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Anteroposterior Difference in EEG Sleep Depth Measure is Reduced in Apnea Patients

Eero Huupponen,[1,4] Antti Saastamoinen,[1] Atte Joutsen,[2] Jussi Virkkala,[3] Jarmo Alametsä,[1] Joel Hasan,[2,3] Alpo Värri,[1] and Sari-Leena Himanen[2]

In the present work, mean frequencies of FFT amplitude spectra from six EEG derivations were used to provide a frontopolar, a central and an occipital sleep depth measure. Parameters quantifying the anteroposterior differences in these three sleep depth measures during the night were also developed. The method was applied to analysis of 30 all-night recordings from 15 healthy control subjects and 15 apnea patients. Control subjects showed larger differences in sleep depth between frontopolar and central positions than the apnea patients. The relatively reduced frontal sleep depth in apnea patients might reflect the disruption of the dynamic sleep process caused by apneas.

KEY WORDS: sleep EEG; automatic analysis; sleep depth; apnea.

INTRODUCTION

Sleep apnea is a common sleep disorder with a prevalence of 4% in adult men and 2% in adult women.(1) Each apnea event is defined as a respiratory pause lasting at least 10 s due to upper-airway obstruction. If the obstruction is only partial, the resulting airflow limitation is called a hypopnea. A patient with severe sleep apnea can have up to 600 apnea events per night.

The standard visual sleep staging(2) (denoted as RKS) is performed with a 30-s time resolution using six sleep stages: W (wake), REM (rapid eye movement sleep), S1 (lightest sleep), S2, S3, S4 (deepest sleep). Conventional sleep parameters, like sleep efficiency index or percentage of sleep stages based on the visual sleep staging poorly reflect the sleep disruption caused by apneas and hypopneas.(3–5) Thus,

[1]Signal Processing Laboratory, Tampere University of Technology, Korkeakoulunkatu 1, FIN-33101, Tampere, Finland.
[2]Department of Clinical Neurophysiology, Tampere University Hospital, Finland.
[3]Section of Clinical Neuroscience, Finnish Institute of Occupational Health, Helsinki, Finland.
[4]To whom correspondence should be addressed; e-mail: eero.huupponen@tut.fi.

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there is a need for more sensitive methods to characterize sleep EEG during sleep and to reveal possible sleep disturbances. Automated methods for the analysis of sleep EEG recordings are being developed aiming to assist analysis work of large amounts of data and also to provide objective descriptions of the sleep process.[6–9] Automated techniques could also be useful in quantifying sleep EEG phenomena that are difficult to define by visual analysis.

Based on studies on EEG power spectrum, absolute EEG amplitudes (or power values) vary from subject to subject. Delta activity is known to decline with age.[10–13] Sleep deprivation is known to result in an enhancement of slow-wave activity and to induce topographic-specific changes in the slow wave range.[14,15] The observed increase of EEG slow-wave activity after high sleep pressure was significantly more pronounced in the fronto-central than in parieto-occipital derivations. It is obvious that delta activity is very important in sleep EEG analysis, but due to its variability amplitude thresholds are not very desirable.

Synchronization Measures of Sleep Depth

It is well known that as the synchronization state of cortical neuron increases during deepening sleep, the EEG activities get slower and the amplitudes get larger.[16] Measures based on spectral complexity, for instance, mean frequency and spectral entropy,[17–21] reflect the cortical synchronization by getting lower along increasing synchronization and *vice versa*. These measures have the advantage of being independent of absolute EEG amplitudes.

The awake state can be well differentiated from other sleep stages by mean frequency measure[17] and also the sleep stages from each other to a large extent. In one recent work complexity measure was studied to differentiate sleep and awake states with resulting accuracy ranging from 91 to 97%.[21] Rezek and Roberts[18] studied spectral entropy, autoregressive (AR) model order, and approximate entropy in characterization of signal complexity in sleep and anesthesia EEG. Deep sleep resulted in lower spectral entropy values than light sleep. FFT based methods were recommended over AR modeling.

In a recent study we quantified sleep depth with mean frequency of EEG amplitude spectrum of the C4-A1 EEG channel.[22] The results showed that the automatically quantified percentage of light sleep was higher in apnea patients than control subject while no statistical difference was found in slow wave sleep (SWS) percentages between the groups. This indicated that healthy subjects achieved a better overall cortical synchronization during sleep than apnea patients.

