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Quantitative EEG Changes in Excessive Daytime Sleepiness

By

Haiyan Yan

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Dr. Roger Broughton

Department of Cellular and Molecular Medicine
University of Ottawa
Ottawa, Ontario, Canada

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Abstract

Excessive daytime sleepiness (EDS) is the most common presenting symptom to sleep medicine clinics and has major socio-economic consequences in industrialized societies. Several approaches have been developed to assess EDS including subjective estimates, performance effects and the rapidity of falling asleep (sleep latency) under standardized conditions, most frequently as the Multiple Sleep Latency Test (MSLT). All have definite drawbacks. It is well known, however, that the on-going EEG is sensitive to variations in alertness/sleepiness levels. This project tested the applications of quantified EEG to the detection and analysis of alertness/sleepiness levels as measured by the MSLT.

Twelve age and gender matched normal subjects under rested and (one night) sleep deprived conditions and twelve sleepy untreated obstructive sleep apnea (OSA) patients underwent quantitative EEG analyses immediately before MSLT nap sessions. Mean sleep latency was significantly shorter as one compares rested controls, OSA patients and sleep-deprived controls. At both the O1 and O2 electrode sites (referential recording), the Alpha Attenuation Test (AAT) showed significantly lower AAT values as one compares rested controls, sleep-deprived controls and OSA patients. The values of absolute spectral power for the two theta bands were significantly higher in sleep deprived control subjects than in rested controls. There was an increase of absolute power

spectral values for all frequency bands in OSA patients compared to rested and sleep deprived normal subjects. The significant differences between three groups in individual electrode sites were not as strong and consistent as were the total (mean of 8 electrodes) values. These results demonstrate that spectral analysis can be a sensitive measure of EDS. However, its ability to diagnose sleepiness remains uncertain. Further studies are warranted.

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Dedication

This thesis is dedicated to my parents, my husband Guoqiang and our daughter Monsa.

Contents

List of Tables

List of Figures

Introduction

Excessive daytime sleepiness (EDS) is very frequent in industrial societies. Surveys have found that between 0.5% and 12% of the population complain of excessive sleepiness (Roth et al. 1994). Variations in prevalence depend on the particular subpopulation sampled and the specific question asked. In normal subjects EDS may be due to sleep deprivation, shift work, jet lag and substance intake. EDS is also very common in medical sleep disorders (T. Roth et al. 1994) including obstructive sleep apnea syndrome, narcolepsy-cataplexy syndrome, idiopathic hypersomnia, chronic insufficient sleep and circadian rhythm disorders. Regardless of its cause, EDS creates major problems with work, education, traffic accidents, cognition and other domains (Broughton et al. 1981, T. Roth et al. 1994).

A variety of approaches to quantify EDS have been developed. They include subjective estimates, self-assessed behavioral effects, performance effects, electroencephalogram (EEG) measures, evoked potential measures, and sleep latency tests such as the Multiple Sleep Latency Test (MSLT). However, all of our current approaches for detecting and quantifying EDS have major limitations. An optimal EDS test should be sensitive, reliable, relatively brief and be able to detect differences between sleepiness from sleep deprivation in normal subjects and "pathological" sleepiness in EDS patients.

In considering the approaches currently in use for investigating excessive daytime sleepiness, it is essential to separate measures done in wakefulness

which can predict increased propensity to fall asleep (i.e., detect "sleepy wakefulness") from measures which detect the actual presence of physiological drowsiness.

Measures of Daytime Sleepiness

1. Self-Report Measures

Some of the first attempts to quantify sleepiness were subjective self-reports that consist of documenting the individual's assessment concerning levels of energy, ability to function, desire for sleep, and probability of falling asleep under various conditions. The main measures include the Stanford Sleepiness Scale (Hoddes et al. 1972), the 10 cm visual-analog scale (VAS) (Monk et al. 1983), the activation/deactivation check list (Thayer 1978), the Epworth Sleepiness Scale (Johns 1991), and the Sleep-Wake Activity Inventory (Rosenthal et al. 1993).

The Stanford Sleepiness Scale was one of the first systematic attempts to quantify sleepiness. This seven point scale uses a subjective rating approach designed to quantify individual perceptions of sleepiness ranging from (1) "feeling active and vital; wide awake" to (7) "almost in reverie; sleep onset soon; lost in struggle to remain awake". Although it has been shown to be an accurate predictor of objective sleepiness after one night of total sleep deprivation (Hoddes et al. 1973, Glenville et al. 1978), the Stanford Sleepiness Scale

becomes a poor predictor after only a few nights of partial sleep deprivation (Herscovitch and Broughton 1981). It is totally unreliable when excessive daytime sleepiness is chronic (Valley and Broughton 1981, Carskadon and Dement 1982a).

The 10 cm visual-analog scale requires the individual to intersect a 10 cm line that is labeled "very sleepy" at one end and "very alert" at the other. The distance between the left end of the line and the point of intersection represents the VAS score. Although it provides a continuum rather than discrete levels of sleepiness/alertness, the VAS score fails to correlate well with objective measures of sleepiness such as the Multiple Sleep Latency Test (MSLT) (Johnson 1991).

Thayer's activation-deactivation adjective check list (AD-ACL) instructs subjects to indicate the degree to which each adjective on a hypothetical activation continuum describes his or her feelings at any given moment (Thayer 1978). The subject then chooses from a four point rating scale as follows: (1) definitely feel, (2) feel slightly, (3) cannot decide, and (4) definitely do not feel. Although this checklist was designed to identify a host of feelings ranging from extreme excitement through to overwhelming sleepiness, there is no relationship between the AD-ACL and the MSLT across the day (T. Roth et al. 1994).

The Epworth Sleepiness Scale measures a person's general level of daytime sleepiness by inquiring about the likelihood of falling asleep under eight different situations commonly encountered in daily life ranging from those with low to those with high activity levels (Johns 1991). Total scores on the Epworth

Sleepiness Scale correlate with MSLT scores in medical conditions with chronic sleepiness such as narcolepsy and sleep apnea (Johns 1992). However, the Epworth Sleepiness Scale is not designed to be used in the presence of short-term conditions such as acute sleep loss which can also influence sleep tendency (Mitler 1996).

In clinical practice, sleepiness often is confused with fatigue, tiredness, and lassitude. Moreover, some patients will respond by denying sleepiness, when it exists. Therefore a multidimensional self-report scale, the Sleep-Wake Activity Inventory has been developed which includes psychic distress and behavioral activation factors in addition to the sleepiness factor (Rosenthal et al. 1993). This inventory has shown to reliably predict MSLT scores (Rosenthal et al. 1993).

2. Performance Tests

Performance tests were amongst the earliest approaches to assess excessive daytime sleepiness (Wilkinson 1965) and have been intensively studied (Webb 1982, Monk 1991, Broughton and Ogilvie 1992). Some tests are insensitive to excessive daytime sleepiness either inherently or from sensitivity to the effects of motivation. The latter is particularly a factor in many short, highly challenging psychomotor tasks (Valley and Broughton 1981, 1983) and memory tasks (Aguirre et al. 1985). Early studies suggested that to be sensitive a task must be prolonged and boring (Wilkinson 1965). Wilkinson (1968) developed cognitive tasks that are lengthy, repetitive and devoid of feedback.

He found them to best permit researchers to detect degradations in performance following sleep loss or disruption of the circadian cycle. However, Lisper and Kjellberg (1972) identified shorter tests that proved sensitive in a variety of settings. Wilkinson has been responsible for the development of several portable performance tasks (Wilkinson and Houghton 1975). Such work has led to the appearance of relatively brief (approximately 10 min), portable and computer-based performance tests. These shorter tasks, including simple and choice reaction time tests (Glenville et al. 1978, Godbout and Montplaisir 1986) and brief tests of divided attention (Roehrs et al. 1990), have proven to be sensitive detectors of excessive daytime sleepiness while being relatively resistant to motivational effects.

Direct correlation of the MSLT with measures of performance under normal conditions has not been very promising (Nicholson and Stone 1986). However, several studies have found that, when sleepiness is at maximal levels, correlation with performance is high. For example, MSLT scores after sleep deprivation (Carskadon and Dement 1982a), after administration of sedating antihistamines (Nicholson and Stone 1986), or after benzodiazepine administration (Roth and Roehrs 1985), correlate with measures of performance; and performance measures even prove at times to be more sensitive than MSLT (Roehrs 1986). Such findings suggest that significant sleepiness is necessary to induce performance decrements.

3. Routine EEG

The EEG is generated by the nerve cells of the cerebral cortex which line the surface of the brain hemispheres. The fluctuations of electrical potentials recorded in the scalp EEG reflect changes of a steady electrical charge on the cell membrane modified by impulses arriving from other cells. Although one might expect that the complex neuronal activities of the brain would result in rather irregular EEG waves, the EEG of human subjects, awake and at rest, commonly contains rhythmic activity in the cortex. Such rhythmicity depends on synchronizing impulses from a central pacemaker which generates rhythmical activity through a network consisting of thalamic projection neurons, thalamic interneurons, and feedback loops (Steriade et al. 1998). The interaction of other activating centers with the pacemaking center and/or the cortex may cause so-called "desynchronization" of rhythmical activity (Lesch and Spire 1990)

For EEG recording, electrodes are placed according to the international "10-20 system" (Jasper 1958). It is a simple proportional method that determines each electrode's scalp location in relation to the skull's anterior-posterior and coronal dimensions as measured from easily determined landmarks (inion-nasion, external auditory meati). Each electrode is then connected to an amplifier which compares the electrical activity of that electrode in relation to either another active and usually neighboring electrode (bipolar method) or a distant referential, ideally noncephalic, electrode (monopolar method). Each recording system is referred to as a channel; and the pattern of electrodes displayed at any one time is called a montage.

EEG waves are often divided into four groups by frequency: delta, theta, alpha and beta (Lesch and Spire 1990). Alpha is defined as 8-12 Hz activity. The alpha rhythm is a posteriorly and often relatively symmetrically distributed sinusoidal rhythm usually with an amplitude of 20-100 μV in awake normal individuals between the ages of 10 and 65 years. It is best seen while comfortably resting awake with eyes closed. The alpha rhythm is distributed over both occipital head regions with a field distribution often extending to parietal and posterior temporal areas, often with slightly greater amplitude on the right side. Beta defines the frequency band above 12 Hz and its amplitude is usually below 15-20 μV. Beta activity is usually symmetrically distributed over frontal and central areas and is almost universally present in normal elderly subjects. Beta activity increases or appears when subjects become drowsy (early stage 1) in approximately 30% of population for a few seconds before typical stage 1 drowsiness become evident. Theta activity defines the frequency band of 4 to just under 8 Hz; and its amplitude is typically less than 20-30 μV. Theta appears in some drowsy normal subjects as the alpha rhythm disappears. Delta is activity with a frequency of less than 4 Hz. Delta is always pathological in the awake normal adult. But during sleep it becomes the dominant frequency of the deeper slow wave sleep stages (stage 3 and 4).

The ongoing (spontaneous) EEG is the most sensitive known real-time indicator of alertness / drowsiness levels. However, it has not been proven that visual analysis of the waking EEG can predict latent sleepiness. EEG signs of existing physiological drowsiness and sleep onset have long been recognized in

normal subjects (Loomis et al. 1937, Gibbs and Gibbs 1952) and in EDS patients (Pond 1952, Gastaut and Roth 1957, Daly and Yoss 1957, Roth 1964). The posterior alpha rhythm often slows (by 0.5-2.0 Hz), may diffuse anteriorly, then fragments and disappears. It is replaced by a mixed frequency EEG characterized predominantly by theta activity maximum at, and spreading from, midline frontal and central scalp regions. Changes in beta are difficult to assess visually, due to their low amplitude and at times due to obscuring muscle artifacts. Vertex negative sharp waves may occur, and "waxing and waning" of ongoing brainwave patterns is typical (Oswald 1962) before sleep becomes fully established with fronto-central 11.5-15 Hz sleep spindles (sigma waves), K-complexes, and increasing delta activity which is maximum in frontopolar regions (Brazier 1949).

The EEG continuum from wakefulness to stage 2 sleep has been divided into as many as 5-7 substages by various authors (Roth 1961, Bente 1965, Häkkinen 1972, Ulrich and Frick 1986). These intermediary changes are ignored in the standard sleep staging rules of Rechtschaffen and Kales (1968). However, even "minor" slowing and diffusion of alpha (substage 1A of Gastaut and Broughton, 1965) correlates with a marked (54%) decrease of performance efficiency from full waking levels on a sensitive vigilance task (Valley and Broughton 1983).

Researchers usually only monitor central leads and occasionally occipital leads. The striking spatiotemporal changes, which accompany fluctuations in sleepiness/alertness levels during wakefulness and during the sleep onset

process are therefore ignored. A rare full scalp EEG description of these changes is available in Santamaria and Chiappa (1987).

4. Slow eye movements (SEMs) and submental electromyogram (EMG)

A difference in electrical potential exists between the anterior and posterior parts of the eye with the anterior portion being about 0.1 mV positive relative to the back. The recorded magnitude and polarity of this electrical field change relative to the fixed recording electrode changes as the eye moves. Slow eye movements (SEMs) are prominent when subjects are in a drowsy physiological state during the transition between wake and sleep (Torsvall and Akerstedt 1988, Akerstedt and Gillberg 1990). Submental electromyogram (EMG) levels in general decrease during drowsiness and sleep; and they show minimal or no tonic activity in REM sleep (Berger and Oswald 1962).

5. Sleep Latency (SL)

The time to fall asleep under standardized conditions is a widely used measure of EDS. In the Multiple Sleep Latency Test or MSLT (Carskadon and Dement 1977, Richardson et al. 1978), subjects are requested to try and fall asleep during four or five 20-min scheduled naps separated by 2 hr intervals across the daytime. The sleep latency (time between the point at which the lights are turned off and when the first sleep is detected on the EEG) is

determined for each nap; then the mean sleep latency is calculated and interpreted.

The MSLT is a well-validated research and clinical tool that is now used throughout the would. It is a straightforward objective measure of daytime sleep tendency which is based on the assumption that sleepiness is a state of physiological need which leads to an increased tendency to rapidly fallg asleep. One of the most important features of the MSLT is that it clearly reflects the effects of experimental sleep deprivation (Carskadon and Dement 1981, 1982b). If prior sleep is reduced from baseline levels, the MSLT shows an increase in sleep tendency (shorter mean sleep latency). The test is sensitive to the effects of age, sleep deprivation and most sleep disorders with EDS.

A mean sleep latency of less than 5 minutes on the MSLT has been viewed as evidence for pathological sleepiness. Mean latencies of 5-8 minutes are generally considered as a gray borderline or zone; and latencies of more than 8 minutes are usually considered normal. The MSLT is based on the assumption that "those individuals who are sleepy will fall asleep more quickly than those who are not" (Hartse et al. 1982).

This might be true in general, but there are several exceptions. For example, false negatives can be noted in sleepy patients with problems of sleep onset including insomniacs (Stepanski et al. 1988) and the head-injured (Manseau and Broughton 1990). As well, false positives have been reported in non-sleepy normal subjects, especially regular nappers (Broughton et al. 1988). Moreover, there is some degree of overlap between the pathological group and

controls (Roth et al. 1980, Broughton et al. 1988). Hence, it appears that the MSLT measures the ability to initiate the sleep process combined with physiological sleep pressure, and not the latter alone.

The MSLT is not without other limitations. First, sleep latency is not entirely an objective measure, as the decision on the precise moment of sleep onset is based on human visual judgment. Second, the MSLT is very inefficient in that it requires 8-10 hrs to complete the measurement of persistent EDS. Thirdly, the MSLT does not provide a measure of sleep propensity (probability) while the subject is still awake. Finally, it requires interruption of daily activities.

Alternatives to the MSLT have therefore been developed. One such alternative is the Maintenance of Wakefulness Test (MWT) (Mitler et al. 1982a). This test requires that the subject, who is monitored for EEG sleep onset, sits in a chair in darkened room and follows a request to remain awake for 20 or 40 minute recording sessions. Hartse et al. (1982) found a prolonged sleep latency as a result of the instruction to remain awake, compared to asking the subject to go to sleep, as is done in the MSLT. Although the MWT may seem to produce a simple prolongation of daytime sleep latencies, detailed comparisons of the MSLT and the MWT have disclosed that the two tests do not correlate well in patients who complain of excessive sleepiness. Moreover, the MWT is as cumbersome and expensive as MSLT; and there is marked discordance with the MSLT, the primary and most widely used EEG measure of sleep latency.

Other alternatives to the MSLT include the Repeated Test of Sustained Wakefulness (RTSW) (Hartse et al. 1982), the single-nap Polygraphic Score of

Sleepiness (B. Roth et al. 1986), and the Modified Assessment of Sleepiness Test (Erman et al. 1987). None of these alternatives has produced improved sensitivity. For all these tests, factors other than sleep pressure affect sleep latency including compliance to instructions and learned ability for falling asleep.

6. Event Related Potentials (ERPs)

The electrical signals generated by the central nervous system (CNS) in response to stimuli have received considerable attention in the awake human, particularly the long-latency, endogenous or cognitive so-called event-related potentials (ERPs). These electrical signals reflect synchronous activity in cortical and subcortical areas and typically occur up to 500 ms poststimulation.

Stimuli presented to sleeping humans evoke electrical signals similar to those seen in awake humans, especially for some of the earlier components ($\leq$ 200 ms). Stimuli presented to a sleeper also evoke signals distinctly different from those evoked in an awake subject. These sleep-specific components are generally of long onset latency ($\geq$ 300 ms) and in on-going EEG are typically referred to as the *K-complex* (M. Roth et al. 1956, Bastien and Campbell 1992) .

The waking simple auditory evoked potential to tone stimuli has shown significant differences between untreated narcoleptics and controls (Broughton et al. 1982); but high variability precluded its use for EDS diagnosis. On the other hand, the waking P300 component, a positive potential occurring roughly 300 ms after stimulation, is substantially reduced in sleep deprived normal

subjects (Campbell et al. 1980, Kok et al. 1992) and in narcoleptics (Aguirre and Broughton 1984, 1987, Ollo et al. 1987). It is almost as sensitive as the MSLT in untreated narcoleptics, but is less accurate for diagnosis (Broughton et al. 1988). To a degree, this measure suffers from its state sensitivity; that is, it can be a highly labile measure that changes from moment to moment (T. Roth et al 1994). The significant disadvantage of ERPs, of course, is the need to stimulate subjects and to average responses across significant periods of time. The technique is therefore of limited interest in detecting and monitoring ongoing fluctuations of alertness/sleepiness.

7. Quantitative EEG

Quantitative EEG (QEEG) is the mathematical processing of digitally recorded EEG in order to analyze specific components, transform the EEG into a format or domain that elucidates relevant information, and associate the numerical results with the EEG data for subsequent review or comparison. There are various techniques for the automatic detection of particular EEG components, quantification of background rhythms and sleep EEG staging. Computer EEG studies of physiological drowsiness and sleep stages have been done using two basic approaches. One is power spectral analysis (Matousek and Petersen 1983, Belayavin and Wright 1987, Torvall and Akerstedt 1987, Ogilive et al. 1991) and its variants (frequency filtering - O'Hanlon and Kelley 1977; autocorrelation - Hakkinen 1972; and cross-correlation - Montplaisir et al.

1990). The other is period amplitude analysis (Ktonas and Gosalia 1981, Pigeau et al. 1981) and its variants (period analysis - O'Hanlon and Beatty 1977).

Power spectral analysis is a technique for the analysis of EEG data in the *frequency* domain. It divides the EEG into its component frequencies following a fast Fourier transform (FFT). FFT is a mathematical transformation procedure designed to evaluate stationary processes in a time series of data by generating a sine/cosine decomposition of the time series. It assumes that a complex wave can be accurately described by a series of sine/cosine statements or values that vary in magnitude and phase, and thus combine to create the siginal data. The Nyquist equation states that the digitization rate should be greater than twice the highest frequency of interest. For example, if the frequency range of interest were to be 0.1 – 35 Hz, the digitization rate should be 70 Hz.

