggest that increased Beta activity occurs specifically in association with primary insomnia (PI) (Lamarche and Ogilvie 1997; Nofzinger *et al*. 1999; Perlis *et al*. 2000), is elevated throughout polysomnographic (PSG) sleep [both during NREM and REM sleep (Freedman 1986; Merica *et al*. 1998)] and may vary with clinical state (Jacobs *et al*. 1993).

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Recently, our group replicated the finding that patients with PI exhibit more Beta activity (14–35 Hz) during NREM sleep and extended this finding to show that the high frequency activity[1] extends into the Gamma (35–45 Hz) but not the Omega spectrum (45–125 Hz) (Perlis *et al*. 2001). In addition we found that average NREM Beta activity was correlated with subjective–objective discrepancies for total sleep time and tended to be correlated with subjective–objective discrepancies for sleep latency. These results confirm that high frequency activity (HFA) is increased in PI and also serve to illustrate that increased HFA, (1) does not occur within a frequency range that is characteristic of electromyographic artifact (Bonnet and Arand 1995) but appears to be limited to EEG frequency domains that are associated with sensory and cognitive processing (Basar-Eroglu *et al*. 1996; Galambos *et al*. 1981; Jefferys *et al*. 1996; Joliot *et al*. 1994; Llinas and Ribary 1993; Makeig and Inlow 1993; Makeig and Jung 1996; Pantev 1995; Pulvermuller *et al*. 1995; Sheer 1976; Spydell

et al. 1979; Steriade *et al.* 1993; Tiitinen *et al.* 1993, 1997; Varner *et al.* 1984), and (2) appears to be, as predicted by the Neurocognitive Model (Perlis *et al.* 1997), negatively correlated with the perception of PSG sleep.

While there is now a fair amount of data to suggest that patients with insomnia exhibit increased Beta activity during PSG sleep (Freedman 1986; Jacobs *et al.* 1993; Lamarche and Ogilvie 1997; Mercia and Gaillard 1992; Merica *et al.* 1998; Nofzinger *et al.* 1999; Perlis *et al.* 2001), little is known about how such activity in patients with insomnia varies in accordance with sleep cycle, sleep stage, as a function of time elapsed from sleep onset or systematically in relation to other power spectra. To our knowledge only two studies provide controlled information on these topics. Freedman (1986) undertook an analysis in which Beta activity (16–30 Hz) was assessed by stage of sleep. In this study, the first unambiguous minute of each stage of sleep was assessed power spectrally to determine the relative preponderance of Beta activity. He found that Beta activity was increased in stage one and in REM sleep in patients with insomnia compared with good sleeper controls (GS).

Merica *et al.* (1998) undertook an analysis in which they evaluated Beta activity by NREM and REM cycle. They found, that Beta activity (14.75–30.00 Hz) in patients with insomnia was increased throughout the night for both NREM and REM sleep.

In the present study, we attempt to further characterize Beta activity during PSG sleep by re-evaluating the data from our prior study (Perlis *et al.* 2001). In that study, NREM profiles were created by averaging the spectral data from the first three NREM cycles. In the present analysis, we extend our prior work by evaluating in terms of cycle, stage and time elapsed from sleep onset the temporal distribution of Beta activity in patients with PI and secondary insomnia and in GS.

METHODS

General protocol

All subjects in these analyses took part in one of two pilot studies undertaken at the University of Rochester Sleep Research Laboratory (URSRL). Subjects were recruited from two sources and were screened in two tier processes to insure that they met the inclusion/exclusion criteria. Each subject spent a minimum of two consecutive nights in the laboratory. The first night served as a adaptation night and these data are used in the present analyses. Subjects who completed either of the two protocols received $150–200 remuneration.

Recruitment

Subjects were recruited via newspaper advertisements and from The Behavioral Sleep Medicine Clinic at the Sleep Disorders Center of Rochester. Each patient underwent a two step evaluation process. First, subjects were interviewed by phone to establish their eligibility for participation. Subjects were ruled out if they reported unstable medical illness, psychiatric conditions other than major depression, sleep disorders or symptoms suggestive of sleep disorders other than PI, shift work, use of medications with central nervous system effects, substance abuse or a recent history of alcohol abuse (within 2 years). Second (after the telephone screen), all potential subjects were interviewed by our clinical research coordinator. The interview included an administration of the Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960) and the Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-L) (Endicott and Spitzer 1978), supplemented by the eating disorders module from the Structured Clinical Interview for DSM-III (SCID). Symptom severity, number of prior episodes, treatment history, medical history and personal and family history of sleep disorders were also ascertained. Prospective subjects also completed several psychometric instruments including the Beck Depression Inventory (BDI) (Beck *et al.* 1988), the Beck Anxiety Inventory (BAI) (Kabacoff *et al.* 1997; de Beurs *et al.* 1997) and the Pittsburgh Sleep Quality Index (PSQI) (Buysse *et al.* 1989). Eligible subjects completed an informed consent at the end of the intake interview. Once enrolled, subjects completed 14 days worth of sleep diaries. These data were used to cross validate each subjects' retrospective assessments of their sleep (provided during the telephone screen and at the intake interview) and to provide an average measure of each subjects' preferred bedtime and risetime.

Subjects

Data from three subject groups were used in the present analysis ($n = 9$ per group). Groups were PI, MDD and GS. The three groups were matched for age, sex and body mass. The overall sample was 66% female and the mean age was 37.5 (± 10.7). All subjects were medication free at the time of the in-laboratory study (See exclusion criteria).

Criteria for PI were as follows:

- the complaint of insomnia and impaired daytime function,
- an indication of learned sleep-preventing associations,
- active help seeking.

The complaint of insomnia had one or more of the following characteristics: >30 min to fall asleep and/or less than two awakenings per night of >15 min duration and/or wake after sleep onset time of >30 min, problem frequency >4 nights/week and problem duration >6 months.

Criteria for MDD were as follows:

- Patients met DSM IV criteria for MDD
  Five or more symptoms which represented a change from previous functioning for a period of at least 2 weeks. Depressed mood and/or loss of interest/pleasure were required for the diagnosis of MDD.
- Patients presented with the complaint of insomnia.

Criteria for GS were that they

- reported no difficulty falling or staying asleep,
- characterized their sleep as restorative and relatively unperturbable.

Exclusion criteria for all three groups were: (1) significant current medical or psychiatric illness other than unipolar

depression (2) sleep disorders other than PI (3) memory impairments (4) history of head injury (5) prescription medication or recreational drug use within 4 weeks of laboratory study and (6) use of SSRIs within 6 months of laboratory study.

Polysomnographic assessment

The recording montage consisted of a 15 electrophysiologic signals. The basic montage included two EOGs referenced to a single mastoid [LOC & ROC], six EEGs referenced to linked mastoids [F3, F4, C3, C4, O1 and O2], a bipolar mentalis EMG, bilateral corrugator EMGs and an EKG. In addition, two channels of tibial EMG and one channel of nasal/oral air flow data were acquired to rule out the presence of occult sleep disorders (e.g. sleep apnea and/or PLMs). All electrophysiologic signals were acquired using a Coulbourn Instruments 16 channel POLYLINC™ system. The EOGs were acquired at a gain of 20 K (3.75 μV/mm equivalent) for an initial frequency bandwidth of 0.3–100 Hz (24 dB/octave). The EMGs were acquired at a gain of 20 K for an initial bandwidth of 30–1000 Hz. The EEGs were acquired at a gain of 20 K for an initial bandwidth of 0.3–1000 Hz. The EEG signals were also passed in series to six Coulbourn Instruments V75–48 band-pass filters (48 dB/octave) set at 0.25–125 Hz. Digital acquisition was governed by Stellate Harmonie-Luna™ software and accomplished by a BSMI 519 A-to-D board. The A-to-D board has a notch filter at 60 Hz and a 1 pole (6 dB/octave) low pass filter at 300 Hz. The base sampling rate was 512 Hz. On-line decimation was used so that variable sampling rates could be obtained. The variable sampling rates, which were calculated based on the Nyquist frequency (sampling = 2 × highest frequency of interest), were as follows: EOGs at 16 Hz, EEGs at 256 Hz and EMGs at 512 Hz. The final digital display was additionally modified by digital filtering for optimal on-screen display (no effect on quantitative analysis). The digital band-pass filter settings were as follows: EOGs at 0.3–4 Hz, EEGs at 0.3–20 Hz, EMGs at 30–250 Hz.