Mean frequency (AR and FFT spectra), spectral entropy (AR and FFT spectra), fractal dimension and delta amplitude were compared in sleep depth quantification in healthy subjects.[23] SWS (S3, S4) could be well separated from other sleep stages as well as from awake state. FFT based mean frequency measure provided the best overall agreement to all RKS Non-REM stages being 71.3 and 58% for young and old subjects, respectively, followed by FFT based spectral entropy with 68.7 and 57.7%. The delta amplitude provided markedly poorer results, with 65.3 and 28.5%, respectively.

Other Sleep Depth Measures

Multiple other measures for sleep depth quantification have also been presented. Period analysis, where zero crossings per second were counted, resulted in an agreement of 69% with visual RKS staging.[24] Low frequency EEG was quantified via absolute delta amplitude and so called low-frequency continuity ranging 0–100%, describing how much of the current slow-wave activity is continued in near-term future EEG, were studied.[25] The slow sleep continuity measure did not depend directly on absolute EEG amplitudes. Smoothing was applied to reduce the noise. The results showed that delta amplitude and low-frequency continuity both decreased with increasing age. Delta amplitudes were larger in females while low-frequency continuity did not differ between genders. Discussion addressed the point that absolute amplitude measures would give more deep sleep to women despite possibly equally deep true sleep.

Delta, sigma and beta oscillations in frontal, central and parietal sites, smoothed with a 180-s moving-average window, were studied via cross-correlation and the results indicated similar time-courses despite spatial differences in power levels.[26] A rather similar outcome resulted in our previous study in healthy subjects[27] where a strong correlation was found in very slow sleep depth oscillations between different EEG channels with period times longer than 50 s.

A so-called spectral frequency index (SFx) has also been presented to quantify the sleep depth.[28] SFx was obtained on the basis of the FFT spectrum, so that the relationships of three frequency bands were combined in a non-linear manner to provide a measure of sleep depth, ranging from 33 to 100%, with small values indicating deep sleep. The validation with healthy subjects showed that the median values of the SFx measure during different RKS stages were 83, 68, 63, 51, 44 and 42% in W, REM, S1, S2, S3 and S4, respectively. In a further application of the SFx measure, the outcome showed that apnea patients spent more time awake and that their sleep was more superficial than control subjects.[29]

The reviewed spectral measures resemble each other, providing fairly similar type of outputs and can be used for sleep depth quantification. The FFT based mean frequency is a good measure and this is why it was used in the present work. Although it is assumed that sleep is an uniform state,[2] there still may be spatial differences in the sleep depth measure. The aim of the present work was to develop automated measures for comparison of sleep depth measures computed along the anteroposterior axis and apply them to analysis of recordings from control subjects and apnea patients.

MATERIALS AND METHODS

Recordings

Sleep EEG recordings from a total of 30 persons, 15 healthy control subjects and 15 apnea patients, were studied. Both groups consisted of seven females and eight males. Ages of subjects of control group ranged from 27 to 63 years, with a median of 46 years while the apnea patients' ages ranged from 28 to 61 years

with a median of 47 years. There was no statistical difference between the groups in terms of age, tested with Mann–Whitney U-test. The healthy control subjects had no history of excessive daytime sleepiness or sleep complaints. The apnea patients were included by clinical picture and subjective complaints of apnea according to the International Classification of Sleep Disorders[30] and an apnea–hypopnea index ≥10 events/h. All recordings were scored into sleep stages by the standard RKS method.[2] Twenty-five of the recordings were part of a larger study[31] and five recordings were polygraphies of apnea patients in Tampere University Hospital.

The subjects retired to bed between 10 and 12 p.m. and they were allowed to sleep maximally 8 h. Seven EEG channels Fp1-A2, C3-A2, O1-A2, Fp2-A1, C4-A1, O2-A1, A2-A1, two EOG channels and submental muscle tonus were recorded. In addition tibialis anterior muscle tonus, body position, electrocardiogram, nasal airflow, thoracoabdominal respiratory movements and blood oxygen saturation were recorded. Recordings were digitized with a 200 Hz sampling rate.