Power changes in a specific frequency range can reflect changes in frequency of events within the constituent frequency bands. For example, the alpha frequency band ranges from 8 – 12 Hz. When the alpha rhythm becomes slower (e.g. 7.5 Hz), as can occur in drowsiness, the spectral power in the band will decrease. In power spectral analysis each of these frequency subcomponents is allocated a power value (area under the curve) which is the square of the magnitude of the FFT. The resulting spectral power (typically in μV^2) may be integrated or averaged across the frequencies of interest. Spectral analysis provides an efficient quantification of overall broadband rhythms present in an EEG epoch. Because it is an averaging process over a given time

window, it does not characterize well certain EEG details, in particular transients such as sleep spindles or K-complexes.

Period amplitude analysis is a *time* domain (versus frequency domain) EEG analysis technique. It is essentially based on filter techniques and subsequent counting of the number of waves of a certain frequency plus computation of their amplitude. Period amplitude analysis is computationally simpler than power spectral analysis and makes fewer assumptions about the underlying structure of the data being analyzed. Also, power spectral analysis cannot distinguish between wave amplitude and wave incidence, as does period amplitude analysis. Since period amplitude analysis treats the EEG as a superposition of waves with particular individual periods and amplitudes, it can be used for detailed EEG quantification by measuring the duration and peak amplitude between successive EEG wave zero-crosses.

While power spectral analysis efficiently quantifies overall power trends by combining incidence and amplitude information for a particular EEG frequency band, period amplitude analysis offers more resolution in EEG analysis as it detects details in amplitude and wave-duration incidence which are lost in spectral analysis. Whereas power spectral analysis relates to a process in which one tries to fit a series of continuous (periodic) sinusoidal functions to the whole length of the data in the EEG epoch under investigation; in period amplitude analysis, individual half- or full-waves of the EEG are examined, one at a time, for their duration and amplitude. As a result, the concept of "frequency" is different in the two techniques. In power spectral analysis,

"frequency" refers to the frequency of the periodic sinusoidal wave which is present in the epoch, while in period amplitude analysis the term "frequency" refers to the inverse of the period between consecutive zero-level crossings of the EEG. Periodic amplitude analysis loses all information not involving zero-crossing.

Both power spectral analysis and period amplitude analysis are quantification tools which enable the investigator to estimate the "amount" of activity in various EEG frequency bands of interest. However, power spectral analysis involving decomposition of the EEG data into Fourier components can quantify the power in low-frequency EEG activity which possibly exists as a slowly varying trend (i.e., variation in base-line level) in the EEG epoch, and which may not manifest itself as a visually obvious event. On the other hand, period amplitude analysis cannot quantify such phenomena because faster events, such as well-defined beta waves, are superimposed on the slow fluctuations. These faster events do not provide well-defined zero-crossings, and are thereby "masked" by the slow fluctuations.

Power spectral analysis shows particular promise in detecting and quantifying sleepiness in the awake EEG. Corsi-Cabrera and colleagues (1992) found that after sleep deprivation the awake EEG shows an increase in spectral power expressed either as absolute (μV^2) or relative (% of whole frequency range) values, for theta, alpha and beta frequency bands. Brunner et al. (1993) reported that after sleep deprivation significant changes in the delta and alpha ranges were obtained in both the eyes open fixating and eyes closed conditions.

Power densities in their high delta band (3.75-4.5 Hz) were significantly increased and in the alpha range (9.25-10 Hz) were decreased.

Other studies have suggested that EEG power density increases in theta/alpha frequency range across prolonged periods of wakefulness (Torsvall et al. 1987, Gundel & Witthoft 1983, Akerstedt & Gillberg 1990, Cajochen et al 1995). Belyavin and Wright (1987) found marked increases in theta (4-7 Hz) activity coupled with decreases in beta (14-21 Hz) particulate when performance was poor and concurrent vigilance was low. Increasing alertness within wakefulness induces a reduction of theta and alpha frequency activities leading at times to a "low voltage fast" EEG (Niedermeyer 1993).

One possible mechanism for this increase in spectral power of the slower EEG frequencies is suggested by the 2-process model of sleep/wake regulation (Borbély 1982, Daan et al. 1984). It postulates that two processes play a dominant role: a sleep/wake dependent process (Process S) and a sleep/wake independent circadian process (Process C). Process-S, a homeostatic process, is reflected in the spectral power of low delta EEG frequencies which are believed to progressively increase across wakefulness and show an exponential decline during sleep. The level of Process S at sleep onset is therefore a function of prior wake time. Process C is reflected by the daily rhythmic variation of sleep propensity and is assumed to be controlled by a circadian oscillator. Sleep deprivation by increasing wake time would then lead to an increase in process-S with the prediction of consequent increases in EEG spectral power of the lower frequencies during both wakefulness and recuperative sleep.

EEG spectral power changes in the predicted direction of greater increase in the slower EEG frequencies have also been described for patients with EDS (Matousek and Petersén 1983, Matousek 1988). But such studies have either used bipolar rather than referential recordings (which makes power estimates dubious; due to cancellation of in-phase activities) or have not been compared to more standard EDS measures (e.g., MSLT or performance). One exception is the "alpha attenuation test" or AAT which is the ratio of eyes closed /eyes opened alpha spectral power in wakefulness. It is based upon the fact that sleepiness, when compared to fully alert wakefulness, is associated with an increase abundance and magnitude in the alpha rhythm (8-12) during eyes opened but a decrease during eyes closed. Therefore, the higher the AAT value, the greater the alertness level. Stampi et al. (1993, 1995) reported that this test correlates well with the MSLT in rested and sleep-deprived normal subjects.

Normal versus so-called "Pathological" Sleepiness

Presently, no fundamental differences in sleepiness have been documented between sleep-deprived normal subjects and sleep disordered patients. If normal persons are sufficiently sleep deprived, they can experience irresistible sleep attacks and their results can overlap with the EDS patient range on both performance testing (Glenville et al. 1978, Herscovitch and Broughton 1981) and MSLT (Carskadon and Dement 1979, 1981). The main difference of

note is that sleepiness in sleep deprived normal subjects is rapidly reversible by obtaining sufficient recovery sleep; however, similar attempts to extend sleep in patient groups do not improve pathological EDS.

EDS is not a homogeneous state. It can consist of qualitatively different substates. Snyder (1963) reviewed the evidence for the existence of three basic biological states: wakefulness, NREM sleep (synchronized sleep, quiet sleep), and REM sleep (desynchronized sleep, active sleep). Broughton (1992) proposed the existence of qualitatively different sleepiness states based on fundamentally different biological mechanisms. Such different states of sleepiness could reflect any of the following: sleep deprivation, sleep satiation, circadian desynchrony, selective pressure for REM sleep or NREM sleep, incomplete awakening from sleep ("sleep inertia"), impaired waking arousal, and impaired sleep onset mechanisms. Sleepiness created by such fundamentally different mechanisms would be expected to show qualitative differences in a number of parameters including subjective experience, EEG measures (e.g. quantitative EEG features, event-related potential parameters), sleep measures (e.g. nocturnal sleep structure, MSLT) and so forth.

Quantitative EEG holds much promise for further defining these EDS states. In the Allen et al. (1995) study, awakenings from REM sleep in normal subjects led to lower spectral power in the awake sigma EEG frequency range prior to sleep re-entry into REM compared to into NREM sleep. It is possible that long-term EDS in patients with sleep disorders might produce subtle

cumulative changes in quantitative EEG measures which are not present in normal subjects after acute sleep deprivation.

The main goal of this current study has been to assess whether quantitative EEG (spectral analysis) can meet the needed desiderata for an optimum measure of EDS in the awake "sleepy" state (awake sleep propensity).

METHODS

Subjects:

Three groups of volunteer subjects participated in this study: (1) 10 male and 2 female normal rested controls (mean age 54.6 ± 6.5 years); (2) the same normal subjects after one night of total sleep deprivation; (3) 10 male and 2 female obstructive sleep apnea (OSA) patients with pathological sleepiness (mean age 53.2 ± 11.6 years) recruited from the Ottawa Hospital (General Campus) Sleep Disorders Clinic.

All subjects had a prior full history, physical examination, sleep questionnaire, overnight polysomnogram (PSG) and next-day MSLT. Female subjects were studied between days 5 to 15 of the menstrual cycle. Normal controls were chosen who habitually slept 6 to 8 hours, had no sleep problems, no CNS active medication, an apnea index ≤ 3/hr, periodic leg movements in sleep (PLMs) ≤ 5/hr, and an MSLT SL > 15 min. Controls were also studied after one night of total sleep deprivation confirmed by ambulatory EEG monitoring (Medilog 9000 system). OSA patients with sleepiness were diagnosed and selected using criteria of an apnea index > 20/hr, variable SaO_2 levels, PLMs ≤ 5/hr and MSLT SL ≤ 7 min. OSA patients were tested before being treated with nasal continuous positive airway pressure (nCPAP).

Data gathering:

After diary documentation of at least 1 week of habitual night sleep patterns, daytime recordings for quantitative EEG were done in a sound attenuated, climatically controlled sleep laboratory with the physiological variables being amplified and recorded by a Melville Sandman Digital Sleep Analysis System. Recordings followed the guidelines of Pivik et al. (1993) and involved a 19 EEG channel montage (international 10-20 system, Jasper 1958) of: Fp1, Fp2; F7, F3, Fz, F4, F8; T3, C3, Cz, C4, T4; T5, P3, Pz, P4, T6, O1 and O2. Each electrode was referred to a common linked-mastoid reference with a 10-kOhm resistor between M1 and M2. This full scalp EEG coverage was chosen so as to be compatible with a commercial EEG topographic mapping software package the analyses of which do not form part of this thesis. For the Q-EEG analyses reported here data was derived from either the average of 8 standard EEG electrodes or from a single EEG electrode. Gold cup electrodes were used. The impedance of the electrode-electrolyte-skin contact was kept less than 5000 Ohms. The recordings also included a bipolar electro-oculogram (EOG), which linked electrodes above the right and below the left eye, a submental electromyogram (EMG) and an electrocardiogram (EKG).

All EEG data underwent AD conversion (analog to digital conversion) at 200 Hz with a flat frequency response from 0.2-30.0 Hz using the Sandman system and was stored on CD disks. This sampling rate exceeds considerately the maximum EEG frequency of interest (30-35 Hz) in scalp recordings, and the demands of the Nyquist equation.

MSLT:

The study involved an MSLT test with four 20 min nap periods beginning at 1000, 1200, 1400 and 1600h following the procedural guidelines of Carskadon et al. (1986) except that: (1) the pre-nap waking EEG was sampled under standardized conditions; and (2) sleep, when it occured, was permitted for up to 10 min within each period. The MSLT measures were the 4-nap mean SL and sleep stage amounts (min). As well, all stage changes (shortest duration 2.5 sec) were visually scored as sustained wakefulness, fragmented wakefulness (for both during eyes opened and eyes closed), stages 1A, 1B, 2 and REM sleep, as in Valley and Broughton (1983).

Quantified EEG Analysis:

15 min. before each nap subjects had post-calibration wake recordings done for 3 min. each of eyes closed and eyes open fixating on a point 60 cm in front of the head. Minimization of artifacts was achieved by coached relaxation of jaw and scalp muscles. Thereafter, at the appropriate clock times, the lights were turned off and subjects were requested to fall asleep. EEG data were divided into the traditional frequency bands of: delta-1 (0.2-1.9 Hz), delta-2 (2.0-3.9), theta-1 (4.0-5.9), theta-2 (6.0-7.9), alpha-1 (8.0-9.9), alpha-2 (10.0-12.9), beta-1 (13.0-18.9) and beta-2 (19.0-25.9). For each subject, 20 artifact-free 5-second mini-epochs were selected in both the eyes closed and eyes open conditions.

Spectral analyses were performed using a program written in the laboratory (by M. Rivers) using the MatLab software package which calculates the fast Fourier Transform on 5-second mini-epochs with a resolution of 0.2 Hz. Spectral analyses following Fast Fourier Transform on artifact-free wake segments were used to quantify absolute power in frequency bands and also to generate power ratios. The main measures were the alpha attenuation test (AAT) based upon the occipital electrodes alone and autospectral power (both absolute and relative) averaged across 8 electrodes (F3, Fz, F4, C3, Cz, C4, O1, O2). Both measures were compared to mean SL on MSLT.

In order to determine whether the epochs selected for Q-EEG analyses were equivalent in respect to alertness levels, all epochs were later scored as to whether or not any slow eye movements (SEMs) were present. This measure was expressed as an SEM index which calculated the average of how many second of each 5-second epochs had SEM activity. The SEM index was later compared between all three groups.

Analysis/Statistics:

The large amount of data generated in quantitative EEG studies has led researchers to adopt various methods of data reduction prior to statistical analyses (Dumermuth and Molinari 1987, Wong 1991). Following the strategy detailed by R. Bencivengia in Wong (1991), an integrated approach to data analysis (i.e., estimation, classification, and hypothesis testing) was adopted for this study. Analysis of variance (ANOVA) and multiple linear regression were

used respectively to compare categorical variables (e.g., groups, MSLT sessions) and correlate between separate variables (e.g., delta EEG power and AAT index with mean SL). The stability of the experiment-wise error ($p \leq 0.05$) was assessed using the Bonferroni-Holm procedure (Holm 1979) which is a less conservative and more powerful version of the Bonferroni type 1 error adjustment for multiple tests. A two-way factorial (3 x 4) design for groups and time of day effects was used.

Results

1. MSLT

The analysis of sleep latency on MSLT showed a significant difference between the three groups ($p < 0.001$). Post hoc testing (Bonferroni Holm Test) showed significant differences between each two-group comparison (all $p < 0.001$). Mean sleep latency was significantly shorter as one compares the rested control (10.81 ± 0.15 min), OSA patient (9.32 ± 0.15 min), and sleep deprived control (3.81 ± 0.11 min) groups.

2. The alpha attenuation test (AAT)

At both the O1 and O2 sites, the analysis of the ratio of eyes closed to eyes opened for mean alpha power, i.e., the alpha attenuation coefficient (AAC), showed a significant difference between the three groups. The results are presented in Table1 and Figure 1. There was no significant correlation between AAT and MSLT ($p > 0.05$).

Table 1. Comparison of AAC between three groups in both O1 and O2 sites

AAC	O1		O2	
	Alpha 1	Alpha 2	Alpha 1	Alpha 2
Rested Normal	5.63±0.75	2.37±0.27	5.16±0.70	2.44±0.39
Sleep Deprived Normal	3.51±0.60 *	2.43±0.24	3.91±0.55 *	2.73±0.41
OSA Patient	1.72±0.11 *** +	1.24±0.04 ** ++	1.98±0.14 *** +	1.41±0.05 * ++

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs rested normal subjects

+++ $p < 0.001$, ++ $p < 0.01$, + $p < 0.05$ vs sleep deprived normal subjects

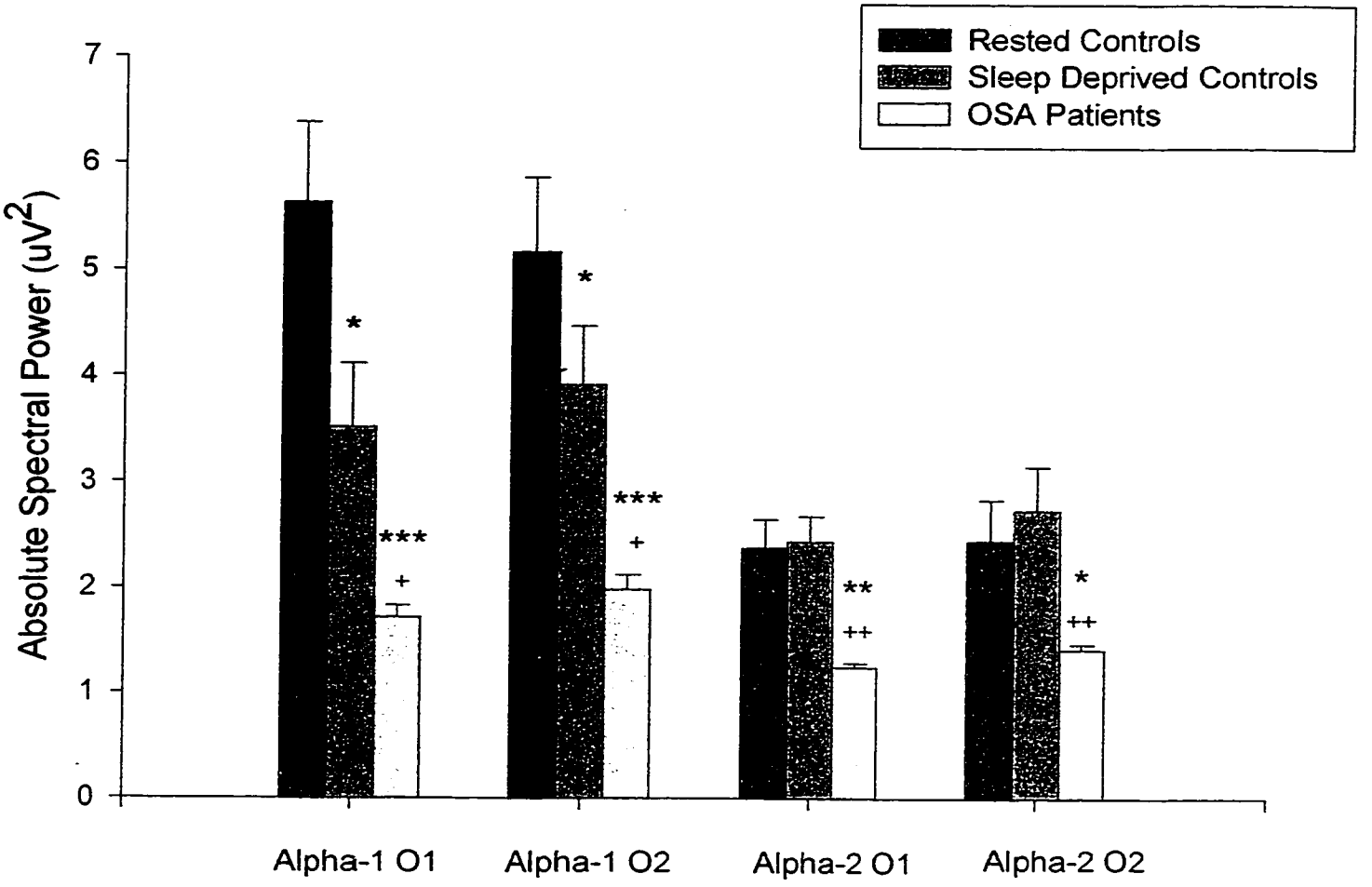

Fig 1. Comparison of AAC between three groups in both O1 and O2 sites.

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs rested controls

+++ $p < 0.001$, ++ $p < 0.01$, + $p < 0.05$ vs sleep deprived controls

3. Absolute and relative power measures

The absolute and relative power spectral values for each of the 8 frequency bands averaged across the 8 electrodes were compared between the three groups (Tables 2 and 3, Figures 2 - 5).