Sleep scoring

The PSGs were scored in 30-second epochs according to Rechtschaffen and Kales (R & K) criteria (Rechtschaffen and Kales 1968). Our scoring procedures slightly deviate from R & K methods and standards in two ways. First, we have both a duration and amplitude criteria for K-complexes. Based on the work of Bastien and Campbell (1992), K-complexes must be at least 50 μV. Secondly, based on early work by Dement and Kleitman (1957), an epoch may be scored as stage 2 sleep, in the absence of spindles and K-complexes for three or more minutes, if between 5 and 19% Delta activity is identified. The PSG scorers were extensively trained by the first author and meet or exceed laboratory interrater criteria of 90%. That is, 90% of epochs must be identified the same as in a master set of 5 standard records scored by the PI. In addition to sleep scoring, scorers identified and coded micro (0.1–7.0 s) and mini (7.1–14.9 s) arousals. Arousals were identified as transient EEG 'speeding', short intervals of 'pen blocking' (amplifier saturation), and/or as phasic intrusions of EMG activity.

The PSG definitions were as follows: Sleep onset was defined as two consecutive epochs of stage 1 or one epoch of stages 2, 3, 4 or REM. An awakening was defined as an instance of more than 1 min of wakefulness occurring after sleep onset. These definitions are the default values for the Stellate Harmonie-Luna™ report generation program. Given these definitions, sleep continuity variables were as follows: (1) sleep latency: amount of time elapsed in minutes from 'lights off' to 'sleep onset' (2) number of awakenings (IWT): number of awakenings that occurred after sleep onset and prior to 'lights on' (3) wake after sleep onset (WASO): was the sum of wake time in minutes from sleep onset to 'lights on' and (4) total sleep time: sum of NREM and REM sleep in minutes from 'lights off' to 'lights on'.

EEG frequency assessment

Power Spectral Analysis (PSA) is a statistical technique for detecting periodicities within time series data. As employed within electroencephalography, the technique is routinely used to decompose complex waveforms into their constituent frequencies. Quantification is accomplished by determining the amount of voltage that occurs per Hz for prespecified bandwidths.

The Digital EEG from night 1 was subjected to PSAs using Stellate Harmonie-Luna™ software. For the present analysis, the spectral window was set for a 2-s interval. Prior to frequency assessment, the data within the two second windows were automatically cosine tapered and detrended (mean detrend) to eliminate nonstationary data. Following the frequency assessment, multiple nonoverlapping windows (15/epoch) were averaged to yield mean power spectral distributions for each sleep scored 30-s epoch (0.5 Hz resolution). Power spectra (μV^2/Hz) for each of the EEG sites were computed for the following bandwidths: Delta-1 (0.5–2.5 Hz), Theta (2.5–7.5 Hz), Alpha (7.5–12.0 Hz), Sigma (12–14 Hz), Beta-1 (14.0–20.0 Hz), Beta-2 (20–35 Hz), Gamma (35–45.0 Hz), and Omega (45.0–125 Hz).

Following the PSA routine, an ASCII data set was created for each subject which contained the following items in a columnar format: Time, epoch, NREM/REM cycle, sleep stage, microarousal events, mini-arousal events, and 8 columns containing absolute power values for each spectral band (Delta–Omega). These files were imported into SAS. Using this platform, each subject's PSA data (for the purpose of the cycle and stage analyses) were manipulated so that (1) waking and movement time epochs and epochs with mini (0.1–7.0 s) or micro (7.1–14.9 s) arousals were deleted (2) relative power values (power per bandwidth over total power) were computed for each site per epoch. Total power was calculated by summing the power values for each of the 8 bandwidths per epoch, and (3) average values by site (e.g. C3/A2 & C4/A1) and average values across site [(C3/A2 + C4/A1)/2] were

calculated for each stage of sleep and for each NREM and REM cycle. The NREM and REM cycles were defined as follows:

- NREM-1 was defined as extending from sleep onset to the first REM period.
- NREM-2 was defined as extending from the last epoch of the first REM period to the first epoch of the second REM period.
- NREM-3 is defined as extending from the last epoch of the second REM period to the first epoch of the third REM period.
- A REM period was defined as 30 s or more of REM sleep. The REM periods were identified as distinct – given 15 consecutive minutes of intervening NREM sleep.

The final output data represented average NREM power (relative power) for the first three NREM cycles. Relative power measures [e.g. (Beta Power/Total Spectrum Power) × 100] were used so as to (1) control for individual difference variability with respect to EEG power and (2) provide a measurement unit that has intuitive appeal, i.e. the percent of total brain activity that falls within each given frequency range. The analyses were limited to the first three cycles in order insure that there was comparable data across groups.

Temporal plots or average compressed band arrays (CBA)

In order to represent the temporal distribution of EEG spectral activity by epoch, average CBAs were constructed for each group (see Fig. 1). These diagrams are essentially X, Y plots where the *X*-axis is relative power, the *Y*-axis is time as delineated in successive epochs and the zero-intercept is sleep onset. While CBA plots are commonly used to portray individual data (e.g. Delta activity across the night) the creation of aggregate plots allows for the resolution of group trends, provided that a common anchor is used and a common underlying rhythms exist. This procedure is analogous to the creation of evoked response potentials (ERPs) and a precedent for the approach may be found in the work of Merica and colleagues (Merica and Blois 1997).

In the CBA diagrams, Beta-1 and Delta activity (relative power/epoch) are double plotted as a function of time from sleep onset. Epochs containing wakefulness, movement times and mini and micro arousals were 'set to missing' prior to the construction of each of the CBA plots. This allowed us to plot unambiguous NREM and REM sleep as a continuous function of time.[2] Beta-1 activity was selected because (1) based on prior analyses, this particular bandwidth best discriminated between diagnostic groups and activity in this domain best correlated with subjective–objective discrepancies for total sleep time (Perlis *et al.* 2001), and (2) it is the least likely of the HFA spectra to be influenced by EMG activity. Delta activity was selected because it is thought to represent/correspond to the discharge of 'sleep pressure' (Borbely 1992; Borbely *et al.* 1981; Brunner *et al.* 1993). The figure itself is constructed as a double plot to allow one to appreciate the inverse relationship between Delta and Beta activity by sleep cycle (e.g. NREM vs. REM and/or cycle 1 vs. cycle 2) and across course of the night.

Analyses

Three sets of analyses were undertaken. In the first, five 3 × 3 Mixed Model ANOVAs were used to assess HFA variation by sleep cycle. The between subject factor was group (PI, MDD and CTRL). The within subject factor was cycle (NREM1–NREM3). In the second, five 3 × 5 Mixed Model ANOVAs were used to assess HFA variation by sleep stage. The between subject factor was group. The within subject factor was sleep stage (stages wake, 1, 2, slow wave sleep, and REM). The dependent variables for both sets of analyses were Delta, Beta-1, Beta-2, Gamma and Omega. Between group follow-up contrasts used Duncan Multiple Range tests which correct for type 1 comparison error rate. The third set of analyses were focused on sleep onset Beta EEG activity. Two *t*-tests were used to evaluate whether the groups differed for (1) relative Beta power immediately following sleep onset, and (2) the rate at which Beta activity dissipated [as measured by linear slope (from sleep onset to the epoch containing the lowest Beta-1 power value during the first NREM cycle)].