Signal Processing

The mean frequency measure, denoted as $f_c(k)$, was computed with one-second time resolution, where k denotes the time in seconds. A sliding 5-s long Saramäki window function[32] was centered at the kth second to weight the corresponding 5-s EEG signal segment (after mean value was subtracted). Zero padding[33] to 2048 samples was used in extracting the FFT amplitude spectrum, denoted as $S[f]$. Frequency resolution of the spectrum was 0.1 Hz. Frequency band ranging from 0.5 to 12.5 Hz was utilized in order to include activities from delta to alpha into the measure. Next, cumulative spectrum $c[f]$ was formed based on $S[f]$ as follows:

$$c[f] = \frac{\sum_{f=0.5}^{f} S[f]}{\sum_{f=0.5}^{12.5} S[f]}.$$

Then corresponding mean frequency $f_c(k)$ was obtained with linear interpolation as $c[f_c] = 0.5$. The value of $f_c(k)$ can be seen to indicate the center of gravity of spectrum $S[f]$, the unit of $f_c(k)$ being Hertz (Hz). In deep sleep, where delta amplitude is large as compared to other EEG activities in the frequency range 0.5–12.5 Hz, the mean frequency $f_c(k)$ became small and in lighter sleep it got higher.

The mean frequency measure was determined for all six EEG channels of the all-night recording separately, denoted as $f_c(\mathrm{Fp1},k)$, $f_c(\mathrm{Fp2},k)$, $f_c(\mathrm{C3},k)$, $f_c(\mathrm{C4},k)$, $f_c(\mathrm{O1},k)$, and $f_c(\mathrm{O2},k)$. No manual artifact rejection was used. These "raw" sleep depth measures, containing quite a bit short-term variation or noise, were then smoothed with a moving 201-s median filter. Transient variations were then filtered out while preserving the more slow changes in the six-smoothed sleep depth measures, denoted as $f_{c201}(\mathrm{Fp1},k)$, $f_{c201}(\mathrm{Fp2},k)$, $f_{c201}(\mathrm{C3},k)$, $f_{c201}(\mathrm{C4},k)$, $f_{c201}(\mathrm{O1},k)$, and $f_{c201}(\mathrm{O2},k)$.

The six smoothed sleep depth measures were then averaged symmetrically between brain hemispheres to provide frontopolar $f_{c201}(\mathrm{Fp},k)$, central $f_{c201}(\mathrm{C},k)$, and occipital $f_{c201}(\mathrm{O},k)$ sleep depth measures. The overall characteristics of these measures is illustrated in Fig. 1 showing the probability density functions of measure

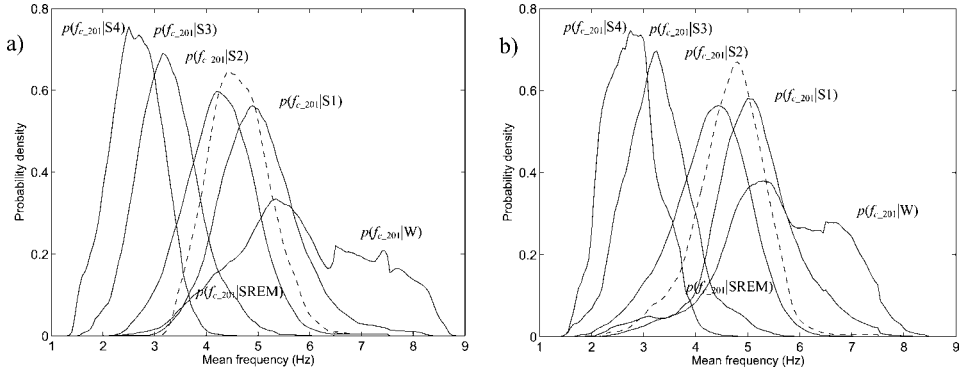

Fig. 1. Probability density functions of the smoothed sleep depth measure $f_{c\_201}(C,k)$ during different RKS sleep stages, in all control subjects (a) and all apnea patients (b). During S4 and S3 mean frequency typically was lower than 3.5 Hz and higher in lighter sleep stages of S1, S2, and REM and W. The probability density $p(f_{c\_201}(C,k) \mid \text{SREM})$ is drawn with a dashed line.

$f_{c201}(C,k)$ in all the data in different sleep stages, showing how sleep depth changed along sleep stages. Further, examples of these measures during all night in two subjects are seen in Fig. 2.

Differences in the three anteroposterior sleep depth measures $f_{c201}(Fp,k)$, $f_{c201}(C,k)$, and $f_{c201}(O,k)$ were the focus of the present work. Two separate analyses (A, B) were developed to quantify these differences, detailed in the following. The analyses were done using TIB and repeated using TST.