Table 2. Comparison of absolute spectral power between the three groups for the 8-electrode average

Absolute Spectral Power	Rested Controls	Sleep Deprived Controls	OSA Patients
Delta-1 *eyes closed*	46.68±3.80	45.25±1.95	61.72±2.85 *** +++
eyes open	29.40±1.44	32.03±1.59	51.66±3.07 *** +++
Delta-2 *eyes closed*	5.94±0.30	5.92±0.18	7.26±0.25 *** +++
eyes open	5.31±0.19	5.93±0.27	7.60±0.44 *** +++
Theta-1 *eyes closed*	4.52±0.16	5.44±0.19 **	6.33±0.34 *** +++
eyes open	3.69±0.12	4.66±0.16 **	6.02±0.41 *** +++
Theta-2 *eyes closed*	7.04±0.30	9.68±0.47 **	11.60±0.88 *** ++
eyes open	4.36±0.20	5.88±0.33 **	6.60±0.42 *** ++
Alpha-1 *eyes closed*	19.12±1.12	15.85±0.86	24.50±1.08 *** +++
eyes open	4.77±0.19	5.76±0.26	9.52±0.46 *** +++
Alpha-2 *eyes closed*	8.23±0.44	9.62±0.60	10.62±0.42 *** ++
eyes open	4.20±0.12	4.57±0.14	7.56±0.35 *** +++
Beta-1 *eyes closed*	5.64±0.16	5.70±0.15	10.05±0.47 *** +++
eyes open	4.56±0.15	4.59±0.13	8.27±0.42 *** +++
Beta-2 *eyes closed*	2.93±0.12	3.29±0.13	5.16±0.23 *** +++
eyes open	2.98±0.14	3.26±0.15	5.24±0.24 *** +++

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs rested controls

+++ $p < 0.001$, ++ $p < 0.01$, + $p < 0.05$ vs sleep deprived controls

Table 3. Comparison of relative spectral power between the three groups for the 8-electrode average

Relative Spectral Power	Rested Controls	Sleep Deprived Controls	OSA Patients
Delta-1 *eyes closed*	0.44±0.01	0.44±0.009	0.45±0.01
eyes open	0.46±0.007	0.45±0.008	0.49±0.01 * +++
Delta-2 *eyes closed*	0.06±0.001	0.06±0.001	0.05±0.002 ** +
eyes open	0.09±0.002	0.08±0.001	0.06±0.001 *** +++
Theta-1 *eyes closed*	0.05±0.001	0.05±0.001	0.04±0.001 * ++
eyes open	0.06±0.001	0.07±0.001 *	0.05±0.001 *** +++
Theta-2 *eyes closed*	0.07±0.002	0.08±0.002	0.08±0.004
eyes open	0.07±0.003	0.09±0.003 ***	0.06±0.003 * +++
Alpha-1 *eyes closed*	0.18±0.008	0.16±0.006 **	0.18±0.007 ++
eyes open	0.09±0.003	0.10±0.004	0.11±0.005 **
Alpha-2 *eyes closed*	0.09±0.004	0.10±0.004	0.08±0.003 +
eyes open	0.08±0.003	0.08±0.003	0.08±0.003
Beta-1 *eyes closed*	0.07±0.002	0.07±0.002	0.07±0.002
eyes open	0.08±0.002	0.08±0.003	0.08±0.002
Beta-2 *eyes closed*	0.04±0.001	0.04±0.002	0.04±0.001
eyes open	0.05±0.002	0.06±0.002	0.06±0.002

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs rested controls

+++ $p < 0.001$, ++ $p < 0.01$, + $p < 0.05$ vs sleep deprived controls

As can be seen in these tables, the absolute power spectral value was more reliable than was the relative power spectral value.

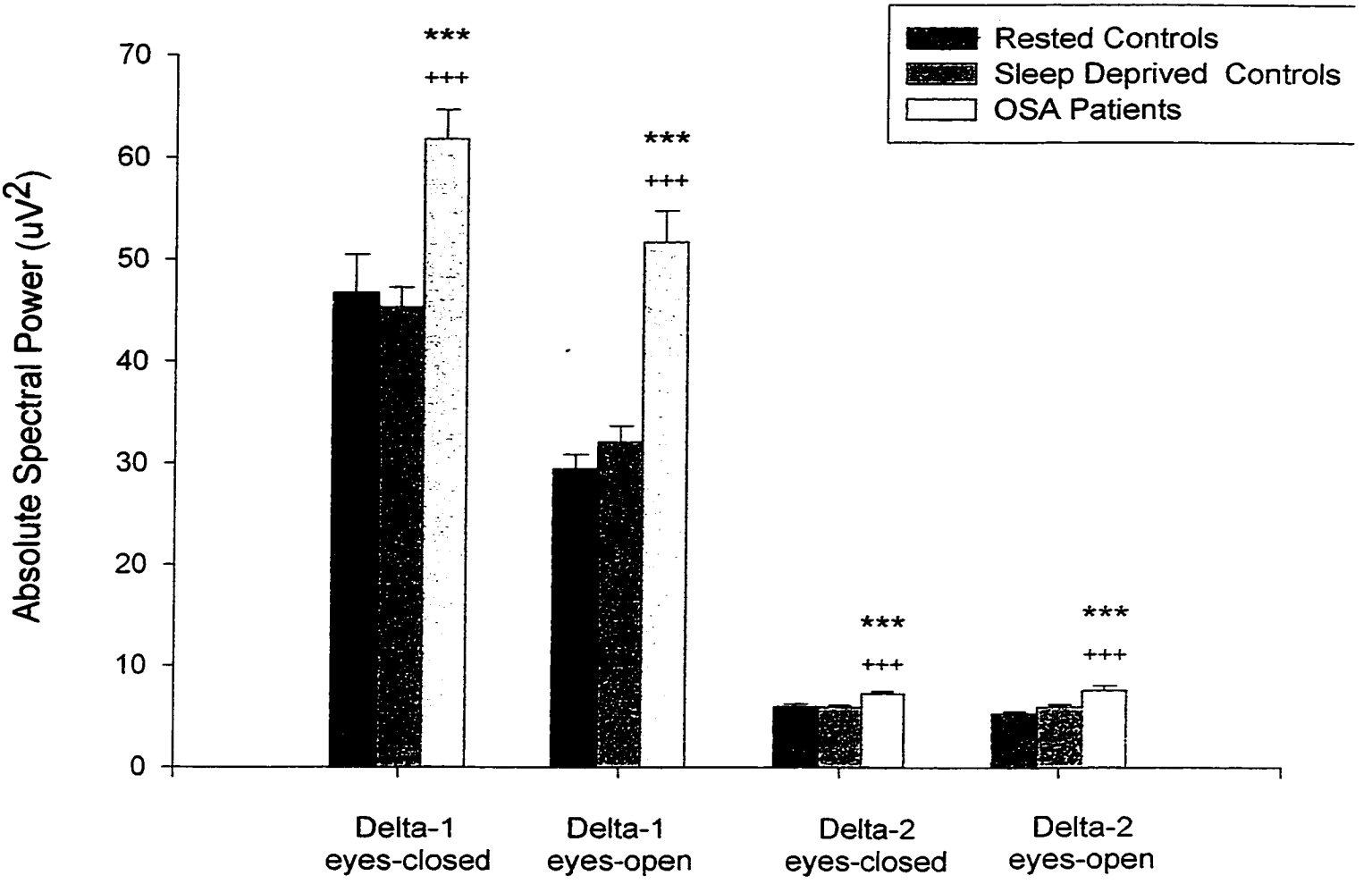

Fig 2. Comparison of absolute spectral power for delta-1 and delta-2 frequency bands (8 electrode average) between three groups

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs rested controls

+++ $p < 0.001$, ++ $p < 0.01$, + $p < 0.05$ vs sleep deprived controls

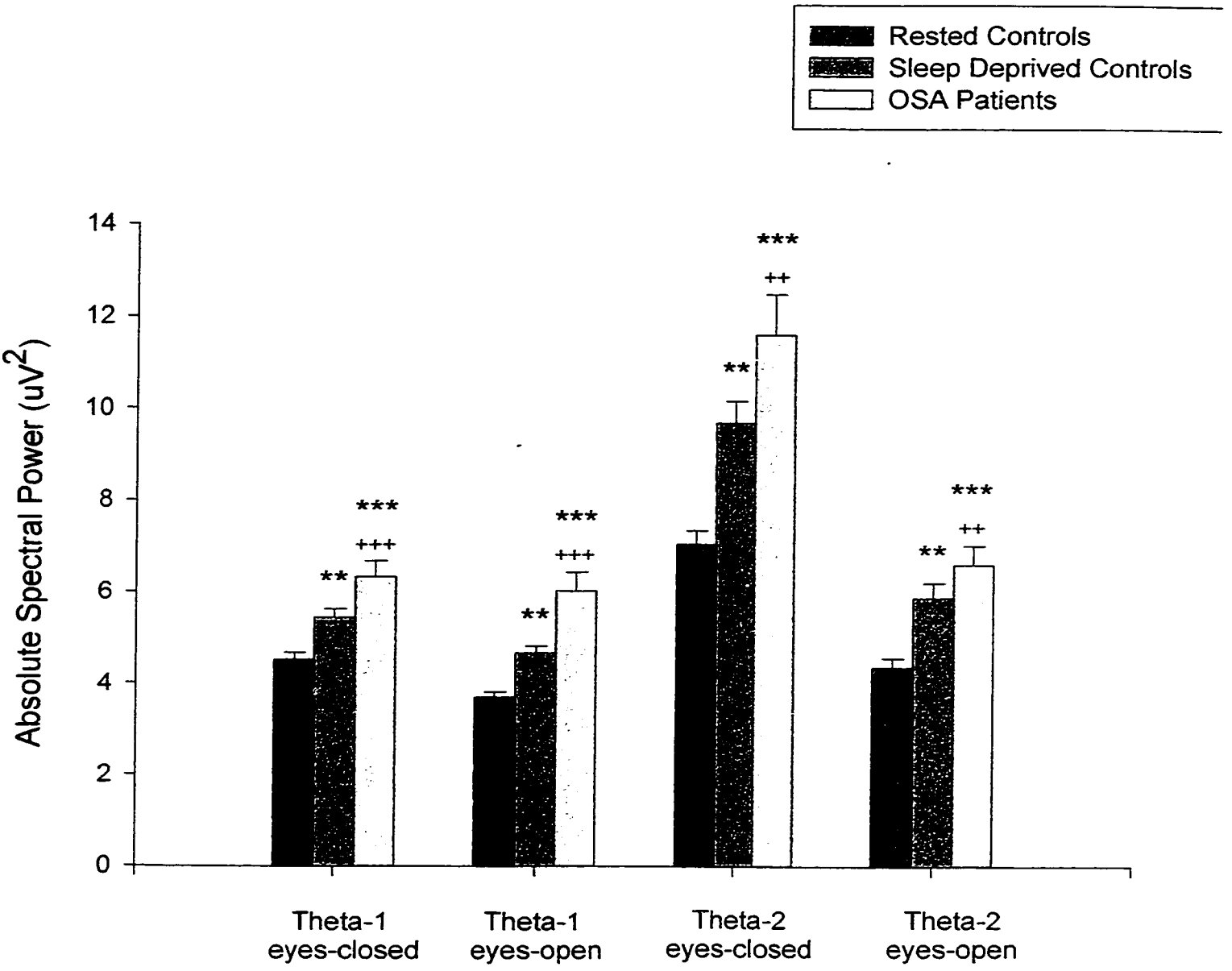

Fig 3. Comparison of absolute spectral power for theta-1 and theta-2 frequency bands (8 electrode average) between three groups

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs rested controls

+++ $p < 0.001$, ++ $p < 0.01$, + $p < 0.05$ vs sleep deprived controls

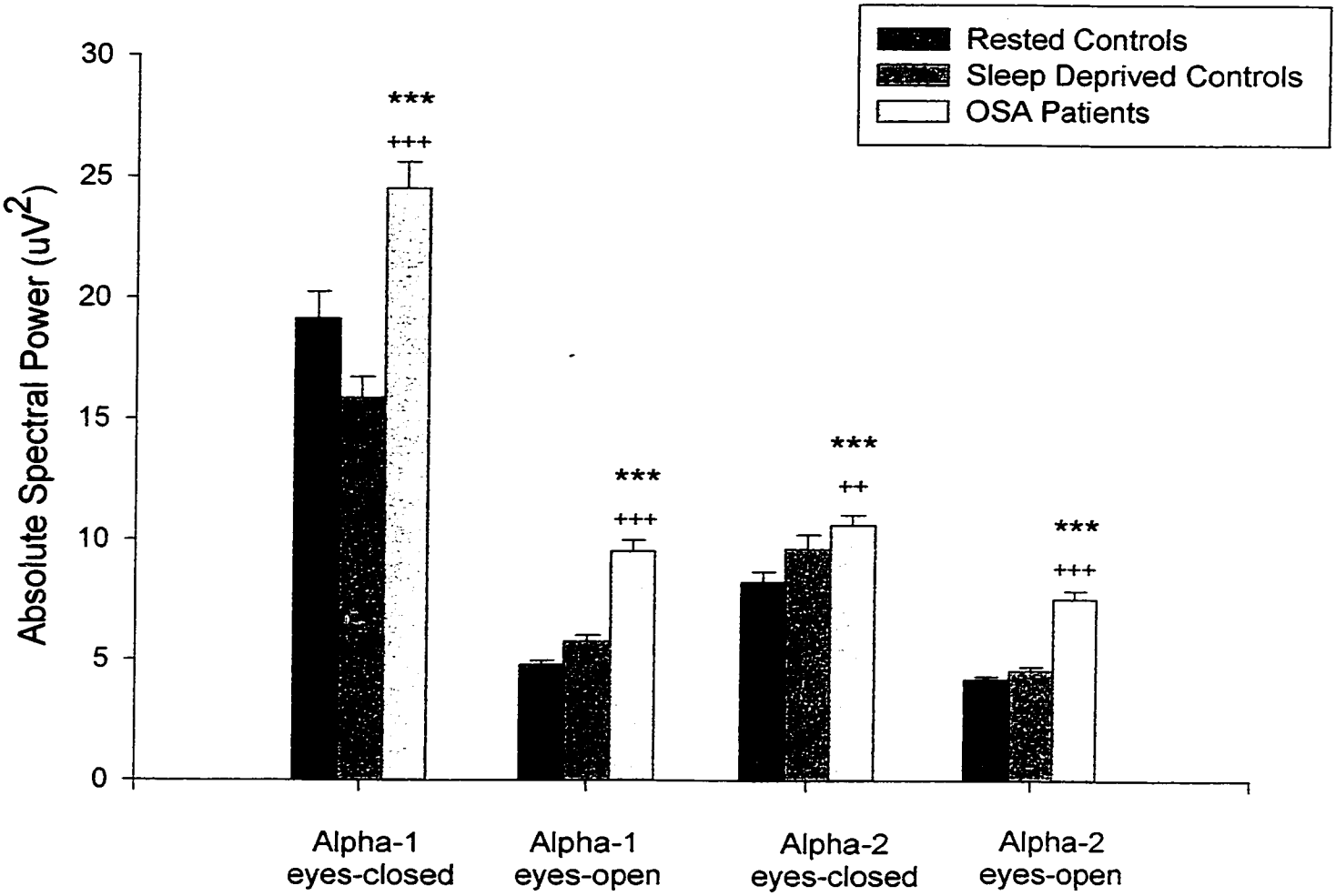

Fig 4. Comparison of absolute spectral power for alpha-1 and alpha-2 frequency bands (8 electrode average) between three groups

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs rested controls

+++ $p < 0.001$, ++ $p < 0.01$, + $p < 0.05$ vs sleep deprived controls

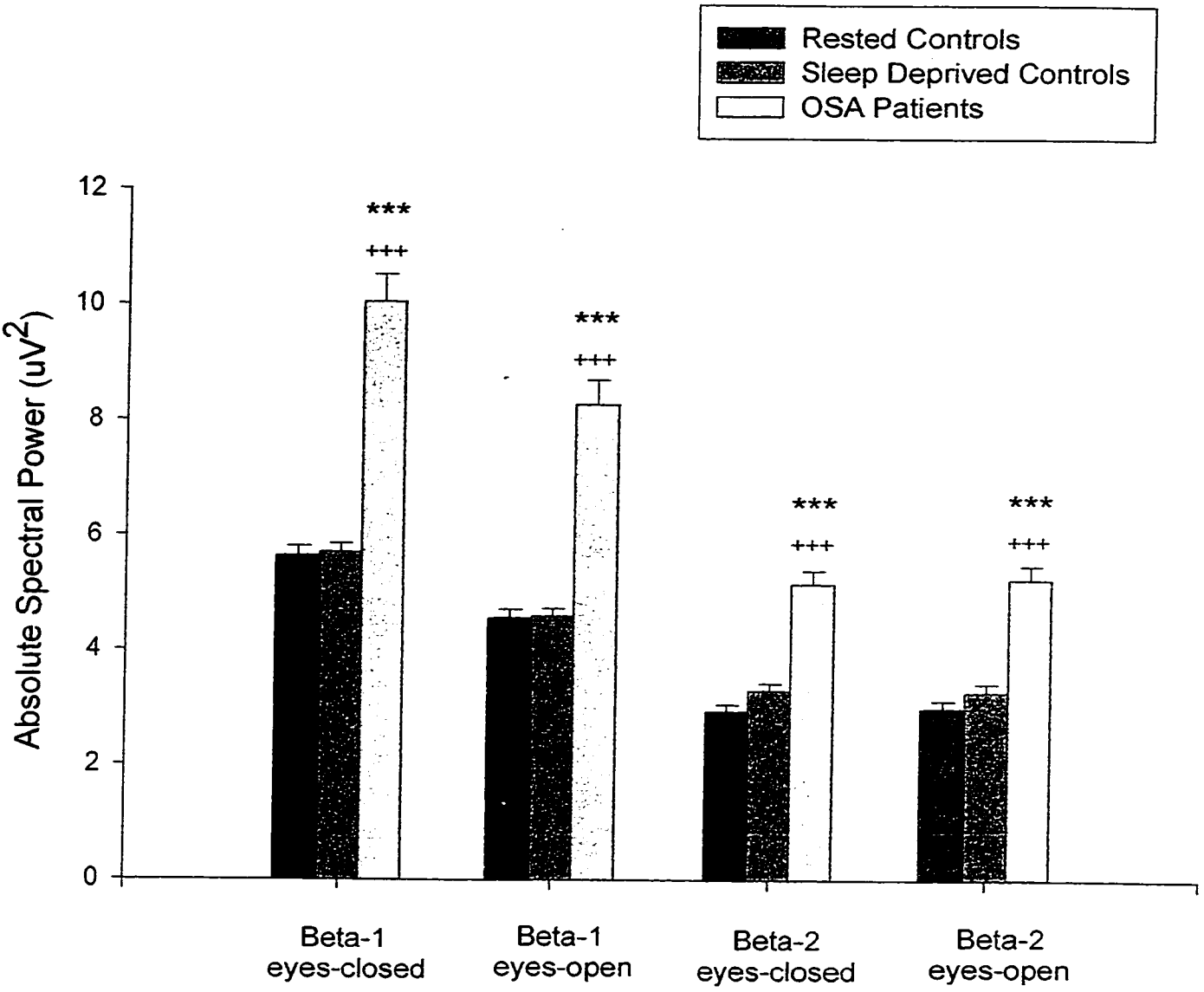

Fig 5. Comparison of absolute spectral power for beta-1 and beta-2 frequency bands (8 electrode average) between three groups

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs rested controls

+++ $p < 0.001$, ++ $p < 0.01$, + $p < 0.05$ vs sleep deprived controls

Rested vs. sleep deprived controls

The values of absolute spectral power for the two theta bands were significantly higher in sleep deprived control subjects (Table 2). There were no significant differences in any of the other frequency bands. For relative spectral power (Table 3), theta activity was significantly higher only in the eyes open condition of the sleep deprived group.

OSA patients vs. rested and sleep deprived controls

There was an increase of absolute power spectral values for all frequency bands in OSA patients compared to both the rested and sleep deprived normal groups (Table 2). But for relative spectral power (Table 3), the results were much more complex. In theta-1, theta-2 and delta-2 bands the values were decreased; and in alpha-1 and delta-1 they were increased.

4. Topographic aspects

The absolute spectral power for each of the frequency bands was compared between the three groups at each of the eight individual electrode sites (Tables 4 – 11, Figures 6 – 21).

As can be observed in all the relevant tables and figures, the significant differences between three groups for individual electrode sites were not as strong and consistent as were the averaged 8-electrode values (see Table 2, 3 and Figure 2 – 5). Significant differences of absolute spectral power measures for individual electrode existed only between OSA patients and normal groups

(rested and/or sleep deprived), whereas there were no significant differences between rested and sleep deprived control groups.