RESULTS

Group characteristics

The groups did not differ on age, sex, body mass index or race. As expected, the groups differed on symptom measures, including the BDI, BAI, HRSD and the PSQI. Depression measures revealed that MDD patients had the most severe symptoms and that PI Ss differed from controls with respect to depression severity, but their scores were within normal limits. On the BAI, both the MDD Ss and the PI Ss exhibited mild levels of anxiety. Finally, the groups differed on the PSQI global measure of sleep disturbance severity (all contrasts). Patients with insomnia scored highest, and the GS scored the lowest (See Table 1). As for the insomnia symptoms, 100% of the patients with insomnia had a complaint of initial insomnia and 55% had a complaint of middle insomnia, 33% had a complaint of terminal insomnia.

Group differences on sleep measures

The groups differed in the expected direction on PSG and subjective measures. Overall, patients with insomnia exhibited the worst sleep continuity profiles, followed by patients with MDD (Table 2).

Group differences on artifact rejection procedures

As noted in the Methods, each subject's PSA data were manipulated so that waking and movement time epochs and epochs with mini (0.5–7.0 s) or micro (7.1–14.9 s) arousals were deleted. Overall, < 2.5% of epochs containing micros and

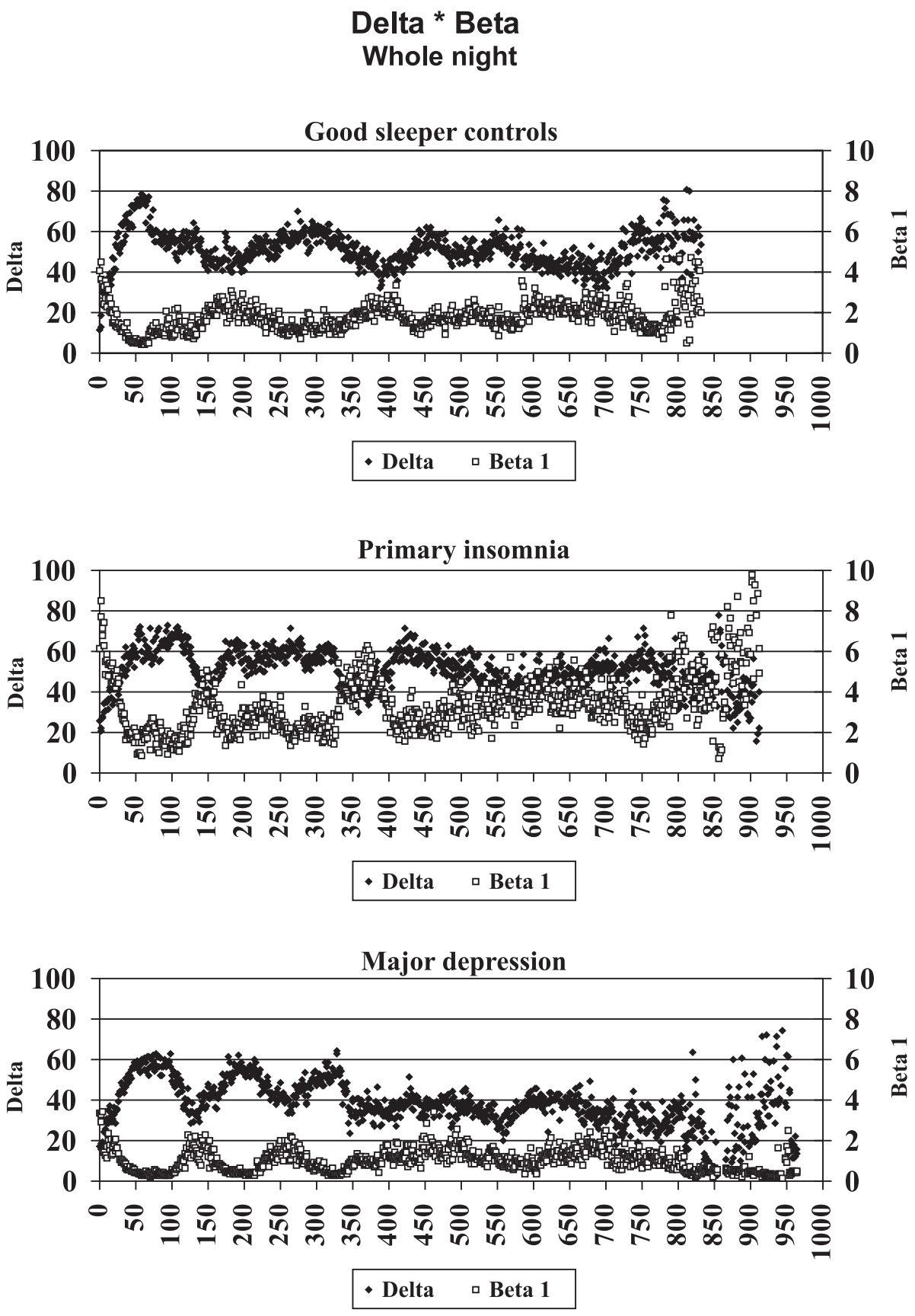

Figure 1. Delta and Beta relative power plotted as a function of time elapsed (30 second epochs) from sleep onset to lights on.

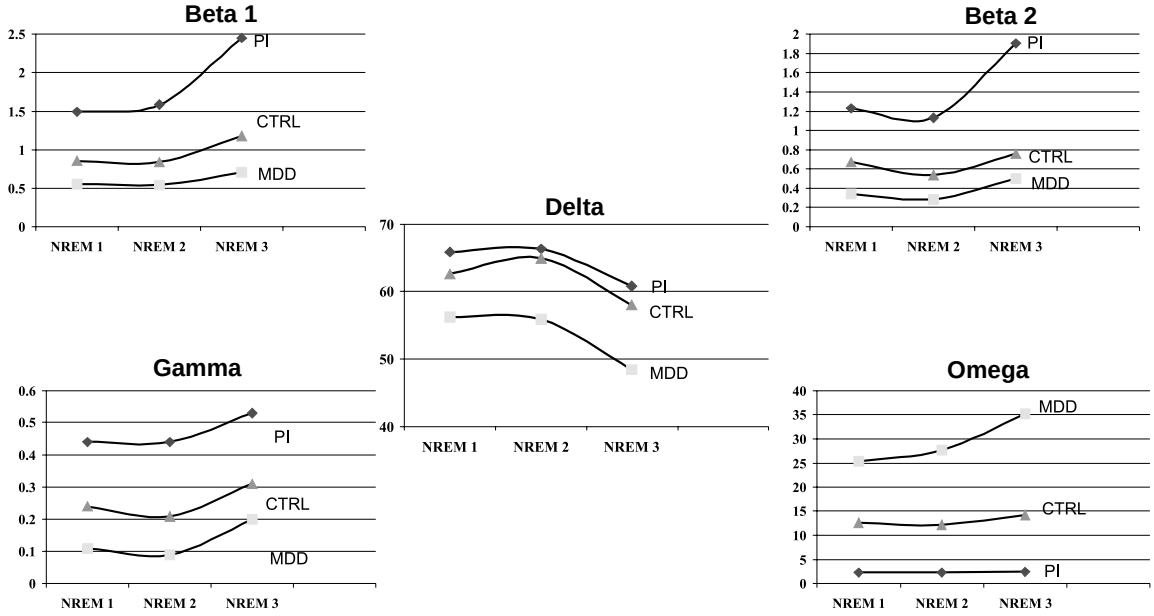

Figure 2. Relative power ([% band/total power]) by NREM cycle.