The power spectral values for both beta-1 and beta-2 frequency bands were significantly higher at frontal electrode sites (F3, Fz, and F4) in OSA patients. At central electrode sites (C3, Cz, C4) both alpha and beta bands showed significantly higher spectral power in the patient group. The spectral power values for all frequency bands (delta, theta, alpha, and beta) were significantly increased in occipital (O1 and O2) sites in the patient group. The results also indicate that there were more frequency bands showing significant differences for right sided electrode sites (F4, C4, and O2) than for left sided one (F3, C3 and O1).

Table 4: Absolute spectral power at F3

Absolute spectral power	Rested Controls	Sleep Deprived Controls	OSA Patients
Delta-1 *eyes closed*	61.50±5.06	66.76±6.62	86.64±12.15
eyes open	35.89±4.55	37.34±4.14	52.90±7.59
Delta-2 *eyes closed*	6.64±0.45	6.65±0.37	8.69±1.31
eyes open	6.08±0.54	6.73±0.78	10.05±1.70 *
Theta-1 *eyes closed*	5.40±0.42	6.58±0.50	7.14±1.13
eyes open	4.46±0.31	5.55±0.42	8.30±1.90
Theta-2 *eyes closed*	8.07±0.70	10.18±1.21	11.38±2.41
eyes open	5.43±0.49	7.36±0.84	7.35±1.26
Alpha-1 *eyes closed*	16.72±2.13	14.01±1.61	19.03±2.29
eyes open	4.76±0.44	5.27±0.52	7.79±1.00 ** +
Alpha-2 *eyes closed*	6.29±0.79	7.00±0.86	7.94±0.88
eyes open	3.63±0.23	3.81±0.23	6.44±0.83 ** ++
Beta-1 *eyes closed*	5.70±0.34	5.71±0.38	9.66±1.15 *** ++
eyes open	4.80±0.33	5.06±0.32	8.92±1.11 *** +++
Beta-2 *eyes closed*	3.23±0.37	3.60±0.42	6.12±0.66 *** ++
eyes open	4.02±0.42	4.77±0.55	7.45±0.68 *** ++

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs rested controls

+++ $p < 0.001$, ++ $p < 0.01$, + $p < 0.05$ vs sleep deprived controls

Table 5: Absolute spectral power at Fz

Absolute spectral power	Rested Controls	Sleep Deprived Controls	OSA Patients
Delta-1 *eyes closed*	66.27±7.27	63.81±7.33	83.00±8.26
eyes open	36.27±3.63	34.87±3.40	53.61±7.46 * +
Delta-2 *eyes closed*	7.77±0.47	8.25±0.66	8.90±0.70
eyes open	7.37±0.61	8.77±1.11	11.81±1.81
Theta-1 *eyes closed*	6.97±0.53	8.96±0.72	8.06±1.11
eyes open	5.93±0.42	7.57±0.59	8.63±1.33
Theta-2 *eyes closed*	10.72±0.98	15.16±2.33	13.74±2.80
eyes open	7.64±0.82	11.15±1.57	8.39±1.32
Alpha-1 *eyes closed*	21.34±2.76	18.41±2.15	23.21±2.88
eyes open	6.22±0.63	7.02±0.70	9.00±1.18
Alpha-2 *eyes closed*	7.63±1.16	8.59±1.13	9.30±1.07
Eyes open	4.03±0.27	4.13±0.26	7.09±0.95 ** ++
Beta-1 *eyes closed*	6.02±0.40	6.30±0.44	10.69±1.40 *** ++
eyes open	4.62±0.35	4.80±0.33	8.69±1.31 ** ++
Beta-2 *eyes closed*	3.31±0.45	3.74±0.44	5.38±0.61 *
eyes open	2.93±0.34	3.26±0.41	5.17±0.58 ** +

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs rested controls

+++ $p < 0.001$, ++ $p < 0.01$, + $p < 0.05$ vs sleep deprived controls

Table 6: Absolute spectral power at F4

Absolute spectral power		Rested Controls	Sleep Deprived Controls	OSA Patients
Delta-1	*eyes closed*	63.38±5.90	72.74±6.72	81.76±11.23
	eyes open	34.45±4.31	34.68±3.87	49.28±8.07
Delta-2	*eyes closed*	6.26±0.36	6.35±0.37	7.72±0.71
	eyes open	5.79±0.45	6.76±0.80	11.18±1.95 * +
Theta-1	*eyes closed*	5.25±0.36	6.36±0.42	7.19±1.24
	eyes open	4.37±0.30	5.48±0.41	7.74±1.36 *
Theta-2	*eyes closed*	7.80±0.67	10.09±1.22	11.50±2.25
	eyes open	5.15±0.45	7.32±0.76	7.23±1.17
Alpha-1	*eyes closed*	16.97±2.17	14.29±1.67	16.99±1.26
	eyes open	4.90±0.44	5.44±0.48	7.83±1.02 *
Alpha-2	*eyes closed*	6.59±0.94	7.21±1.01	8.49±1.16
	eyes open	3.71±0.23	4.05±0.24	6.71±1.05 ** +
Beta-1	*eyes closed*	5.36±0.35	5.65±0.40	10.28±1.58 ** ++
	eyes open	4.78±0.40	4.93±0.35	9.31±1.50 ** ++
Beta-2	*eyes closed*	3.18±0.43	3.51±0.42	5.38±0.65 ** +
	eyes open	3.86±0.47	4.26±0.53	6.71±0.79 ** ++

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs rested controls

+++ $p < 0.001$, ++ $p < 0.01$, + $p < 0.05$ vs sleep deprived controls

Table 7: Absolute spectral power at C3

Absolute spectral power		Rested Controls	Sleep Deprived Controls	OSA Patients
Delta-1	*eyes closed*	60.63±26.26	36.29±3.42	58.01±6.66
	eyes open	30.01±6.48	29.84±4.58	50.54±7.68
Delta-2	*eyes closed*	5.43±0.30	5.84±0.48	6.52±0.47
	eyes open	5.39±0.48	5.82±0.61	6.24±0.50
Theta-1	*eyes closed*	4.04±0.26	5.12±0.37	5.87±0.75 *
	eyes open	3.34±0.19	4.16±0.31	4.97±0.72
Theta-2	*eyes closed*	6.43±0.58	8.30±0.84	13.22±3.22
	eyes open	3.78±0.29	5.48±0.54	6.89±1.44
Alpha-1	*eyes closed*	17.56±2.58	14.70±1.89	27.05±3.34 * ++
	eyes open	4.69±0.49	5.31±0.60	11.14±1.63 *** +++
Alpha-2	*eyes closed*	8.09±0.90	8.28±0.89	11.32±1.30
	eyes open	4.60±0.33	4.69±0.38	8.80±1.21 *** +++
Beta-1	*eyes closed*	6.44±0.37	6.75±0.44	12.55±1.54 *** +++
	eyes open	5.35±0.49	5.85±0.62	9.87±1.32 ** ++
Beta-2	*eyes closed*	3.21±0.26	3.56±0.30	7.09±1.02 *** +++
	eyes open	3.26±0.39	3.74±0.46	6.77±1.00 ** ++

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs rested controls

+++ $p < 0.001$, ++ $p < 0.01$, + $p < 0.05$ vs sleep deprived controls

Table 8: Absolute spectral power at Cz

Absolute spectral power	Rested Controls	Sleep Deprived Controls	OSA Patients
Delta-1 *eyes closed*	36.53±3.73	37.48±2.67	53.84±4.72 ** ++
eyes open	33.97±3.95	37.93±5.16	54.90±7.29 *
Delta-2 *eyes closed*	6.77±0.40	7.29±0.60	7.76±0.51
eyes open	7.16±0.63	7.85±0.93	7.65±0.67
Theta-1 *eyes closed*	5.45±0.40	6.95±0.56	6.89±0.84
eyes open	4.82±0.34	5.84±0.47	6.26±0.86
Theta-2 *eyes closed*	9.05±0.87	11.82±1.37	13.26±2.89
eyes open	5.89±0.66	8.59±1.12	7.18±1.25
Alpha-1 *eyes closed*	20.13±2.69	18.61±2.39	24.52±2.75
eyes open	5.77±0.61	6.79±0.74	9.31±1.16 *
Alpha-2 *eyes closed*	8.20±1.19	9.30±1.29	10.59±1.03
eyes open	4.04±0.25	4.39±0.28	7.81±0.95 *** +++
Beta-1 *eyes closed*	6.19±0.41	6.28±0.44	11.25±1.32 *** +++
eyes open	4.55±0.33	4.82±0.38	8.80±1.15 *** +++
Beta-2 *eyes closed*	3.31±0.42	3.99±0.49	5.90±0.66 ** +
eyes open	2.91±0.37	3.34±0.47	5.52±0.63 *** ++

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs rested controls

+++ $p < 0.001$, ++ $p < 0.01$, + $p < 0.05$ vs sleep deprived controls

Table 9: Absolute spectral power at C4

Absolute spectral power	Rested Controls	Sleep Deprived Controls	OSA Patients
Delta-1 *eyes closed*	34.06±4.57	33.98±3.26	53.38±6.73 * +
eyes open	23.45±1.88	30.68±5.39	47.70±8.38 *
Delta-2 *eyes closed*	4.80±0.28	5.02±0.33	6.17±0.46 *
eyes open	4.82±0.36	5.18±0.48	5.94±0.58
Theta-1 *eyes closed*	3.87±0.26	4.67±0.32	6.38±1.08 *
eyes open	3.27±0.23	4.00±0.32	5.55±1.06
Theta-2 *eyes closed*	6.10±0.56	7.45±0.75	12.18±2.56 *
eyes open	3.63±0.31	5.17±0.51	6.67±1.16 *
Alpha-1 *eyes closed*	16.70±2.47	13.51±1.76	23.52±2.58 ++
eyes open	4.47±0.47	4.99±0.35	9.88±1.29 *** +++
Alpha-2 *eyes closed*	7.70±1.00	7.77±0.98	11.05±1.26
eyes open	4.20±0.30	4.16±0.27	8.65±1.21 *** +++
Beta-1 *eyes closed*	5.75±0.39	5.68±0.36	10.81±1.40 *** +++
eyes open	4.89±0.47	4.61±0.26	8.87±1.34 ** ++
Beta-2 *eyes closed*	2.72±0.24	3.18±0.28	4.99±0.56 *** +++
eyes open	3.11±0.44	2.99±0.28	4.72±0.55 * +

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs rested controls

+++ $p < 0.001$, ++ $p < 0.01$, + $p < 0.05$ vs sleep deprived controls

Table 10: Absolute spectral power at O1

Absolute spectral power	Rested Controls	Sleep Deprived Controls	OSA Patients
Delta-1 *eyes closed*	28.96±4.67	25.94±2.58	44.42±5.80 * +
eyes open	23.82±2.95	26.88±4.37	59.87±12.74 ** +
Delta-2 *eyes closed*	6.10±2.05	4.27±0.46	5.20±0.49
eyes open	3.14±0.32	3.49±0.30	4.05±0.30
Theta-1 *eyes closed*	2.84±0.48	3.63±0.37	4.48±0.54 *
eyes open	1.86±0.22	2.52±0.22	3.22±0.48 *
Theta-2 *eyes closed*	5.02±1.19	5.52±0.68	9.09±1.84
eyes open	1.90±0.21	2.80±0.30	4.58±0.94 **
Alpha-1 *eyes closed*	27.07±5.94	11.60±1.97	28.89±3.86 +
eyes open	4.17±0.63	6.24±1.19	10.97±10.72 *** +
Alpha-2 *eyes closed*	11.78±1.84	17.16±3.15	13.39±1.28
eyes open	5.27±0.61	6.44±0.74	7.56±0.85
Beta-1 *eyes closed*	5.40±0.73	4.95±0.38	7.55±0.73 * +
eyes open	4.02±0.55	3.46±0.25	5.77±0.69 * ++
Beta-2 *eyes closed*	2.37±0.26	2.53±0.21	3.31±0.36
eyes open	2.01±0.29	1.86±0.14	2.85±0.37 * ++

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs rested controls

+++ $p < 0.001$, ++ $p < 0.01$, + $p < 0.05$ vs sleep deprived controls

Table 11: Absolute spectral power at O2

Absolute spectral power	Rested Controls	Sleep Deprived Controls	OSA Patients
Delta-1 *eyes closed*	20.85±2.50	27.46±4.04	41.55±6.07 **
eyes open	17.11±2.06	24.74±4.32	43.92±8.48 ** +
Delta-2 *eyes closed*	3.78±0.69	3.67±0.46	4.47±0.35
eyes open	2.71±0.41	2.81±0.24	3.92±0.35 *
Theta-1 *eyes closed*	2.28±0.33	2.88±0.30	4.66±0.73 ** +
eyes open	1.45±0.11	2.14±0.17	3.50±0.71 **
Theta-2 *eyes closed*	3.09±0.34	4.09±0.48	8.46±1.59 *** ++
eyes open	1.43±0.11	2.34±0.24	4.53±0.82 *** ++
Alpha-1 *eyes closed*	16.61±2.78	21.03±4.53	30.63±3.75 *
eyes open	3.21±0.40	4.99±0.84	10.23±1.44 *** +++
Alpha-2 *eyes closed*	9.57±1.62	13.24±2.10	12.93±1.30
eyes open	4.10±0.40	4.73±0.47	7.40±0.89 *** +
Beta-1 *eyes closed*	4.35±0.47	4.26±0.33	7.60±0.97 ** ++
eyes open	3.49±0.48	3.18±0.27	5.91±0.90 * ++
Beta-2 *eyes closed*	2.08±0.25	2.20±0.18	3.13±0.39 *
eyes open	1.72±0.19	1.86±0.17	2.68±0.39 *

*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ vs rested controls

+++ $p < 0.001$, ++ $p < 0.01$, + $p < 0.05$ vs sleep deprived controls

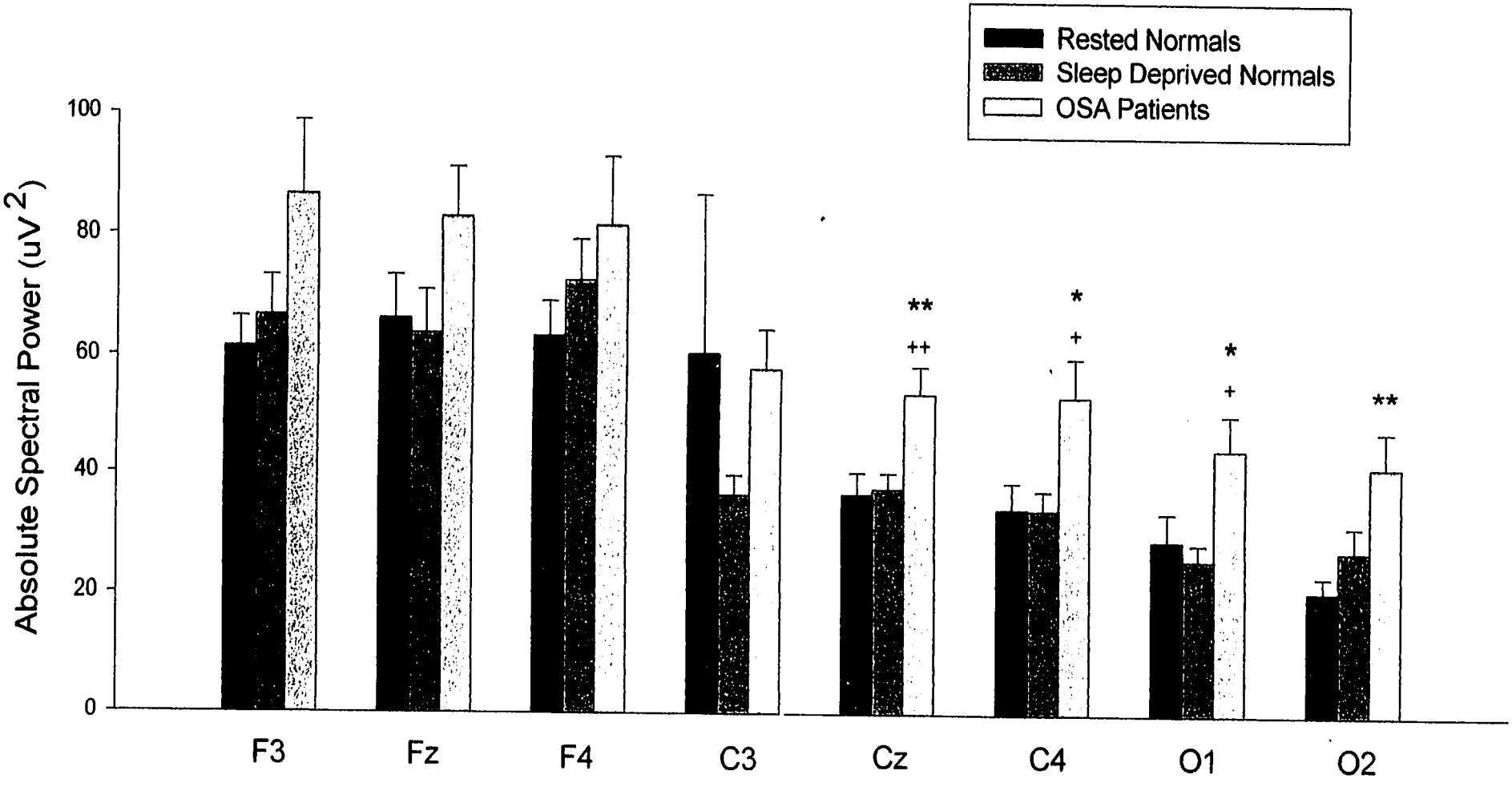

Fig 6. Power Spectral Values of Delta-1 for eyes-closed condition at 8 electrodes

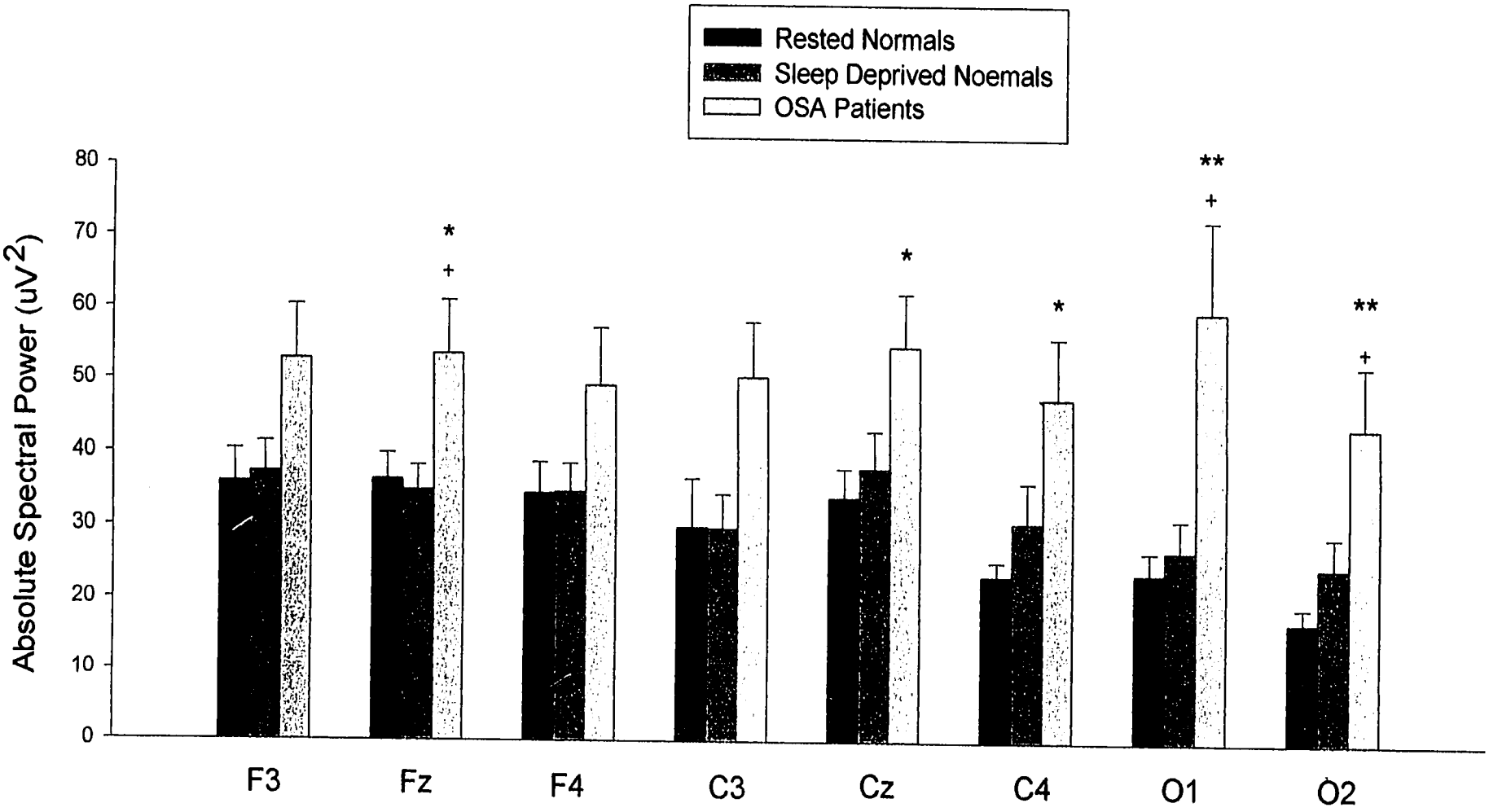

Fig 7. Power spectral values of delta-1 for eyes-open condition at 8 electrodes

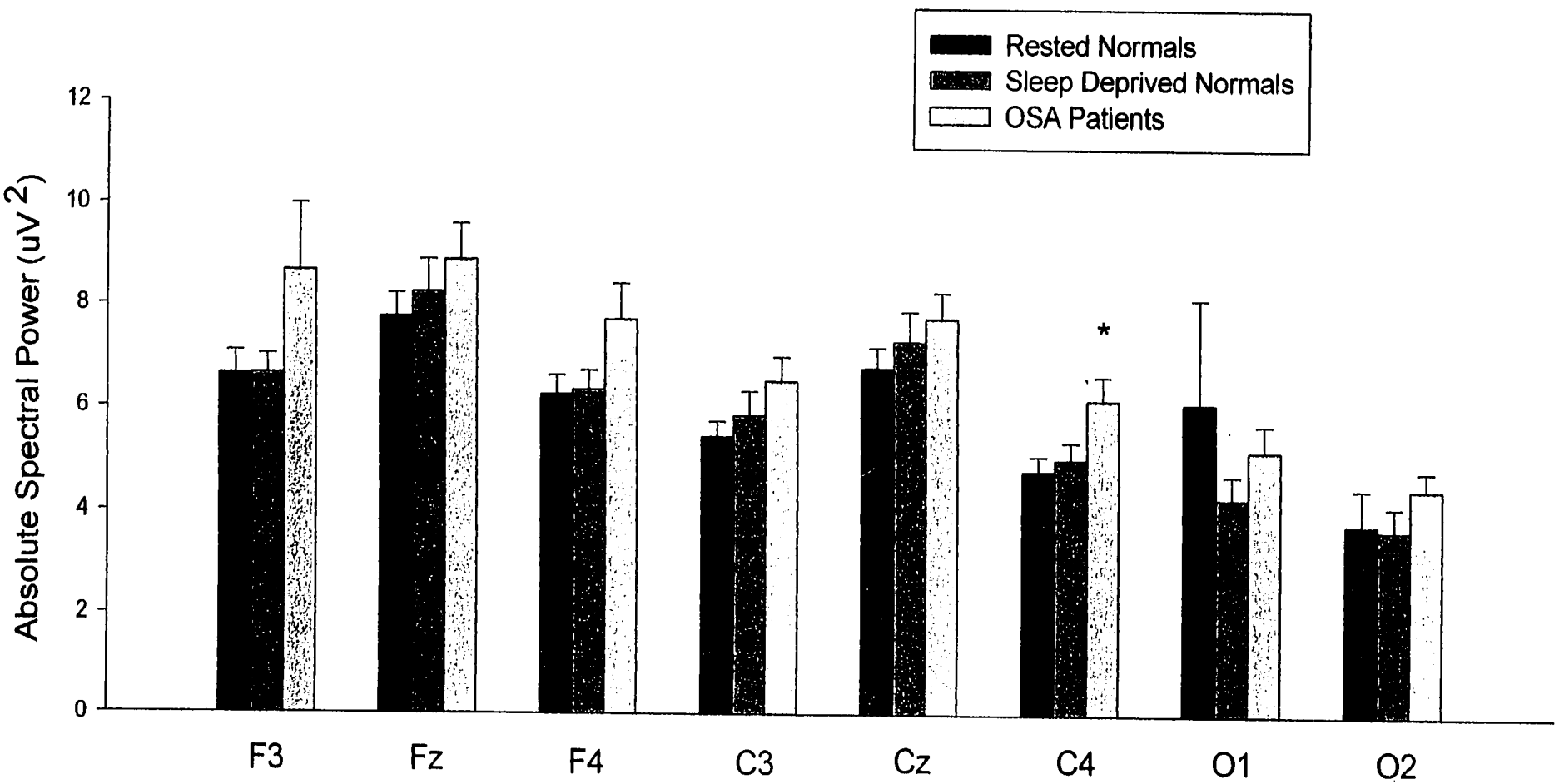

Fig 8. Power spectral values of delta-2 for eyes-closed condition at 8 electrodes

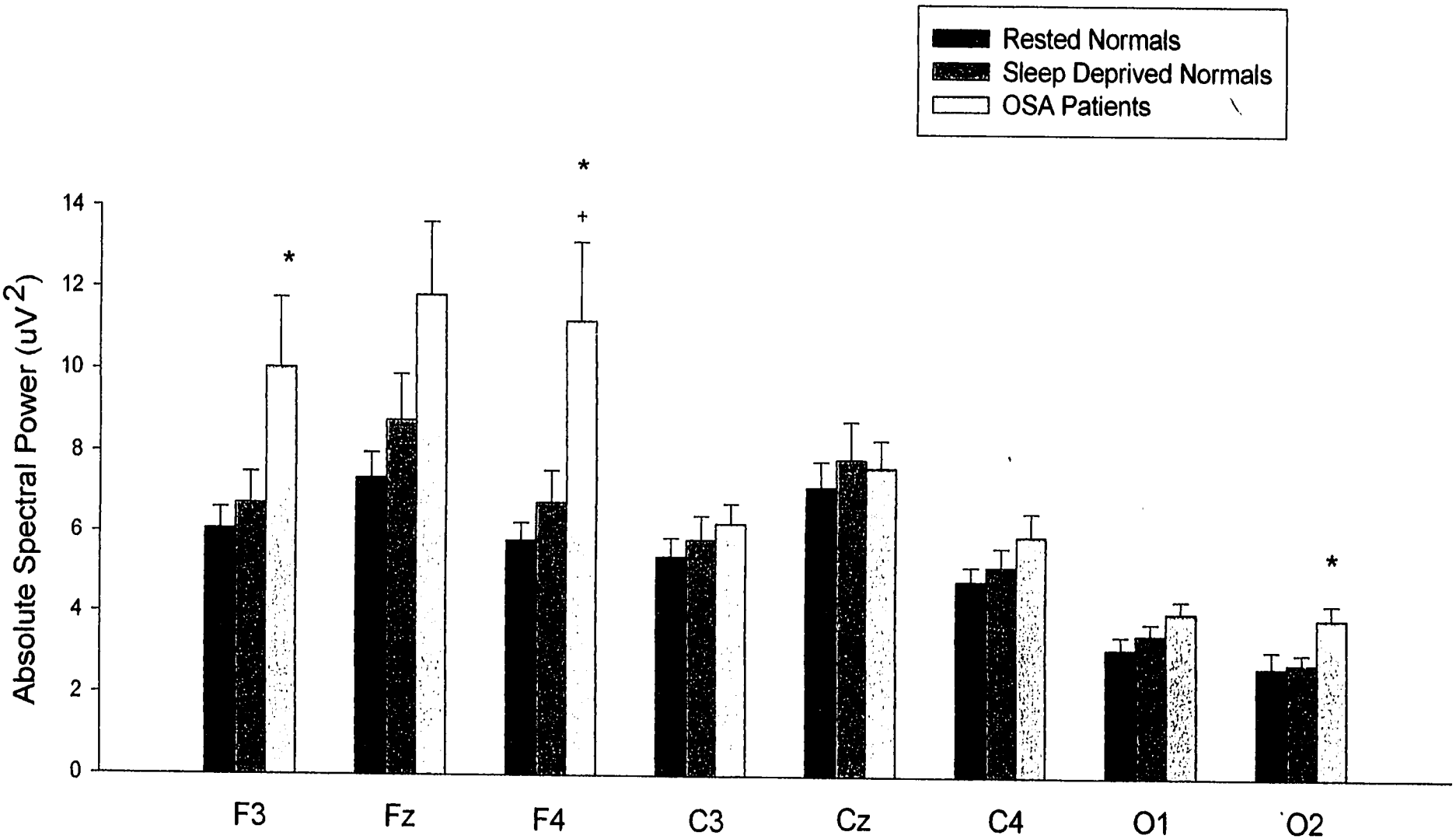

Fig 9. Power spectral values of delta-2 for eyes-open condition at 8 electrodes

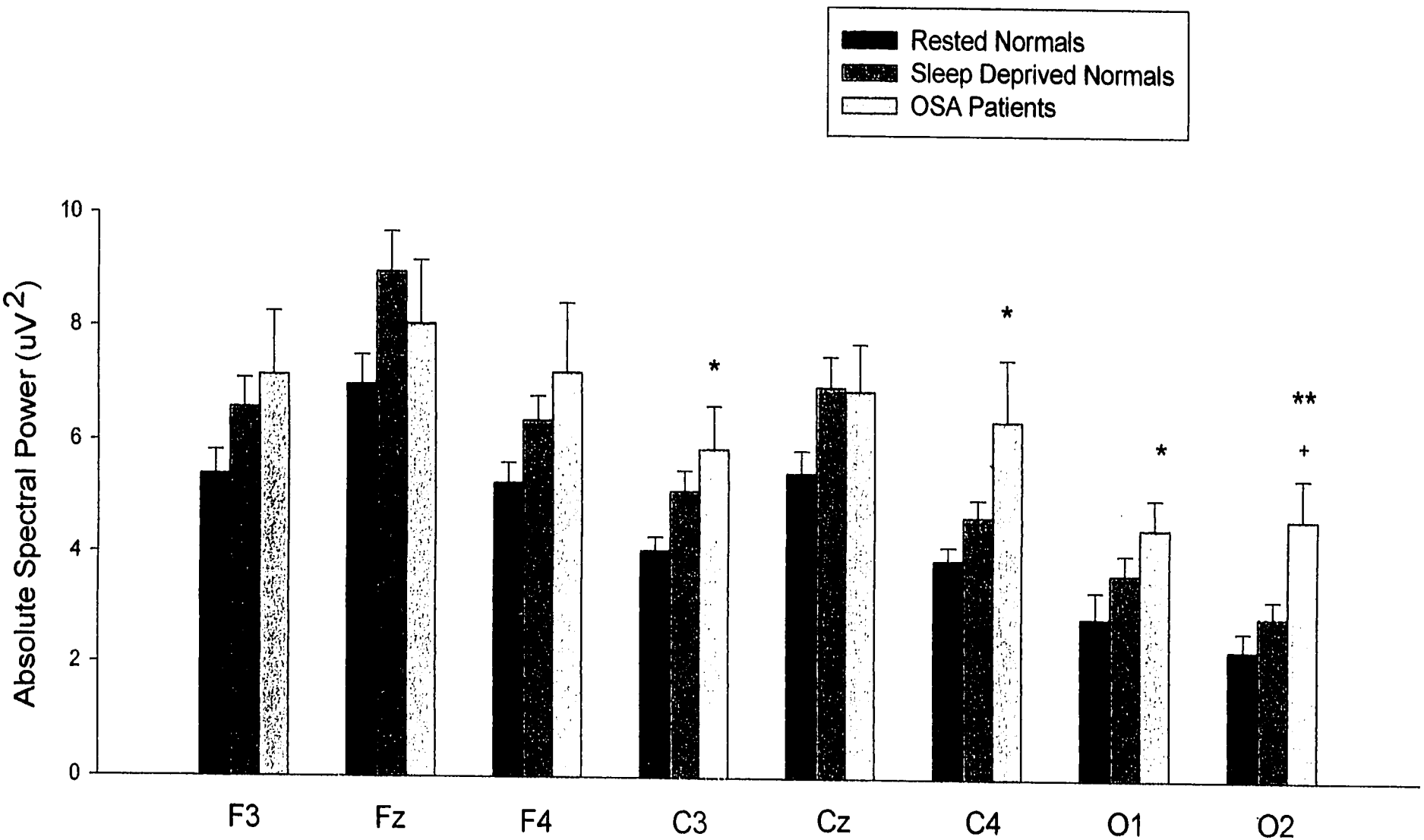

Fig 10. Power spectral values of theta-1 for eyes-closed condition at 8 electrodes

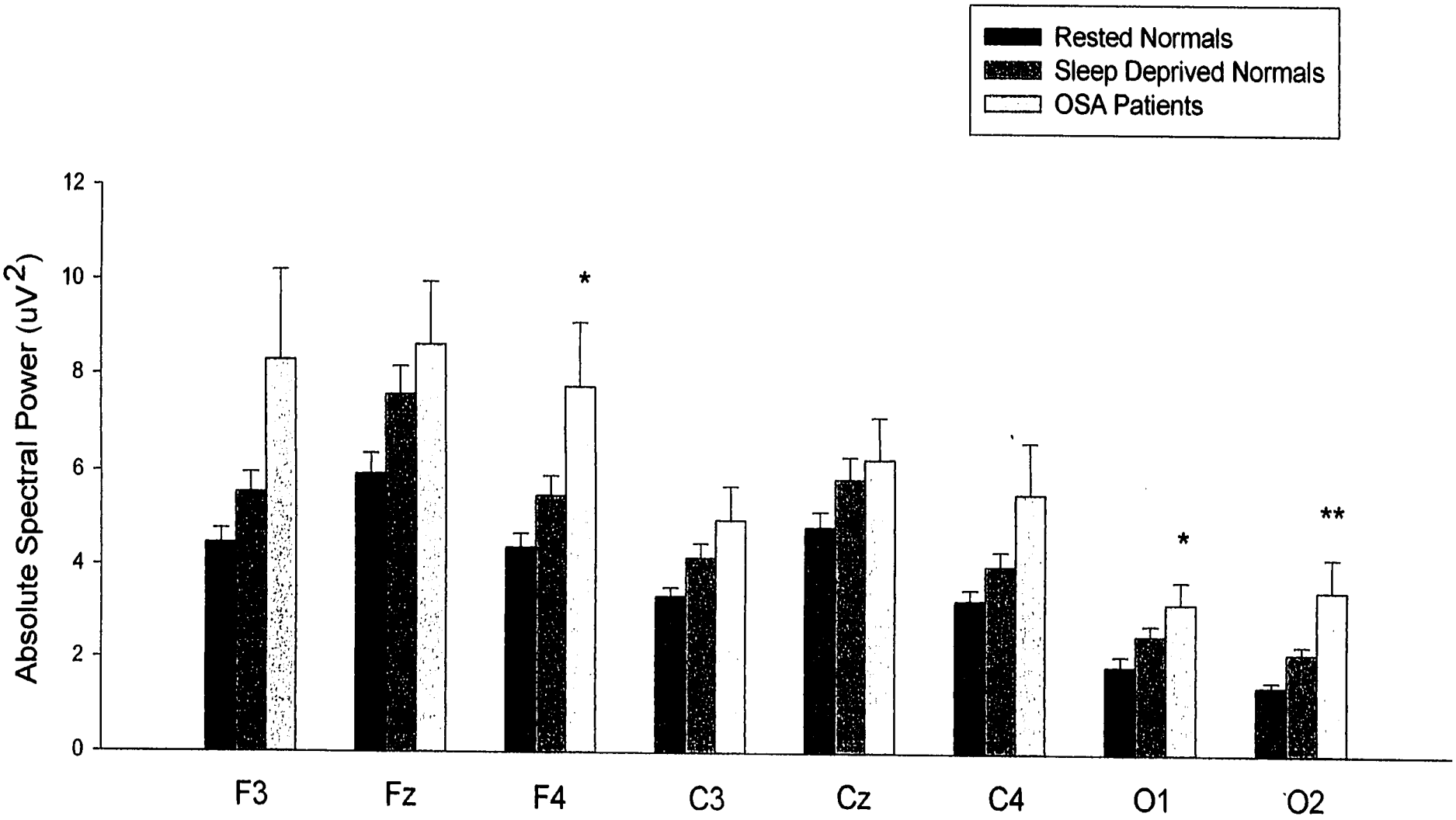

Fig 11. Power spectral values of theta-1 for eyes-open condition at 8 electrodes

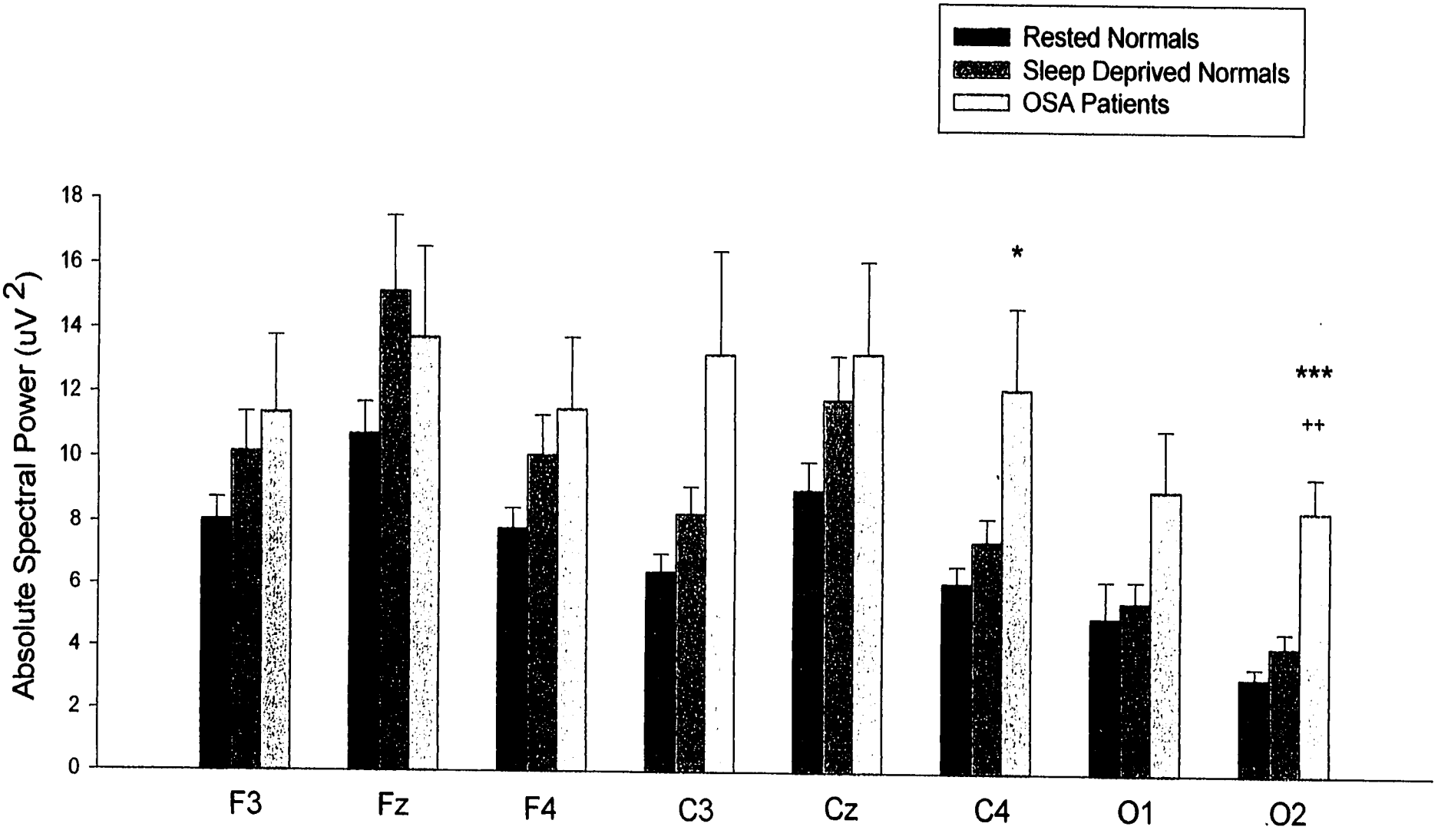

Fig 12. Power spectral values of theta-2 for eyes-closed condition at 8 electrodes