Table 1 Demographic and psychometric data

	PI	*MDD*	*CTRL*	*ANOVA*	*PI vs. MDD*	*PI vs. CTRL*	*CTRL vs. MDD*
Demographic measures							
Height	65.1 (3.7)	68.0 (5.2)	65.0 (3.8)	NS	–	–	–
Weight	135.9 (24.4)	158.1 (28.3)	142.3 (23.1)	NS	–	–	–
Age	36.5 (10.8)	38.3 (10.6)	38.1 (11.2)	NS	–	–	–
Race*	66.7%	70.4%	66.7%	NS*	–	–	–
Sex:%F	66.7%	66.7%	66.7%	NS*	–	–	–
Psychometric measures							
BDI	6.0 (3.0)	21.1 (7.0)	1.1 (0.9)	0.0001	$P < 0.05$	$P < 0.05$	$P < 0.05$
BAI	6.4 (6.8)	10.6 (6.6)	1.7 (1.8)	0.0414	NS	NS	$P < 0.05$
HRSD	3.5 (2.1)	16.6 (3.9)	0.0 (0.0)	0.0001	$P < 0.05$	$P < 0.05$	$P < 0.05$
PSQI	11.2 (1.6)	8.7 (1.1)	2.0 (1.2)	0.0001	$P < 0.05$	$P < 0.05$	$P < 0.05$

Follow up contrasts use Duncan's Multiple Range tests. This test controls the type I comparisonwise error rate.
*Represents the proportion of the sample that was Euro-American.
**Chi Square.

minis and $<23\%$ of epochs scored as Wake or MT were identified and removed prior to the calculation of NREM averages. A contingency analysis of the number of epochs deleted by group revealed that more Micros and Minis were removed from the MDD group while more epochs scored as MT or wake were removed from the PI records. Please note that the artifact rejection procedure is only relevant for the quantitative analyses and not affect Fig. 1. In the case of the latter (the graphic representation of Beta and Delta activity), waking and movement time epochs and epochs with mini (0.1–7.0 s) or micro (7.1–14.9 s) arousals were not deleted but rather the epoch values were designated as missing prior to creating the average plots. In this way the time domain was preserved within and across groups.[2]

Group differences on PSA by NREM cycle

Table 3 and Fig. 1 present the Delta and HFA PSA data by NREM cycle for each group. Both formats are presented so that the reader may have access to the data and the easier to interpret graphic representations. For Delta power, only a cycle effect was evident, i.e. Delta activity tended to diminish across NREM cycles. Post hoc comparisons (within group) revealed that patients with PI ($P < 0.04$) and MDD ($P < 0.05$) exhibited significant declines in relative Delta power from the second to the third NREM cycle. The GS subjects tended to exhibit the same trend ($P < 0.06$). For HFA, main effects for cycle (average NREM activity) and group (PI, MDD, CTRL) were evident. The main effect for cycle was that Beta-1, Beta-2, and Gamma tended to increase

Table 2 Sleep continuity measures

	PI	*MDD*	*CTRL*	*ANOVA*	*PI vs. MDD*	*PI vs. CTRL*	*CTRL vs. MDD*
PSG Measures							
SL	21.8 (17.9)	9.5 (9.3)	7.9 (6.8)	0.05	$P < 0.05$	$P < 0.05$	NS
IWT	9.3 (3.7)	2.1 (1.7)	4.7 (3.9)	0.0004	$P < 0.05$	$P < 0.05$	NS
WASO	72.9 (74.5)	24.1 (48.7)	21.0 (16.4)	0.08	NS	$P < 0.05$	NS
TST	323.7 (82.6)	366.7 (64.0)	348.3 (32.5)	0.37	NS	NS	NS
Sleep diary measures							
S_SL	79.6 (89.0)	22.2 (28.1)	17.6 (18.1)	0.05	$P < 0.05$	$P < 0.05$	NS
S_IWT	2.4 (1.3)	3.1 (2.3)	1.8 (1.0)	0.30	NS	NS	NS
S_WASO	76.1 (89.1)	23.6 (40.3)	16.2 (23.7)	0.08	NS	$P < 0.05$	NS
S_TST	278.9 (119.7)	363.13 (58.9)	370.0 (47.4)	0.05	$P < 0.05$	$P < 0.05$	NS

Follow up contrasts use Duncan's Multiple Range Test. This test controls the type I comparisonwise error rate.

from first NREM cycle to the third NREM cycle where the primary increase occurred in the third cycle. A similar trend was evident for Omega but this did not reach significance. The main effect for group was that patients with PI exhibited the highest levels of Beta-1, Beta-2 and Gamma and the lowest levels of Omega. The group × cycle data were significant for Beta-1 and Omega. These interactions indicate that patients with

- PI exhibit greater increases in Beta-1 from NREM2 to NREM3, and
- MDD exhibit a robust increase in Omega activity from NREM1 to NREM2 and from NREM2 to NREM3. Neither trend is evident for the PI or CTRL Ss.

Group differences on PSA by sleep stage

Table 4 presents the PSA data by sleep stage. The main effect for group was significant for Beta-1, Beta-2 and Omega. Gamma tended to be significant ($P < 0.06$). As with the prior analyses, subjects with PI exhibited the most Beta and Gamma activity while subjects with MDD exhibited the most Omega activity. The main effect of stage was significant for all the bandwidths within the high frequency domain. In general, HFA decreases from stage 1 sleep to Delta sleep and there is a resurgence of HFA during REM sleep. The group × stage interactions were significant, or tended to be significant, for each of the bandwidths except Gamma. In this instance, follow up Duncan Multiple Range tests suggest that there are group differences within this spectral domain as well. In general, patients with PI exhibit more stage 1 and stage 2 Beta-1 activity, more REM and SWS Beta-2 activity, and more stage 2 and SWS Gamma activity.

Temporal plots or average compressed band arrays (CBA)

While descriptive only, several overarching trends, irrespective of group, are apparent when one visually assess the three group CBA plots (Delta by Beta power from sleep onset to sleep offset). First, Delta activity, as one would expect, appears to predominate in the first half of the night with at least two

Table 3 PSA measures – NREM relative power by cycle

	Delta (0.5–2.5 Hz)	*Beta-1 (14–20 Hz)*	*Beta-2 (20–35 Hz)*	*Gamma (35–45 Hz)*	*Omega (45–125 Hz)*
NREM cycle 1					
PI Ss	65.87 (10.03)	1.49 (0.57)	1.23 (0.59)	0.44 (0.29)	2.29 (1.71)
MDD Ss	56.24 (26.05)	0.56 (0.37)	0.34 (0.30)	0.11 (0.11)	25.3 (31.5)
CTRL Ss	62.58 (22.34)	0.86 (0.44)	0.67 (0.39)	0.24 (0.19)	12.58 (27.5)
NREM cycle 2					
PI Ss	66.27 (7.59)	1.58 (0.62)	1.31 (0.58)	0.44 (0.33)	2.38 (2.02)
MDD Ss	55.89 (27.01)	0.54 (0.41)	0.29 (0.15)	0.09 (0.03)	27.7 (33.9)
CTRL Ss	64.88 (23.40)	0.84 (0.61)	0.54 (0.28)	0.21 (0.12)	12.19 (26.8)
NREM cycle 3					
PI Ss	60.81 (11.00)	2.45 (1.10)	1.90 (1.26)	0.53 (0.42)	2.49 (2.37)
MDD Ss	48.37 (31.30)	0.71 (0.52)	0.50 (0.33)	0.20 (0.16)	35.2 (39.8)
CTRL Ss	58.03 (23.32)	1.18 (0.85)	0.76 (0.57)	0.31 (0.32)	14.2 (26.8)
Group	0.5381	0.0003	0.0001	0.0065	0.0973
Cycle	0.0001	0.0001	0.0466	0.1018	0.0102
Group × cycle	0.8354	0.0335	0.4481	0.9981	0.0247

Power = μV^2/Hz.
Relative power = [(power per bandwidth)/(total power)].