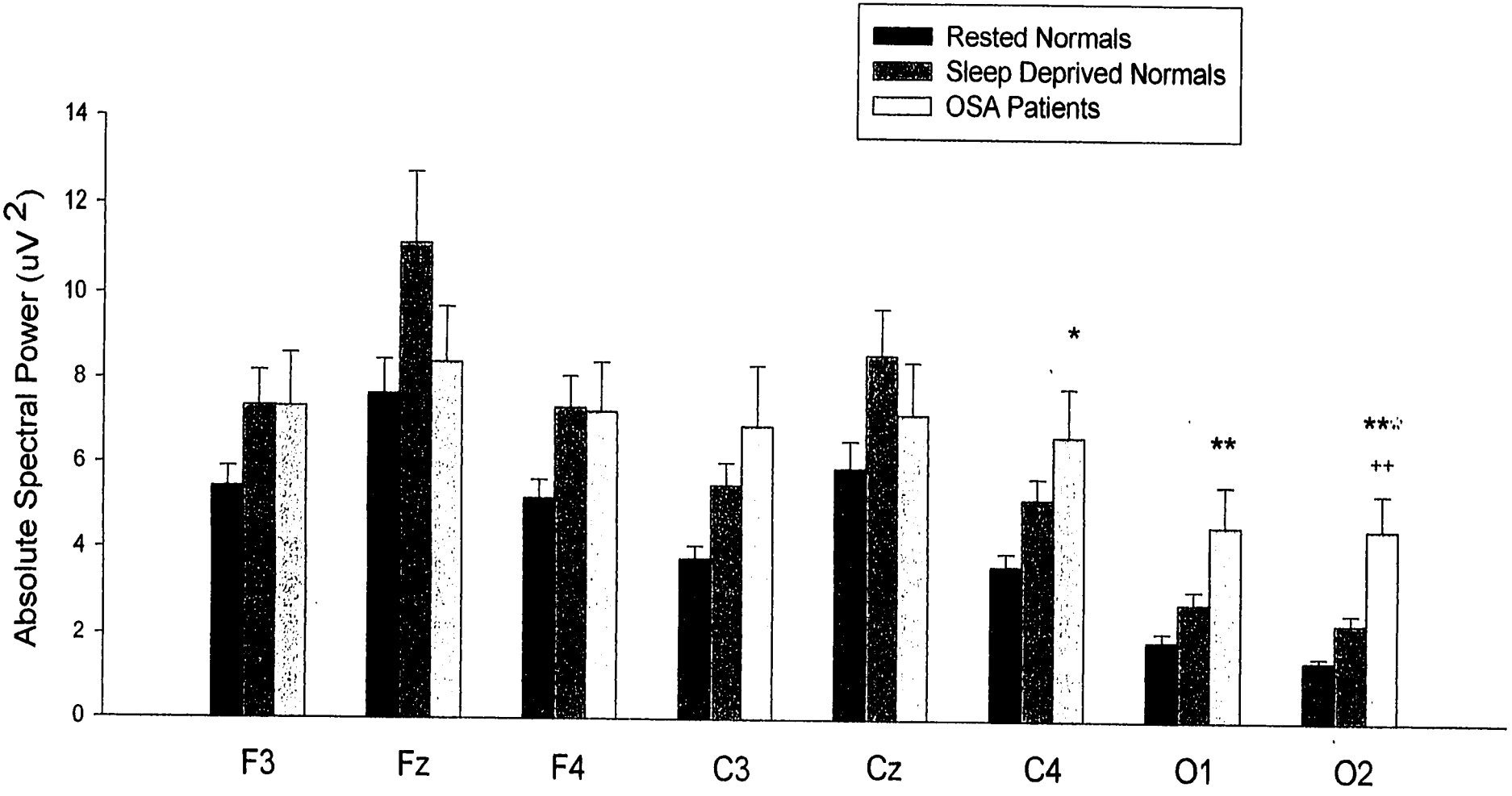

Fig 13. Power spectral values of theta-2 for eyes-open condition at 8 electrodes

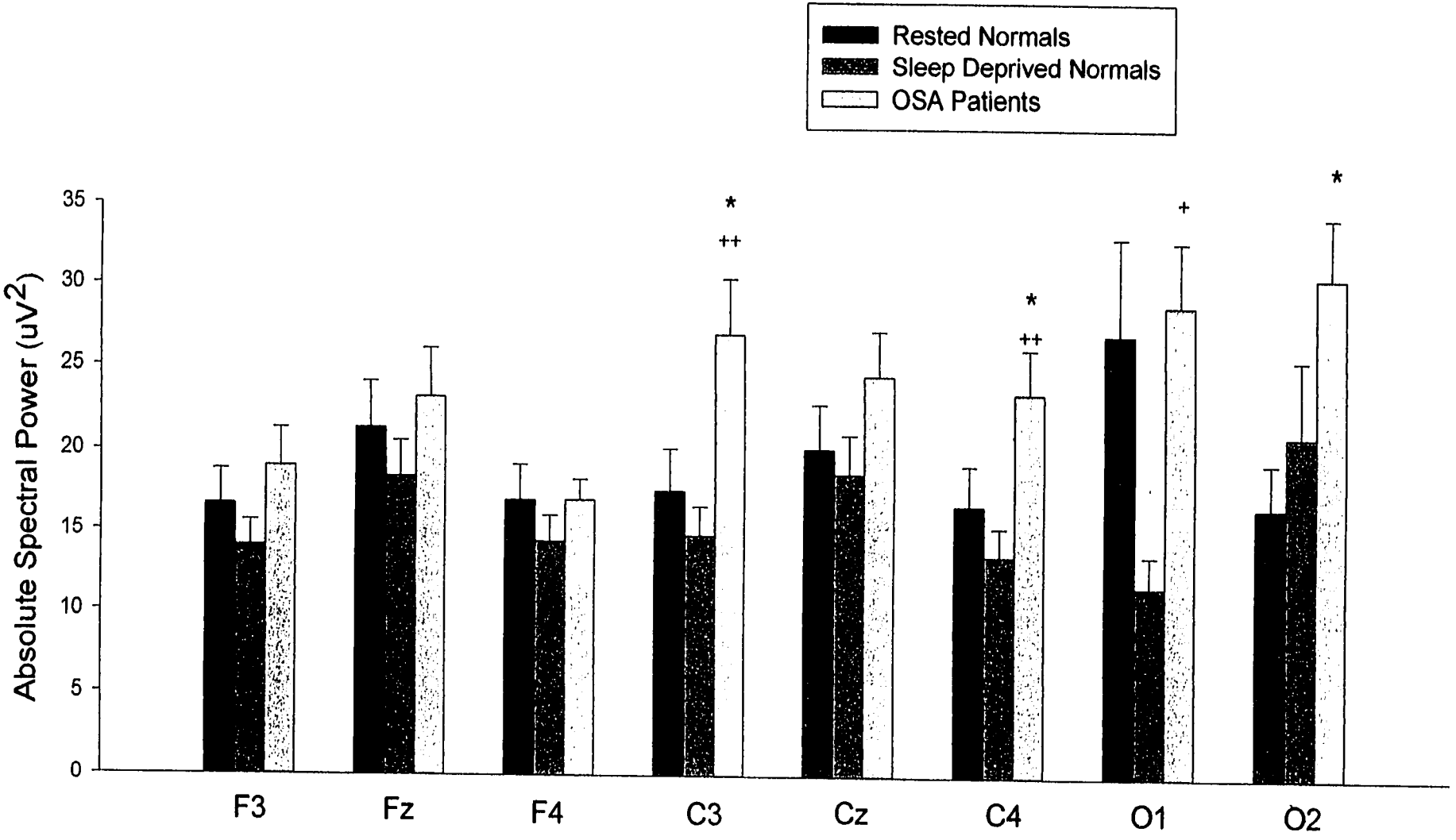

Fig 14. Power spectral values of alpha-1 for eyes-closed condition at 8 electrodes

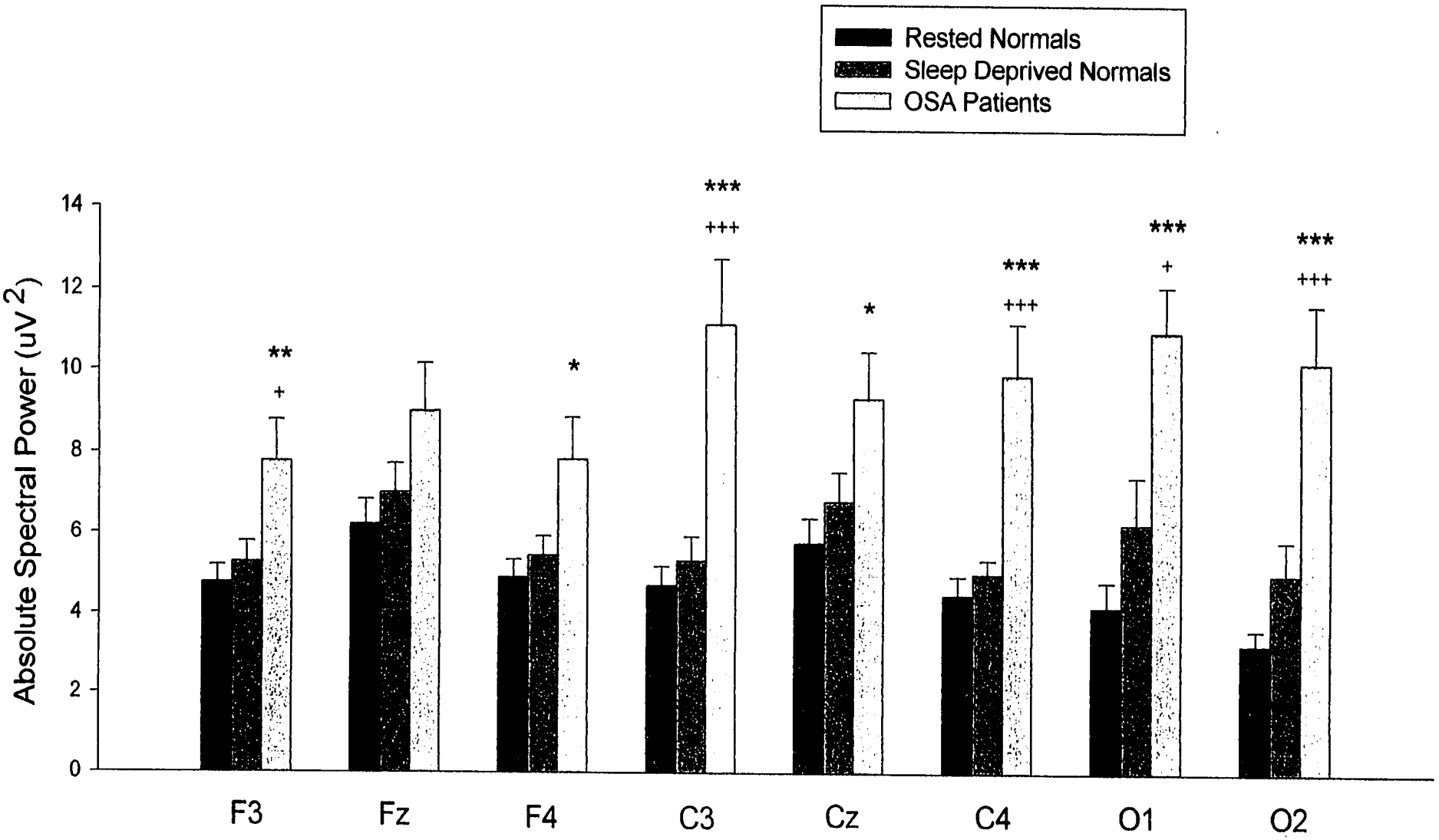

Fig 15. Power spectral values of alpha-1 for eyes-open condition at 8 electrodes

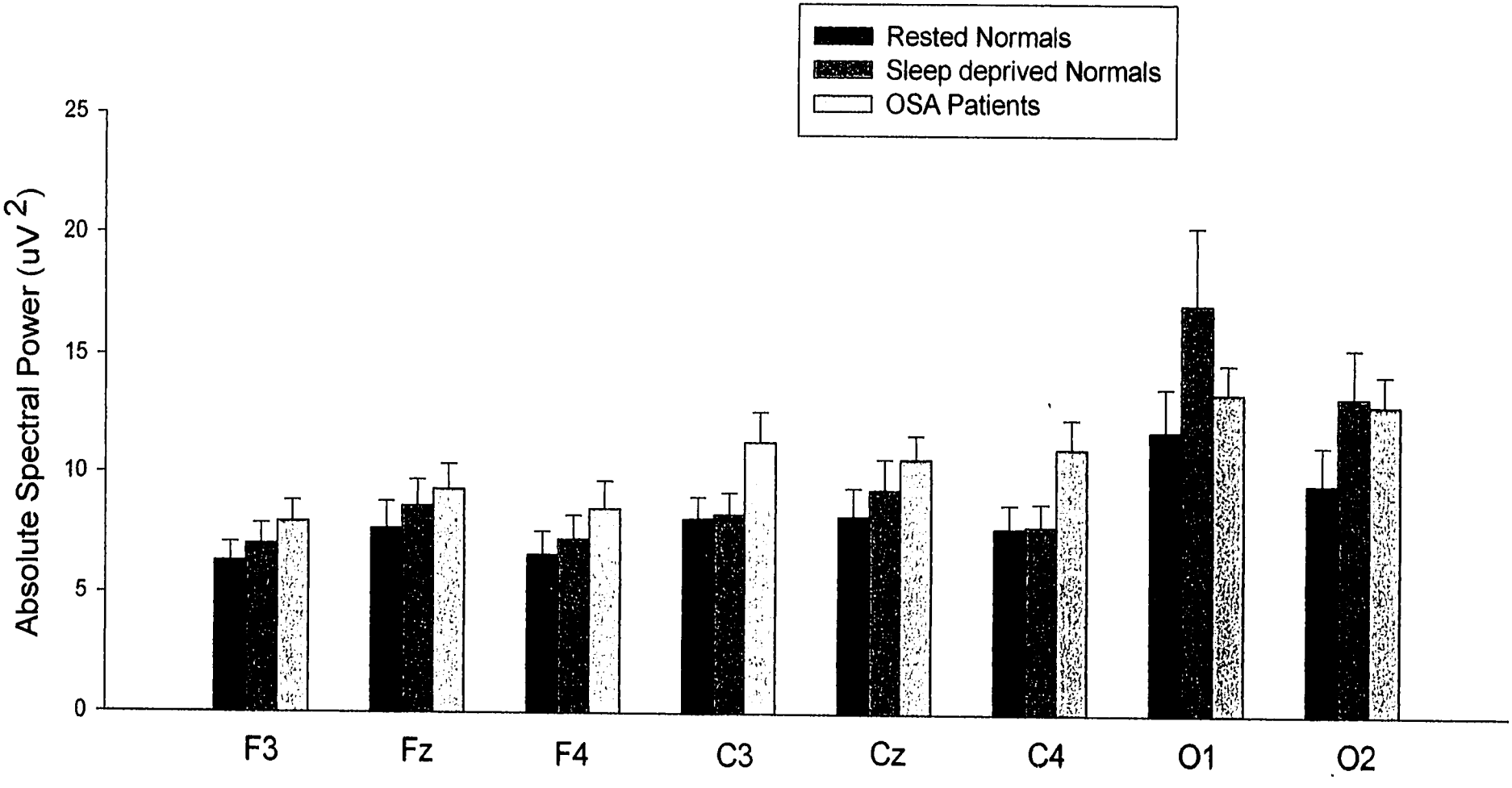

Fig 16. Power spectral values of alpha-2 for eyes-closed condition at 8 electrodes