Table 4 PSA measures – NREM relative power by stage

	PI (P)	*Control (C)*	*MDD (M)*	*GRP* *P vs. C*$^{\Psi}$	*Stage* *P vs. M*$^{\Psi}$	*G × S* *C vs. M*$^{\Psi}$
Central Beta-1				0.0001	0.0001	0.0371
Stage wake	4.70 (2.54)	4.16 (2.46)	2.40 (1.14)	NS	$P < 0.05$	$P < 0.05$
Stage 1	5.86 (1.24)	3.87 (1.95)	2.04 (1.86)	$P < 0.05$	$P < 0.05$	$P < 0.05$
Stage 2	2.74 (1.26)	1.32 (0.52)	0.92 (0.63)	$P < 0.05$	$P < 0.05$	NS
Delta sleep	0.63 (0.25)	0.42 (0.22)	0.29 (0.16)	NS	$P < 0.05$	NS
REM sleep	4.27 (1.86)	3.03 (1.19)	1.26 (1.33)	NS	$P < 0.05$	$P < 0.05$
Central Beta-2				0.0010	0.0001	0.0731
Stage wake	9.27 (4.13)	8.76 (4.90)	5.74 (2.85)	NS	NS	NS
Stage 1	8.52 (2.53)	7.19 (3.53)	3.31 (3.05)	NS	$P < 0.05$	$P < 0.05$
Stage 2	2.22 (1.10)	0.89 (0.29)	1.18 (2.18)	NS	NS	NS
Delta sleep	0.45 (0.18)	0.24 (0.10)	0.15 (0.09)	$P < 0.05$	$P < 0.05$	NS
REM sleep	5.51 (3.30)	2.97 (1.95)	1.18 (1.26)	$P < 0.05$	$P < 0.05$	NS
Central Gamma				0.0548	0.0001	0.2178
Stage wake	4.71 (3.28)	4.92 (2.71)	3.13 (1.37)	NS	NS	NS
Stage 1	2.78 (1.20)	3.89 (2.17)	1.68 (1.38)	NS	NS	$P < 0.05$
Stage 2	0.67 (0.41)	0.32 (0.10)	0.16 (0.11)	$P < 0.05$	$P < 0.05$	NS
Delta sleep	0.14 (0.08)	0.07 (0.03)	0.04 (0.03)	$P < 0.05$	$P < 0.05$	NS
REM sleep	1.01 (1.21)	0.62 (0.38)	0.20 (0.22)	NS	$P < 0.05$	NS
Central Omega				0.0251	0.0001	0.0196
Stage wake	32.31 (27.55)	39.03 (24.83)	46.74 (30.19)	NS	NS	NS
Stage 1	16.74 (10.26)	21.72 (11.99)	49.18 (37.14)	NS	$P < 0.05$	$P < 0.05$
Stage 2	3.28 (2.21)	4.28 (5.34)	35.34 (37.68)	NS	$P < 0.05$	$P < 0.05$
Delta sleep	0.65 (0.60)	1.66 (2.52)	22.68 (28.34)	NS	$P < 0.05$	$P < 0.05$
REM sleep	2.72 (3.29)	8.68 (12.50)	46.68 (44.51)	NS	$P < 0.05$	$P < 0.05$

$^{\Psi}$ Follow up contrasts use Duncan's Multiple Range tests. This test controls the type I comparisonwise error rate.
Underlined values indicate findings that were not significantly different than values for PI.

clearly discernible periods during which Delta activity is high. Secondly, Beta activity appears highest at sleep onset, diminishes over NREM sleep and recurs at higher levels during REM sleep. Thirdly, Delta activity appears to be inversely related to Beta activity, and that this is particularly true for the first half of the night.

Group differences also appear to be evident within the Delta domain

(1) patients with MDD appear to have less power within this frequency band than their PI and CTRL counterparts but as previously indicated this average effect did not reach statistical significance and (2) Delta power appears to be redistributed in patients with MDD such that there is a bimodal or trimodal (2–3 peaks) distribution of Delta activity. In PI and CTRL subjects, Delta power appears as a more unimodal distribution.

Within the Beta domain patients with PI

(1) appear to exhibit elevations within this frequency band at sleep onset, during REM sleep and for the second half of the night (2) tend to exhibit a great deal of epoch-to-epoch variability, and (3) appear to exhibit steeper sleep onset and sleep offset slopes.

Two of the above group trends were formally evaluated using one-way ANOVAS. It was found that patients with PI exhibit greater Beta-1 power at the first epoch following sleep onset ($P < 0.0045$) and a steeper slope following sleep onset where the linear slope was calculated from sleep onset to the epoch containing the lowest Beta-1 power value during the first NREM cycle ($P < 0.0003$).

Finally, the inverse association between Delta and Beta activity and the clear rhythmicity within the two spectral domains appears to occur most robustly within the first 4–5 h of the night. Patients with PI and MDD, unlike their control counterparts, appear to show a substantial loss of 'coherence' during the last third of the night, although the loss of the inverse-rhythmic association appears to be related to different phenomena. In the patients with MDD, Beta activity appears to diminish within the last hour of sleep while transient increases in Delta activity are apparent. In patients with PI the reverse appears to occur: Delta activity appears to diminish within the last hour of sleep while transient increases in Beta activity are apparent.

DISCUSSION

In the present study, we characterized the cycle, stagewise and temporal distribution of HFA in patients with primary and secondary insomnia and in good sleepers. The findings from the present analysis were that HFA tends to increase across NREM cycles, occurs maximally during stage 1 and during REM sleep, and that each of these effects were exaggerated in patients with PI. In addition, it was found that HFA tends to

be inversely associated with Delta activity and each of the groups in this study appear to exhibit characteristic Delta/Beta patterns following sleep onset.

Does high frequency activity vary by NREM cycle?

Yes. In general, it appears that high frequency EEG activity increases across the course of the night, although the trend across the first three NREM cycles does not appear to be linear. If these results are replicated and extended to show that later NREM cycles also contain an increased proportion of HFA, then these results would indicate that HFA is inversely related to the distribution of Delta power over the course of the night. Such a distribution might reflect one of two possibilities. First, as sleep pressure abates (reflected by diminished Delta activity), this permits a resumption of a type of EEG activity that is associated with wakefulness. Alternatively, the relationship between Delta and Beta activity may reflect the interaction of two processes such that with extended wakefulness there is an increase in putative 'Process S' (Borbely 1987, 1988; Szelenberger 1987) while with extended sleep there is an increase in 'Process W', i.e. a homeostatic regulator associated with propensity for wakefulness. The advantage of the latter perspective is that it suggests that patients with Primary Insomnia do not exhibit a 'Process S' deficiency (Delta power) but may exhibit an abnormal 'Process W' (Beta/Gamma power). This point of view is more or less a re-statement of the 'arousal hypothesis' perspective on insomnia (Bonnet and Arand 1998; Perlis *et al*. 1997) but is, perhaps, conceptually richer. Abnormal Process W implies that homeostatic factors are of relevance whereas traditional hyperarousal theory tends to frame this abnormality as either a stable trait factor or as a form of conditioned arousal.

Two cautionary notes are in order with respect to the possibility that PI is a 'Process W' and not a 'Process S' problem. First, the data for this study were derived from the first in-laboratory study night. Thus, 'first night (Coates *et al*. 1981; Mendels and Hawkins 1967; Toussaint *et al*. 1995) and 'reverse first night' effects (Hauri and Olmsted 1989) may have obscured our ability to detect differences within the Delta domain. Secondly, studies looking at recovery sleep following sleep deprivation protocols in good sleepers and patients with insomnia have found blunted SWS and/or Delta EEG responses in patients with insomnia (Bonnet 1985; Stepanski *et al*. 2000). These kind of data suggest that, at least under probative conditions, patients with insomnia do exhibit Process S abnormalities.

Does high frequency activity vary by sleep stage?

Yes. Our data, like those of Freedman (1986) suggest that HFA (largely within the Beta-1 and Beta-2 ranges) occurs most prevalently during stage 1 and REM sleep, least prevalently during SWS, and that patients with insomnia tend to exhibit greater amounts of HFA than GS during these intervals. Unlike the Freedman *et al*. data, patients with PI in our study also exhibited more stage 2 (Beta-1) and SWS (Beta-2 and Gamma) high frequency EEG activity. The differences between studies may be related to the manner in which the data were obtained and aggregated. In Freedman's study, the first unambiguous minute of each stage of sleep in patients was assessed for Beta activity. In our study, average stage profiles were created. Assuming that both studies findings are accurate, it may be the case that HFA persists into stage 1 and re-emerges during REM sleep but does not occur at the transitions to stage 2 and/or SWS. This is to say, it is possible that at the transitions to deeper sleep, HFA is momentarily suppressed and then subsequently, for unknown reasons, resumes. The moment-to-moment variability apparent in the Beta activity in the patients with insomnia is consistent with this possibility.

Is the occurence of HFA during REM sleep especially meaningful?

Yes. For at least two reasons. First, the occurrence of HFA during REM sleep is consistent with the point of view that HFA is associated with attentional processes and cognitive activity (Basar-Eroglu *et al*. 1996; Galambos *et al*. 1981; Jefferys 1996; Joliot *et al*. 1994; Llinas and Ribary 1993; Makeig and Inlow 1993; Makeig and Jung 1996; Pantev 1995; Pulvermuller *et al*. 1995; Sheer 1976; Spydell 1979; Steriade *et al*. 1993; Tiitinen *et al*. 1993, 1997; Varner *et al*. 1984). Some investigators have even argued that Gamma activity is specifically correlated with REM sleep and is isomorphic for the state of dreaming. (Llinas and Ribary 1993; Llinas *et al*. 1991). Irrespective of specificity, the low levels of HFA in the REM sleep of MDD patients seems to map nicely onto the finding that these patients tend to report 'bland' dreams (Kramer and Roth 1973; Kramer *et al*. 1969; Hauri 1976) Conversely, the elevated levels of HFA in patients with PI may suggest that dream reports from these subjects should be more vivid and/or that nightmares should be more common amongst this population. To our knowledge, however, no surveys have been undertaken which provide data regarding nightmare frequency in insomnia subjects.

Secondly, the occurrence of Beta/Gamma activity at exceptionally high levels during REM sleep substantially diminishes the likelihood that such activity is related to cranio-facial EMG activity. During REM sleep, both the postural (Rechtschaffen and Kales 1968; Tauber *et al*. 1977) and mimetic muscles (Perlis *et al*. 1991, 1995) tend to be electromyographically atonic because of the hyperpolarization of alpha motorneurons (Chase and Morales 1990). While phasic EMG (Chase and Morales 1990; Brunner *et al*. 1990), and even sustained EMG (Perlis *et al*. 1991, 1995), activity may occur during REM sleep, there is no reason to expect that such amounts of activity (with or without artifact rejection) could account for the 5–12-fold increases in REM Beta/Gamma activity over and against stage 2 or SWS levels.

Do Delta and HFA vary temporally?

Our CBA plots, suggest that both Delta and Beta activity exhibit distinct temporal profiles. In general, Delta activity

appears to predominate in the first half of the night with at least two clearly discernible periods. Beta activity appears highest at sleep onset, diminishes over NREM sleep and recurs at higher levels during REM sleep. The temporal variance in Beta/Gamma activity appear to be related to two factors: reoccurrence of HFA during REM sleep and an upward quadratic trend across the night which may or may not reflect or correspond to homeostatic regulation of wakefulness ('Process W'). Both issues have been addressed above.

Not yet addressed are the findings with respect to Delta activity. Interestingly, we did not find (as have other studies) that Delta activity is significantly diminished in patients with MDD. (Borbely 1987, 1988). While there is a precedent for this (Nofzinger *et al*. 1999; Mendelson *et al*. 1987) it is clear from the data in Fig. 1 that, on average, the groups do differ and in the expected direction. At least two interpretations are possible. First, the failure to reach statistical significance may have to do with a variance problem, i.e. such large standard deviations that group trends were not significant. As can be seen in Table 3, this appears to be the case. Inspection of individual CBA plots also supports this position. Patients with MDD appear to either have normal amounts of Delta activity or virtually no Delta activity at all. Typing the groups according to these profiles, in a manner similar to the threshold approach used to study the clinical correlates of REM latency (Giles *et al*. 1987, 1989, 1990, 1989, 1998a, b) might be informative. Second, Kupfer and colleagues (Kupfer and Frank 1989; Kupfer and Frank 1990) and, Giles *et al*. (1996), Giles and Kupfer (1995) have argued that Delta deficits in patients with MDD are not absolute but rather reflect a redistribution of Delta activity across NREM sleep such that the normal exponential decline is replaced by a bimodal distribution. Giles and colleagues argue that this redistribution occurs as a result of the active intrusion of REM sleep into the first NREM cycle (Giles *et al*. 1996; Giles and Kupfer 1995). Our data, at least descriptively, are consistent with this point of view.

Also of importance, is that Beta and Delta activity appear to vary inversely across time. Good sleepers appear to maintain this inverse association for the entire recording period while the patients with insomnia (both groups) appear to lose this characteristic pattern at between 3 and 4 h after sleep onset. It is possible that the preservation of the prototype pattern for roughly the first third of the night may correspond to what Horne and colleagues have deemed 'core sleep'. (Horne 1988) The loss of spectral coherence and the increase in Beta activity in the latter portion of the night in patients with PI may correspond to their tendency toward increased number and/or duration of awakenings.

Two additional points with respect to group differences in the temporal patterning of Delta and Beta activity merit comment. First, Armitage and colleagues have, in several studies, looked at the temporal coherence of Delta and Beta activity in patients with MDD and in good sleepers (Armitage *et al*. 1993, 1999; Fulton *et al*. 1996; Fulton *et al*. 2000) While their data are similar to ours for the MDD subjects, the Delta/Beta phase relationship in good sleepers does not resemble our data. For example, in the study by Fulton *et al*. (2000) Delta and Beta activity covaried in phase. While potentially related to method differences (PSA vs. DPA), it will be important to resolve what constitutes a normal Delta/Beta profile. Second, to the extent that our average plots represent true prototypes, it will be useful to determine what makes each of these plots appear unique and to use these data, e.g. in discriminate function analyses (Merica and Gaillard 1992) to predict group membership. Possible variables might include: Delta/Beta coherence measures (Armitage *et al*. 1989, 1993) Delta and/or Beta slope or function variables (Merica and Gaillard 1992) Beta sleep onset intercept values, Delta and/or Beta NREM mean and variability measures, etc. Such an exercise might speak to the sensitivity and specificity of the EEG patterns described in this report and provide potential clues to the neurophysiologic abnormalities that may give rise to sleep initiation, sleep maintenance, or sleep perception problems.