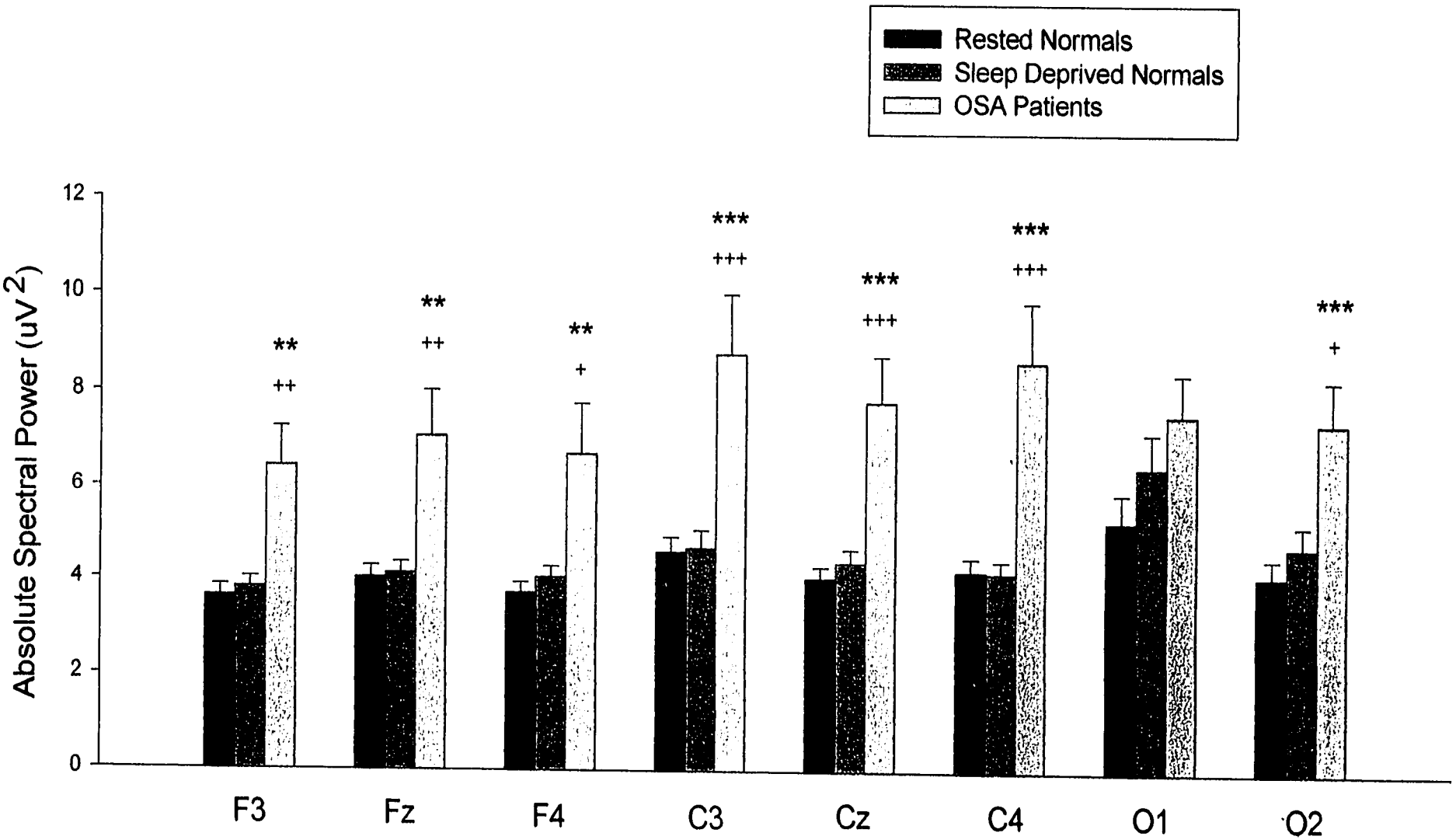

Fig 17. Power spectral values of alpha-2 for eyes-open condition at 8 electrodes

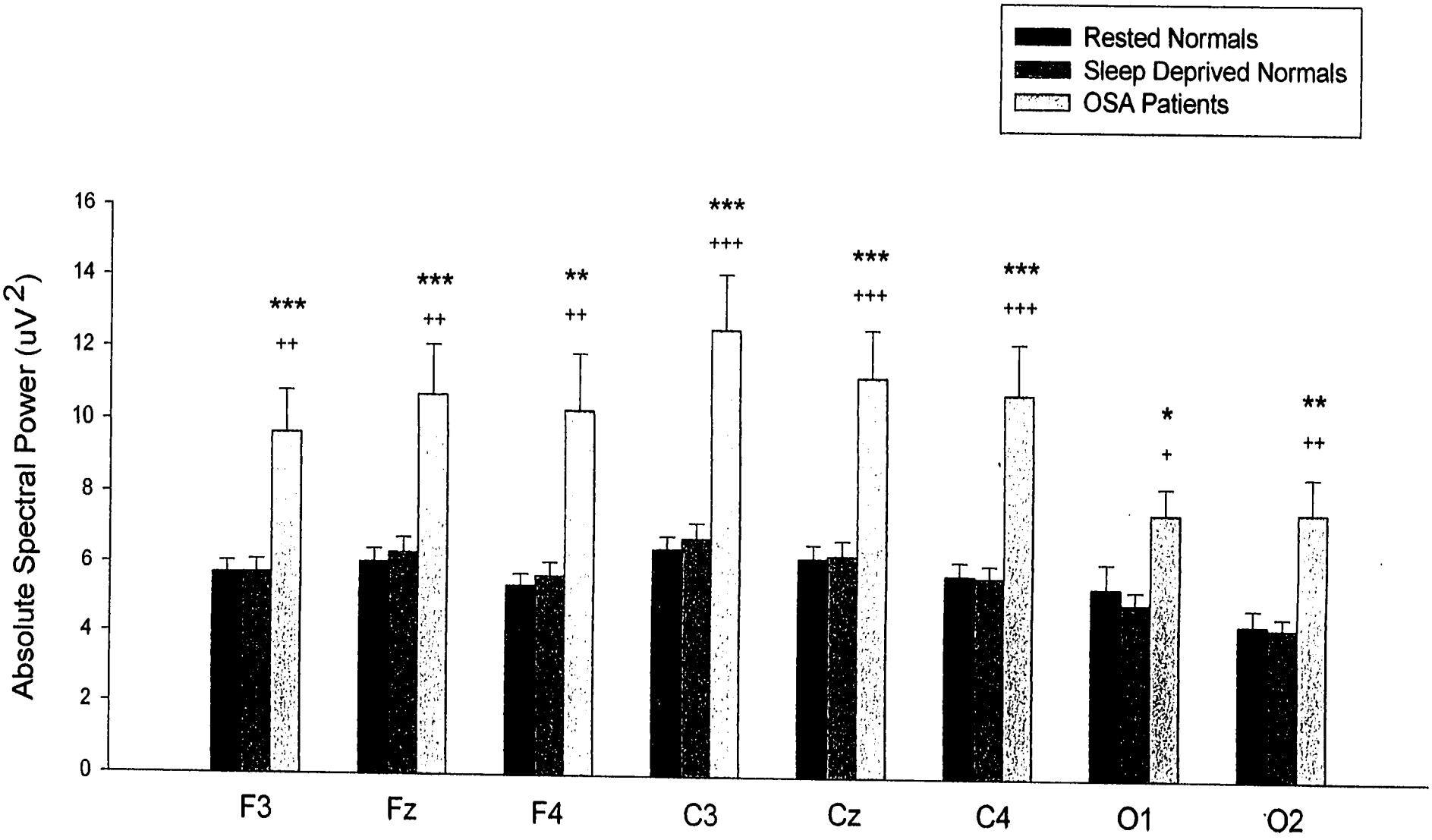

Fig 18. Power spectral values of beta-1 for eyes-closed condition at 8 electrodes

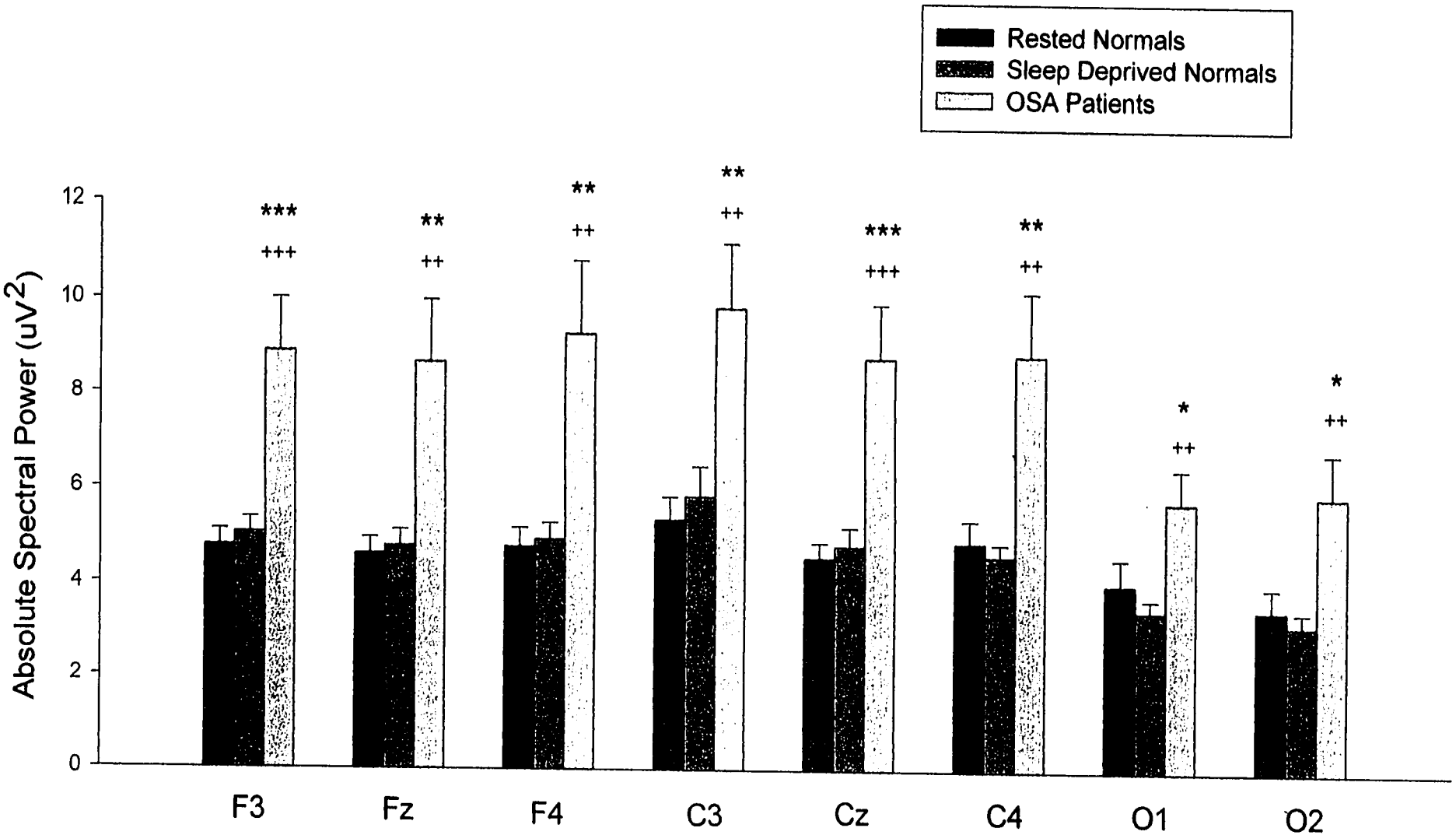

Fig 19. Power spectral values of beta-1 for eyes-open condition at 8 electrodes

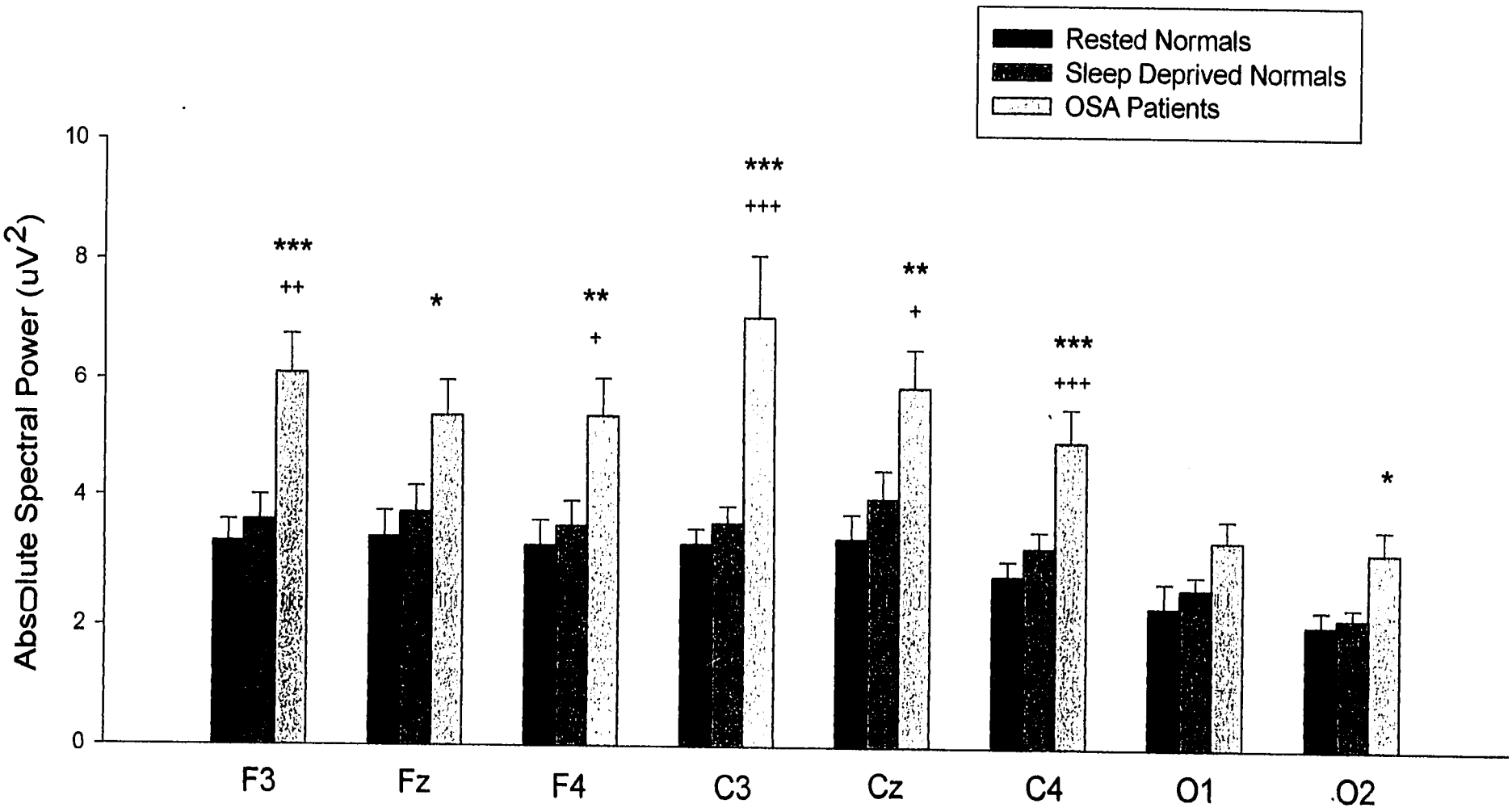

Fig 20. Power spectral values of beta-2 for eyes-closed condition at 8 electrodes

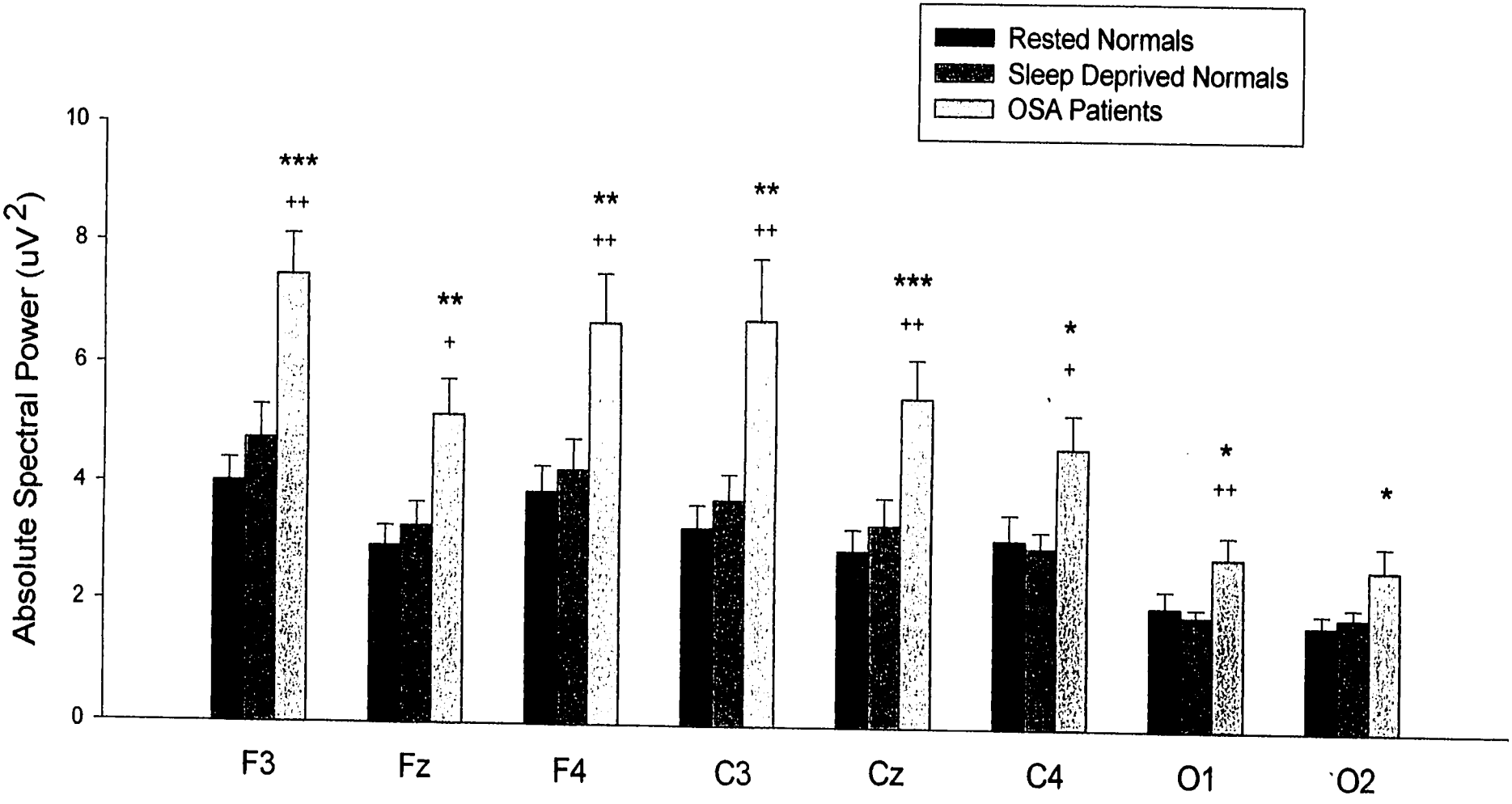

Fig 21. Power spectral values of beta-2 for eyes-open condition at 8 electrodes

5. Correlation of spectral power and sleep latency

The relationships between the mean 8-electrode absolute power spectral values for the 8 frequency bands and sleep latency in three groups for eyes open and eyes closed conditions were analyzed.

Rested controls

The power spectral values for delta-1, theta-1, and theta-2 frequency bands were negatively correlated with sleep latency during eyes closed, but only delta-1 and delta-2 were negatively correlated with sleep latency during eyes open (Table 12). There was no correlation between sleep latency and power spectral value for alpha and beta bands.

Table 12. Correlation between spectral power (8-electrode average) and sleep latency in the rested control group.

Rested controls	eyes open		eyes closed	
	r	p	r	p
Delta-1	-0.278	<0.001***	-0.139	<0.01**
Delta-2	-0.175	<0.001***	-0.095	>0.05
Theta-1	-0.069	>0.05	-0.121	<0.05*
Theta-2	-0.053	>0.05	-0.181	<0.001***
Alpha-1	-0.074	>0.05	-0.075	>0.05
Alpha-2	-0.040	>0.05	-0.085	>0.05
Beta-1	-0.067	>0.05	-0.046	>0.05
Beta-2	-0.057	>0.05	-0.008	>0.05

A graphic display of the data in the significant correlation of delta-1 eyes closed spectral power versus sleep latency is shown in Figure 22. It is evident that the data are not normally distributed and are highly variable. The slope of the least squared fit is relatively flat (r = -0.175).

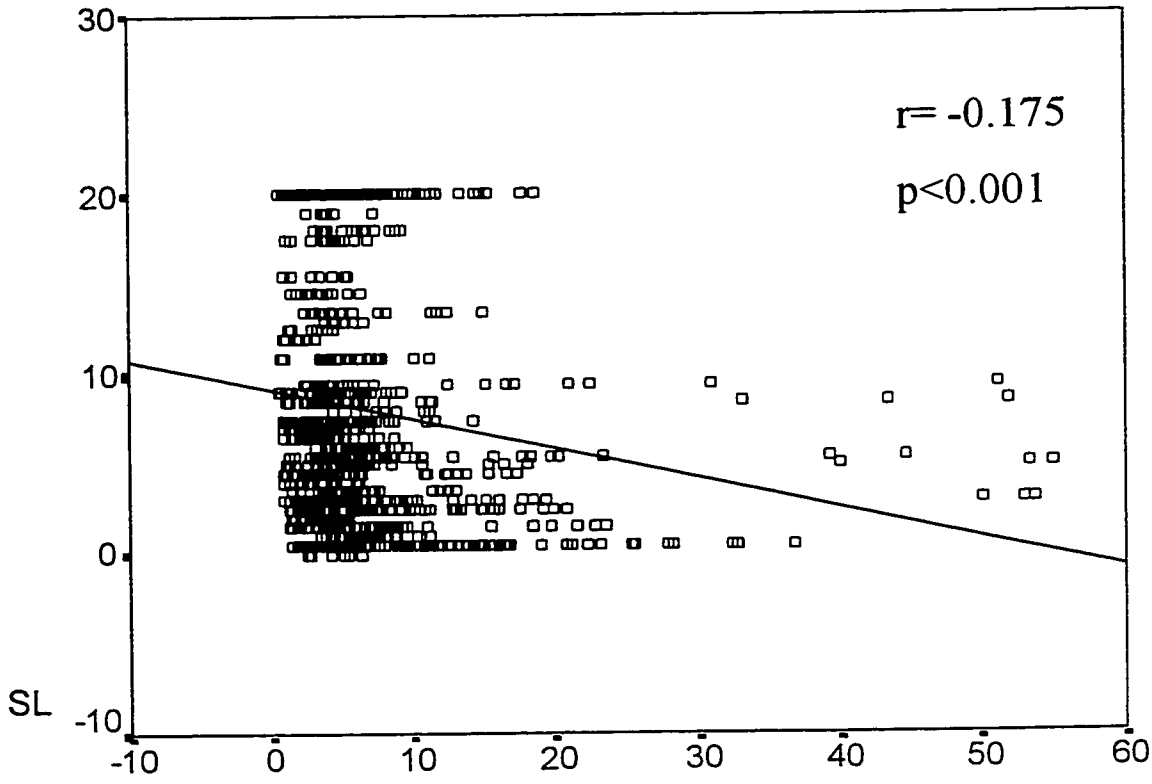

Fig 22. The significant correlation of delta-1 eyes closed spectral power and sleep latency is shown.