REFERENCES

Armitage, R., Hoffmann, R., Loewy, D. and Moffitt, A. Variations in period-analysed EEG asymmetry in REM and NREM sleep. *Psychophysiology*, 1989, 26: 329–336.

Armitage, R., Roffwarg, H. P. and Rush, A. J. Digital period analysis of EEG in depression: periodicity, coherence, and interhemispheric relationships during sleep. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 1993, 17: 363–372.

Armitage, R., Hoffmann, R. F. and Rush, A. J. Biological rhythm disturbance in depression: temporal coherence of ultradian sleep EEG rhythms. *Psychol. Med.*, 1999, 29: 1435–1448.

Basar-Eroglu, C., Struber, D., Schurmann, M., Stadler, M. and Basar, E. Gamma-band responses in the brain: a short review of psychophysiological correlates and functional significance. [Review] [69 refs]. *Int. J. Psychophysiol.*, 1996, 24: 101–112.

Bastien, C. and Campbell, K. The evoked K-complex: all-or-none phenomenon? *Sleep*, 1992, 15: 236–245.

Beck, A. T., Steer, R. A. and Garbin, M. G. Psychometric properties of the BEck Depression Inventory; twenty-five years of evaluation. *Clin. Psychol. Review*, 1988, 8: 77–100.

Bonnet, M. and Arand, D. A. Hyperarousel and insomnia. *Sleep Medicine Reviews*, 1998.

Bonnet, M. H. and Arand, D. L. 24-hour metabolic rate in insomniacs and matched normal sleepers. *Sleep*, 1995, 18: 581–588.

Bonnet, M. H. Recovery of performance during sleep following sleep deprivation in older normal and insomniac adult males. *Percept. Mot. Skills*, 1985, 60: 323–334.

Borbely, A. A. A two process model of sleep regulation. *Hum. Neurobiol.*, 1992, 1: 195–204.

Borbely, A. A. The S-deficiency hypothesis of depression and the two-process model of sleep regulation. *Pharmacopsychiatry*, 1987, 20: 23–29.

Borbely, A. A. The two-process model of sleep regulation: implications for sleep in depression. [References]. In: D. J. K, T. H. M and J. D. B (Eds) *Biological Rhythms and Mental Disorders*. Guilford Press, New York, NY, US, 1988: 55–81.

Borbely, A. A., Baumann, F., Brandeis, D., Strauch, I. and Lehmann, D. Sleep deprivation: effect on sleep stages and EEG power density in man. *Electroencephalogr. Clin. Neurophysiology*, 1981, 51: 483–493.

Brunner, D. P., Dijk, D. J. and Borbely, A. A. A quantitative analysis of phasic and tonic submental E.MG activity in human sleep. *Physiol. Behav.*, 1990, 48: 741–748.

Brunner, D. P., Dijk, D. J. and Borbely, A. A. Repeated partial sleep deprivation progressively changes the EEG during sleep and wakefulness. *Sleep*, 1993, 16: 100–113.

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R. and Kupfer, D. J. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*., 1989, 28: 193–213.

Chase, M. H. and Morales, F. R. The atonia and myoclonia of active (REM) sleep. *Annu. Rev. Psychol*., 1990, 41: 577–584.

Coates, T. J., George, J. M., Killen, J. D., Marchini, E., Hamilton, S. and Thorensen, C. E. First night effects in good sleepers and sleep-maintenance insomniacs when recorded at home. *Sleep*, 1981, 4: 293–298.

de Beurs, E., Wilson, K. A., Chambless, D. L., Goldstein, A. J. and Feske, U. Convergent and divergent validity of the Beck Anxiety Inventory for patients with panic disorder and agoraphobia. *Depression & Anxiety*, 1997, 6: 140–146.

Dement, W. C. and Kleitman, N. Cyclic variations in EEG during sleep and their relation to eye movements, body motility and dreaming. *Neurophysiology*, 1957, 9: 673–690.

Endicott, J. and Spitzer, R. L. A diagnostic interview: the scedule for affective disorders and schizophrenia. *Arch. Gen. Psychiatry*, 1978, 35: 837–844.

Freedman, R. EEG power in sleep onset insomnia. *Electroencephalogr. Clin. Neurophysiology*, 1986, 63: 408–413.

Fulton, M. K., Armitage, R. and Rush, A. J. Sleep EEG coherence abnormalities in individuals at high risk for depression: a pilot study. *Am. J. Psychiatry*, 1996.

Fulton, M. K., Armitage, R. and Rush, A. J. Sleep electroencephalographic coherence abnormalities in individuals at high risk for depression: a pilot study. *Biol. Psychiatry*, 2000, 47: 618–625.

Galambos, R., Makeig, S. and Talmachoff, P. J. A 40-Hz auditory potential recorded from the human scalp. *Proc. Natl. Acad. Sci. United States America*, 1981, 78: 2643–2647.

Giles, D. E. and Kupfer, D. J. Evaluation of the primary sleep defect in familial unipolar depression. *Sleep Res*., 1995, 24: 162.

Giles, D. E., Kupfer, D. J. and Roffwarg, H. P. Abnormal EEG sleep antedates the onset of depression. *Biol. Psychiatry*, 1990, 27: 93A–93A.

Giles, D. E., Kupfer, D. J., Roffwarg, H. P. and Rush, A. J. Polysomnographic parameters in first-degree relatives of unipolar probands. *Psychiatry Res*., 1989, 27: 127–136.

Giles, D. E., Kupfer, D. J. and Perlis, M. L. A test of the primary sleep defect in depression using a family study model. *Biological Psychiatry* (Abstracts. Ref Type: Abstract), 1996.

Giles, D. E., Hoffman, N. H., Perlis, M. L. and Kupfer, D. J. Familial EEG dysregulation: predictor of affective morbidity. *Sleep Research*, 1998a, 25.

Giles, D. E., Jarrett, R. B., Roffwarg, H. P. and Rush, A. J. Reduced rapid eye movement latency: a predictor of recurrence in depression. *Neuropsychopharmacology*, 1987, 1: 33–39.

Giles, D. E., Jarrett, R. B., Biggs, M. M., Guzick, D. S. and Rush, A. J. Clinical predictors of recurrence in depression. *Am. J. Psychiatry*, 1989, 146: 764–767.

Giles, D. E., Searl, K. A., Perlis, M. L. and Kupfer, D. J. Early onset of depression and short REM latency are additive risks for morbidity. *Biol. Psychiatry*, 1998b, 43 (8S), 86S (Abstract).

Hamilton, M. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry*, 1960, 23: 56–62.

Hauri, P. Dreams in patients remitted from reactive depression. *J. Abnorm. Psychol*., 1976, 85: 1–10.

Hauri, P. J. and Olmsted, E. M. Reverse first night effect in insomnia. *Sleep*, 1989, 12: 97–105.

Horne, J. *Why We Sleep*. Oxford University Press, Oxford, England, 1988.

Jacobs, G. D., Benson, H. and Friedman, R. Home-based central nervous system assessment of a multifactor behavioral intervention for chronic sleep-onset insomnia. *Behav. Ther*., 1993, 24: 159–174.

Jefferys, J. G., Traub, R. D. and Whittington, M. A. Neuronal networks for induced '40 Hz' rhythms [see comments]. *Trends Neuroscience*, 1996, 19: 202–208.

Joliot, M., Ribary, U. and Llinas, R. Human oscillatory brain activity near 40 Hz coexists with cognitive temporal binding. *Proc. Natl. Acad. Sci. United States America*, 1994, 91: 11748–11751.

Kabacoff, R. I., Segal, D. L., Hersen, M. and Van Hasselt, V. B. Psychometric properties and diagnostic utility of the Beck Anxiety Inventory and the State-Trait Anxiety Inventory with older adult psychiatric outpatients. *J. Anxiety Disorders*, 1997, 11: 33–47.

Kramer, M. and Roth, T. A comparison of dream content in laboratory dream reports of schizophrenic and depressive patient groups. *Compr. Psychiatry*, 1973, 14: 325–329.

Kramer, M., Baldridge, B. J., Whitman, R. M., Ornstein, P. H. and Smith P. C. An exploration of the manifest dream in schizophrenic and depressed patients. *Dis. Nerv. Syst*., 1969, 30 (Suppl. 30):

Kupfer, D. J., Frank, E., McEachran, A. B., and Grochocinski, V. J. Delta sleep ratio: a biological correlate of early recurrence in unipolar affective disorder. *Arch. Gen. Psychiatry*, 1990, 47: 1100–1105.

Kupfer, D. J., Frank, E., McEachran, A. B. and Grochocinski, V. Delta sleep ratio: a biological correlate of early recurrence in unipolar affective disorder. *Arch. Gen. Psychiatry*, 1989, 47: 1100–1105.

Lamarche, C. H. and Ogilvie, R. D. Electrophysiological changes during the sleep onset period of psychophysiological insomniacs, psychiatric insomniacs, and normal sleepers. *Sleep*, 1997, 20: 724–733.

Llinas, R. and Ribary, U. Coherent 40-Hz oscillation characterizes dream state in humans. *Proc. Natl. Acad. Sci. United States America*, 1993, 90: 2078–2081.

Llinas, R. R. and Pare, D. Of reaming and wakefulness. *Neuroscience*, 1991, 44: 521–535.

Makeig, S. and Inlow, M. Lapses in alertness: Coherence of fluctuations in performance and EEG spectrum. *Electroencephalogr. Clin. Neurophysiol*., 1993, 86: 23–35.

Makeig, S. and Jung, T. P. Tonic, phasic, and transient EEG correlates of auditory awareness in drowsiness. *Cognitive Brain Research*, 1996, 4: 15–25.

Mendels, J. and Hawkins, D. R. Sleep laboratory adaptation in normal subjects and depressed patients ('first night effect'). *Electroencephalogr. Clin. Neurophysiol*., 1967, 22: 556–558.

Mendelson, W. B., Sack, D. A., James, S. P., Martin, J. V., Wagner, R., Garnett, D., Milton, J. and Wehr, T. A. Frequency analysis of the sleep EEG in depression. *Psychiatry Res*., 1987, 21: 89–94.

Mercia, H. and Gaillard, J. The EEG of sleep onset period in insomnia: a discriminant analysis. *Physiol. Behav*., 1992, 52 (2): 199–204.

Merica, H. and Gaillard, J. M. The EEG of the sleep onset period in insomnia: a discriminant analysis. *Physiol. Behav*., 1992, 52: 199–204.

Merica, H. and Blois, R. Relationship between the time courses of power in the frequency bands of human sleep EEG. *Neurophysiol. Clin*., 1997, 27: 116–128.

Merica, H., Blois, R. and Gaillard, J. M. Spectral characteristics of sleep EEG in chronic insomnia. *European J. Neuroscience*, 1998, 10: 1826–1834.

Nofzinger, E. A., Nowell, P. D., Buysee, D. J., Vasco, R. C., Thase, M. E., Frank, E., Kupfer, D. J. and Reynolds, C. F. Towards a neurobiology of sleep disturbance in primary insomnia and depression: a comparison of subjective, visually scored, period amplitude and power spectral density sleep measures. *Sleep*, 1999, 22 (Suppl. 1): S99–S99.

Pantev, C. Evoked and induced gamma-band activity of the human cortex. *Brain Topogr*., 1995, 7: 321–330.

Perlis, M. L., Giles, D. E., Mendelson, W. B., Bootzin, R. R. and Wyatt, J. K. Subjective – objective discrepancies in psychophysiologic insomnia: a neurocognitive perspective. *J. Sleep. Res*., 1997, 6: 179–188.

Perlis, M. L., Fleming, G., Drummond, P. and James, S. Sustained facial muscle activity during REM sleep in depressed subjects and its correlation with self reported depression. *Sleep Res.*, 1995, 24 (Abstract): 176–176.

Perlis, M. L., Andrews, P. J., Orff, H. J., Smith, M. T. and Giles, D. E. High frequency EEG activity in patients with insomnia and in good sleeper controls. *Sleep*, 2001, 24: 1, 1–8.

Perlis, M., Drummond, S. and Bootzin, R. *Sustained Facial Muscle Activity During REM Sleep: A Replication of Previous Findings* (Ref. type: Conference proceeding). Cannes, France, 1991.

Pulvermuller, F., Lutzenberger, W., Preissl, H. and Birbaumer, N. Spectral responses in the gamma-band: physiological signs of higher cognitive processes? *Neuroreport.*, 1995, 6: 2059–2064.

Rechtschaffen, A. and Kales, A. *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. U.S. Government Printing Office, Washington, DC, 1968.

Sheer, D. Focused arousal and 40 Hz EEG. In: R. Knight and D. Bakker (Eds) *The Neuropsychology of Learning Disorders*. University Press, Baltimore, MD, 1976: 71–87.

Spydell, J., Ford, M. and Sheer, D. Task dependent cerebral lateralization of the 40 Hz EEG rhythm. *Psychophysiology*, 1979, 16: 347–350.

Stepanski, E., Zorick, F., Roehrs, T. and Roth, T. Effects of sleep deprivation on daytime sleepiness in primary insomnia [In process citation]. *Sleep*, 2000, 23: 215–219.

Steriade, M., Curro Dossi, R. and Contreras, D. Electrophysiological properties of intralaminar thalamocortical cells discharging rhythmic (approximately 40 HZ) spike-bursts at approximately 1000 HZ during waking and rapid eye movement sleep. *Neuroscience*, 1993, 56: 1–9.

Szelenberger, W. Two-process model of sleep regulation of Alexander Borbely. [Polish]. *Psychiatr. Pol.*, 1987, 21: 490–494.

Tauber, E., Coleman, R. and Weitzman, E. Absence of tonic electromyographic activity during sleep in normal and spatic nonmimetic skeletal muscles in man. *Ann. Neurol.*, 1977, 2: 496–503.

Tiitinen, H., Sinkkonen, J., Reinikainen, K. and Alho, K. Selective attention enhances the auditory 40-Hz transient response in humans. *Nature*, 1993, 364: 59–60.

Tiitinen, H., May, P. and Naatanen, R. The transient 40-Hz response, mismatch negativity, and attentional processes in humans. [Review] [52 refs]. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 1997, 21: 751–771.

Toussaint, M., Luthringer, R., Schaltenbrand, N. and Carelli, G. First-night effect in normal subjects and psychiatric inpatients. *Sleep*, 1995, 18: 463–469.

Varner, J. L., Rohrbaugh, J. W., Paige, S. R. and Ellingson, R. J. Attention-related changes in a computer-extracted 40 Hz EEG rhythm. *Biomed. Sci. Instrum.*, 1984, 20: 81–83.

[1] Throughout this document we will refer to the upper portion of the EEG spectrum (14–45 Hz) as 'high frequency' activity. Although the term 'high' is more appropriate for the description of wave form amplitude, it has the advantage of being consistent with the language that is used to describe analogue and digital filters (e.g. high and low frequency filters).

[2] This procedure was suggested by one of our reviewers and we are grateful for the input. Deletion of waking or MT epochs or the epochs with Micros and Mini arousals varied by group and could have potentially accounted for the 'incoherence' of the Beta/Delta profiles in the 2nd half of the night in the MDD and PI subject plots.