For comparison, Figure 23 shows the raw data and the fitted slope for a non-significant correlation, that chosen being between spectral power in the alpha-1 frequency band, eyes open condition, and sleep latency.

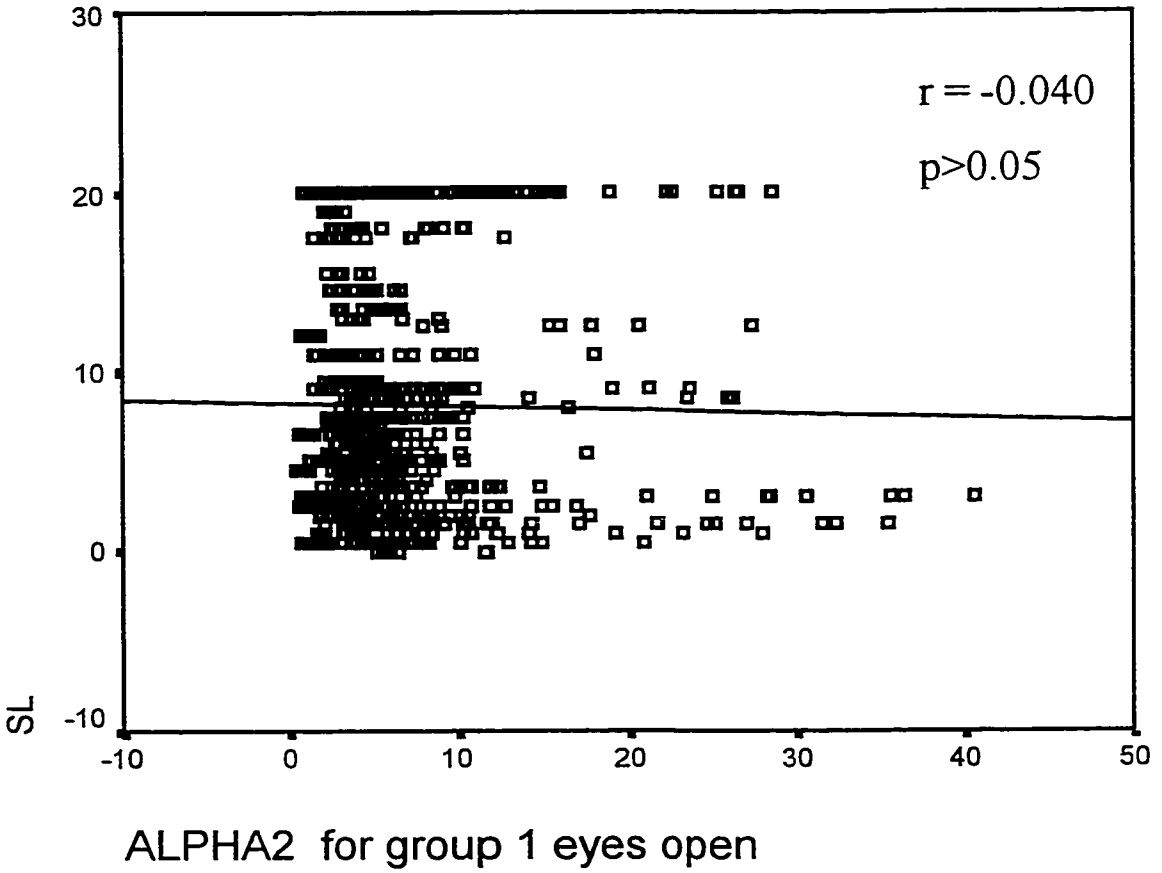

Fig 23. A non-significant correlation is shown for spectral power in the alpha-1 frequency band (eyes open condition) and sleep latency.

Sleep deprived controls

There was negative correlation between sleep latency and power spectral values for delta and theta frequency bands in sleep deprived controls in both eyes open and eyes closed conditions, but not for alpha and beta frequency bands (Table 13).

Table 13. Correlation between spectral power (8-electrode average) and sleep latency in the sleep deprived control group.

Sleep deprived controls	eyes open		eyes closed	
	r	p	r	p
Delta-1	-0.227	<0.001***	-0.275	<0.001***
Delta-2	-0.308	<0.001***	-0.329	<0.001***
Theta-1	-0.264	<0.001***	-0.303	<0.001***
Theta-2	-0.187	<0.001***	-0.246	<0.001***
Alpha-1	-0.099	>0.05	-0.085	>0.05
Alpha-2	-0.042	>0.05	-0.028	>0.05
Beta-1	-0.063	>0.05	-0.009	>0.05
Beta-2	-0.047	>0.05	-0.043	>0.05

OSA patients

In OSA patients, the power spectral values for delta-2 and both theta frequency bands were negatively correlated with the sleep latency and the

power spectral values for beta-2 frequency bands were positively correlated with the sleep latency (Table 14). There was no correlation for alpha bands.

Table 14. Correlation between spectral power (8-electrode average) and sleep latency in the OSA patients group.

OSA patients	Eyes open		Eyes closed	
	r	p	r	p
Delta-1	-0.050	>0.05	-0.050	>0.05
Delta-2	-0.155	<0.001***	-0.132	<0.01**
Theta-1	-0.199	<0.001***	-0.198	<0.001***
Theta-2	-0.136	<0.01**	-0.254	<0.001***
Alpha-1	0.027	>0.05	0.050	>0.05
Alpha-2	0.037	>0.05	0.040	>0.05
Beta-1	0.009	>0.05	0.038	>0.05
Beta-2	0.186	<0.001***	0.187	<0.001***

6. The SEM index

There were no significant differences in SEM indexes (number of second of each 5 second mini-epoch with SEMs) between the three groups (Table 15 and Figure 24). There was a negative correlation between the SEM index and sleep latency in all three groups for both eye conditions (Table 16).

Table 15. Comparison of SEM indexes between three groups.

SEM index	Eyes open	Eyes closed
Rested controls	0.1023±0.036	0.9273±0.100
Sleep deprived controls	0.1369±0.040	0.9477±0.066
OSA patients	0.1279±0.027	0.9354±0.069

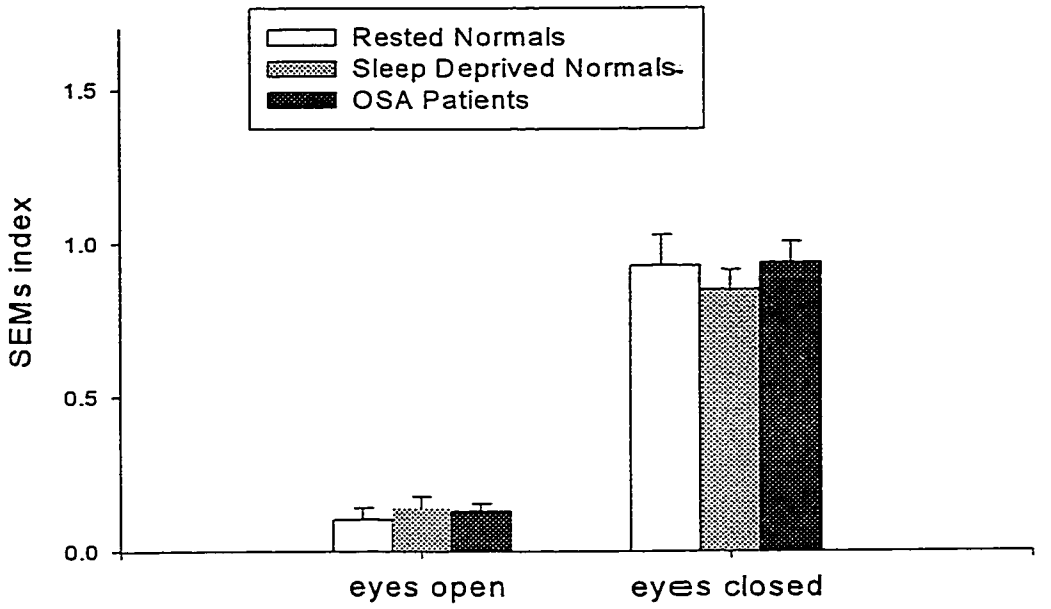

Fig 24. SEM indexes for the three groups

Table 16. Correlation between sleep latency and SEM indexes.

SEMs-SL	Eyes open + closed		Eyes open		Eyes closed	
	r	p	r	p	r	p
Rested Controls	-0.266	<0.05 *	-0.372	<0.01 **	-0.385	<0.01 **
Sleep Deprived Controls	-0.183	<0.05 *	-0.275	<0.05 *	-0.288	<0.05 *
OSA Patients	-0.325	<0.001***	-0.201	<0.05*	-0.446	<0.001***

Discussion

The present study has found that a wide range of EEG spectral differences exist in the waking EEGs of normal rested controls, normal sleep deprived controls and OSA patients. These findings strongly imply that the Q-EEG spectral analysis approach could provide a sensitive measure of EDS in within subject comparisons. Certainly, the technique can rapidly and accurately detect the onset of physiological sleepiness.

SEMs

Prior studies have shown that increased SEM activity is closely correlated with both subjective and behavioral sleepiness (Torsvall and Akerstedt 1988, Akerstdet et al. 1985). In these studies an SEM index was defined and evaluated in the three subject groups for the selected epochs in order to determine whether they were equivalent in regards to alertness/sleepiness levels. There were no differences in the SEM index between the three groups which indicated that equivalent and comparable epochs were selected; specifically, no more epochs were selected in physiological drowsiness in the sleep-deprived or patient groups. The SEM index correlated negatively with sleep latency in all three groups. This indicates that this SEM index reflects in a very sensitive fashion the level of alertness/sleepiness.

MSLT

The MSLT results confirmed that the sleep deprived normal subjects were indeed very sleepy. It is interesting to note that the mean SL in rested controls was considerably shorter than when the test was applied for subject selection prior to the study proper. The cause of this is uncertain. On the other hand, the mean experimental SL in apneic patients was longer than would be expected by baseline subject selection criteria. Nonetheless, all three groups showed significantly differences in the anticipated directions.

Broughton et al. (1988) reported that MSLT mean SL does not completely distinguish narcoleptics and rested normal controls. T. Roth et al (1980) documented similar overlaps for sleep apnea patients and normal controls. As well the MSLT may not closely reflect changes in sleep tendency which occur following treatment of very sleepy patients with narcolepsy or sleep apnea, even through the patients report subjective improvement (T. Roth et al. 1980, Mitler et al. 1982b). The present study suggests that MSLT may be affected by significant individual differences. These may be both constitutive (genetic) and learned difference for late of sleep onset. Moreover, if a person is motivated to appear normal on MSLT, he/she may ignore the instruction ("try to fall asleep.") and decide to try to stay awake during each MSLT nap session.

AAT

In early reports of the AAT (Stampi et al. 1993 and 1995) an alpha frequency band of 8-12 Hz was used. Stampi et al. (1995) observed a

progressive decrease in the AAC in normal subjects throughout 40 hours of sleep deprivation. In this study the alpha frequency band was separated into alpha-1 (8-9.9 Hz) and alpha-2 (10-12.9 Hz) subbands. As predicted, the ratios of mean eyes-closed to mean eyes-open alpha-1 and alpha-2 power (AAC) were significantly smaller for apnea patients compared to normal controls (both rested and sleep deprived). After one night sleep deprivation, the AAC (only for the alpha-1 frequency band) in sleep deprived controls was significantly decreased compared to the rested condition.

These findings are consistent with the results of Stampi et al. (1995) for sleep deprived controls and of Alloway et al. (1997) for narcolepsy. The present study demonstrates that the alpha-1 frequency band is more sensitive than the alpha-2 band for AAT analysis following one night of total sleep deprivation. It is therefore more powerful to narrow the frequency band for AAT than to use a broader 8-12 Hz band.

The present result did not confirm the correlation between AAT and MSLT reported by Stampi et al. (1993, 1995). The Stampi et al. (1995) study demonstrated that the AAC correlated with sleep latency on the MSLT in eight out of 10 sleep-deprived normal participants. However, Alloway et al. (1997) found a significant correlation between mean sleep latency and AAC only in their group of patients with narcolepsy and not within their normal subject group. There are certain protocol differences, which may explain these divergent results. Stampi et al. (1995) measured sleep latency immediately following the

AAT, whereas in Alloway et al. (1997) more than 45 min separated the AAT and MSLT.

In present study the sleep latency was measured immediately following the EEG sampling for AAT. The main reason for its negative finding of absence of correlation between AAC and sleep latency may relate to the relatively longer SL in apnea patients and shorter SL in rested normal controls in the experimental condition compared to the measurement taken at the time of subject selection.

Spectral power analysis

We recorded 19 EEG electrodes for quantitative study 8 of which were analyzed in the present study. The absolute spectral power showed more consistent results than did relative power. The EEG during wakefulness demonstrated increases of power density in the both theta frequency ranges covering the traditional 4.0-7.9 Hz following one night of sleep deprivation in normal subjects, and across the entire 0.2-25.9 Hz frequency range in patients with sleep apnea.

The duration of prior wakefulness modifies the spectral components in the waking EEG. The present study found that the main difference in spectral power in sleepy sleep-deprived normal subjects (one night sleep deprivation) was an increase in absolute and relative power in the theta-1 (4.0-5.9 Hz) and theta-2 (6.0-7.9 Hz) bands. There were no significant changes in adjacent bands. Moreover, there was no significant increase in spectral power of the delta band,

as predicted by the 2-process model of sleep/wake regulation (Borbely 1982). In this model Borbely et al. (1982) hypothesized that delta power is related to an endogenous sleep enhancing factor which accumulates in the brain during the usual waking period, becomes further enhanced during extended sleep deprivation, and is eliminated or inactivated exponentially during sleep. However, this model only predicts Q-EEG changes in the sleep EEG and not in the waking EEG; specifically, it predicts increases in delta activity in the sleep EEG after sleep deprivation (Borbely 1981).

Other studies of sleep deprivation suggest increases in theta power in the waking EEG. Corsi-Cabrera et al. (1992) studied the changes in the waking EEG as a consequence of sleep and sleep deprivation. They recorded 8 electrodes (C3, C4, T3, T4, P3, P4, O1 and O2) and found that the absolute spectral power for theta (3.66-7.32 Hz), alpha-2 (9.77-12.45 Hz) and beta (12.7-25.15 Hz) was significantly higher after one night of total sleep deprivation. Brunner and colleague (1993) analyzed the C3 and C4 electrode sites and found that the power density across the high delta and low theta bands (3.75-4.5 Hz) increased after four nights of partial sleep deprivation (4 hours sleep/per night). Cajochen and colleague (1995) reported that the spectral power values for theta and alpha frequency bands increase during sustained wakefulness. They analyzed two EEG signals (C3 and C4) during wakefulness and found that power density in frequency range of 6.25-9.0 Hz increased, but not in delta frequencies. Moreover, they described a daytime peaking of spectral power in these ranges during the mid-afternoon (so-called "nap zone") which later

decreased prior to the time of evening sleep onset. More recently Merritt et al. (1999) have described an increase in theta spectral power with sleepiness. In the present study only the theta frequency bands were sensitive to one night of sleep deprivation in normal subjects as an index of the awake "sleepy" state.

In the OSA patient group there was a widespread increase in spectral power across all frequency bands. The significant increase of theta band found in sleep deprived normal controls showed a further significant increase in the OSA patients. Morisson et al. (1998) first reported a slowing spectral power in the waking EEG in OSA patients. They analyzed 16 electrode sites and defined four frequency bands: delta (0.75-3.75 Hz), theta (4.00-7.75 Hz), alpha (8.00-12.75 Hz) and beta (13.00-20.25 Hz). They found that absolute delta and theta activity was significantly greater in OSA patients only over the frontal region.

In the present study the increase in spectral power found across all frequency bands appears to reflect dysfunction due to other processes. The main candidates for these effects in patients with sleep apnea would appear to be either recurrent nocturnal hypoxaemia or chronic sleep deprivation probably across many years. My personal belief is that nocturnal hypoxaemia may well play a significant role in changes in the awake EEG. The OSA patients showed increased beta power in the frontal region, increased beta and alpha power in the central region, and increased power in all frequencies in the occipital region. It seems reasonable that the broad increase across all frequency bands and in all scalp regions may represent cortical dysfunction which is due to repeated nocturnal hypoxaemia. Furthermore, Morisson et al. (1998) found a significant

correlation between EEG power changes during wakefulness and the degree of nocturnal oxygen desaturation, thereby supporting the hypothesis that nocturnal hypoxaemia is a primary factor in waking spectral EEG changes in OSA Patients. As mentioned, the EEG changes seen in the present study were not localized to any one region. This measurement of widespread cortical dysfunction may help to explain the wide range of neuropsychological deficits noted in OSA patients.

Although in this study mean SL statistically correlated (negatively) with spectral power in the delta and/or theta frequency bands in all three groups, the Pearson correlation coefficients (r) were too small for clinical diagnostic use. Morisson et al. (1998) found no significant correlations between mean sleep latency on MSLT and Q-EEG variables. These results suggest that the changes of spectral power in the awake EEG cannot predict the sleep latency on MSLT and are not a replacement for the MSLT.

Statistical Analysis

There are several widely recognized problems with this type of data in respect to statistical analysis. The data is very variable and is known to not be normally distributed. The Q-EEG data at the various electrode sites are not independent. More than two hundred repeated ANOVAs with a Bonferroni test on each could cause spurious significances by random error. All these aspects violate the assumptions of the ANOVA test. In practice, however, ANOVA is a very robust statistical procedure, and the assumptions frequently can be violated

with relatively minor effects (Howell 1992). The adjustments proposed by Greenhouse and Geisser (1959) could well be useful for repeated-measures analysis of variance in the face of violation of the underlying assumptions.

Conclusions

1. Spectral power differences in the waking sleep EEG exist between normal rested subjects, normal sleep deprived subjects (after one night TSD) and OSA patients.

2. Increases in spectral power for both theta bands in the waking EEG are present in sleep-deprived normal subjects (after one night of total sleep deprivation).

3. In OSA patients the spectral power of all frequency bands is increased compared to rested and sleep-deprived normal controls. This probably reflects a combination of chronic sleep fragmentation and recurrent nocturnal hypoxemia.

4. Spectral analysis can be a sensitive measure of sleepiness/alertness levels; but its variability appears to be too great to detect sleepy wakefulness.

Abbreviation

AAC	alpha attenuation coefficient
AAT	alpha attenuation test
AD-ACL	activation-deactivation adjective check list
ANOVA	analysis of variance
CNS	central nervous system
CPAP	continuous positive airway pressure
EDS	excessive daytime sleepiness
EEG	electroencephalogram
EKG	electrocardiogram
EMG	electromyogram
EOG	electrooculogram
ERPs	event related potentials
FFT	fast Fourier transform
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
OSA	obstructive sleep apnea
PLMs	periodic leg movements
PSG	polysomnogram
QEEG	quantitative EEG
RTSW	Repeated Test of Sustained Wakefulness
SEMs	slow eye movements
SL	sleep latency
TSD	total sleep deprivation
VAS	visual-anlog scale

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