Analysis (A), Simultaneous Anteroposterior Differences in Sleep Depth Measures

First, the difference between frontopolar and central sleep depth measures at each time instant k, denoted as $\Delta_{C-Fp}(k)$, was needed as well as the difference between occipital and central measures, written as $\Delta_{O-C}(k)$. These two differences were determined also by relating them to current central sleep depth $f_{c201}(C,k)$ to provide relative differences, denoted as $\Delta r_{C-Fp}(k)$ and $\Delta r_{O-C}(k)$. These can be presented formally as follows. The time index k was run through the all-night recording at one-second steps and the differences were formed for each second k as follows:

$$\Delta_{C-Fp}(k) = f_{c201}(C,k) - f_{c201}(Fp,k)$$

$$\Delta_{O-C}(k) = f_{c201}(O,k) - f_{c201}(C,k)$$

$$\Delta r_{C-Fp}(k) = \frac{\{f_{c201}(C,k) - f_{c201}(Fp,k)\}}{f_{c201}(C,k)\}} 100\%$$

$$\Delta r_{O-C}(k) = \frac{\{f_{c201}(O,k) - f_{c201}(C,k)\}}{f_{c201}(C,k)\}} 100\%$$

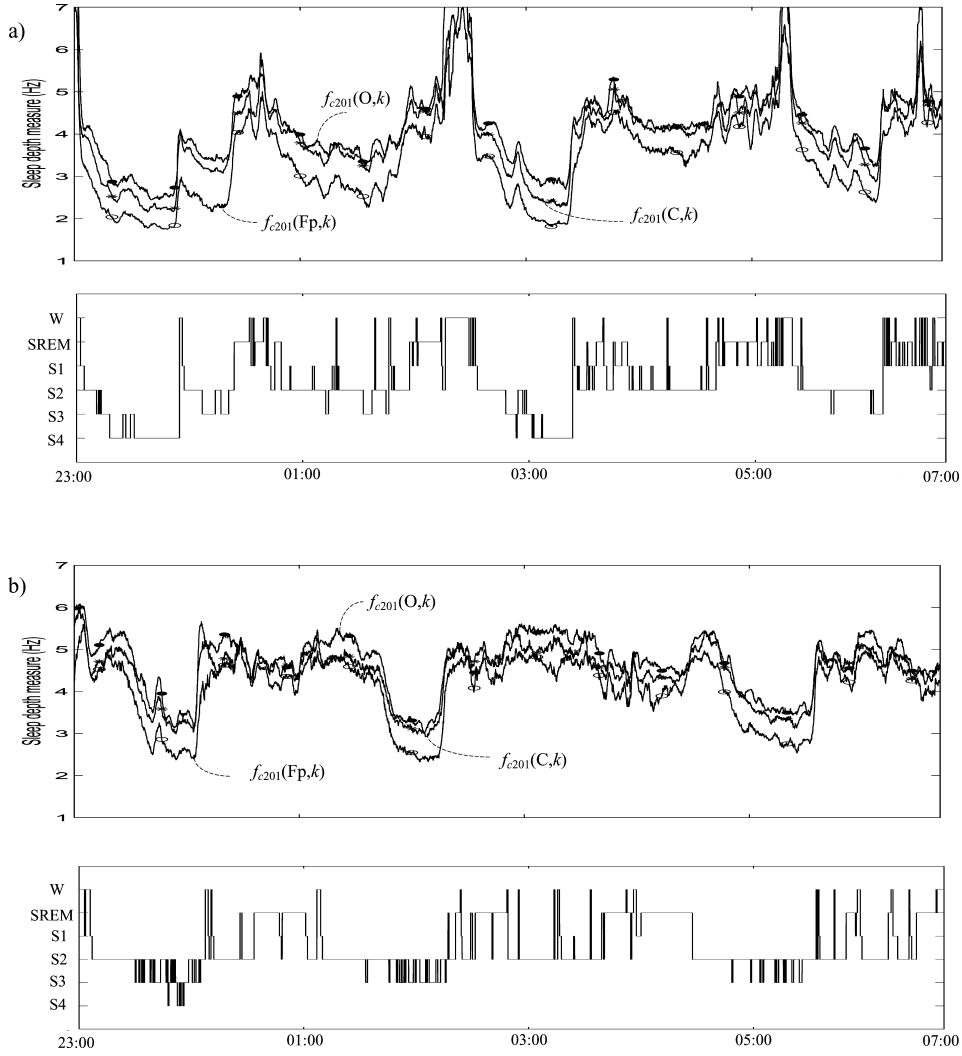

Fig. 2. Example of sleep depth measures along anteroposterior axis during the night, in one control subject (a) and one apnea patient (b). The frontopolarly computed sleep depth measure f_{c201}(Fp,k) is drawn with a line with circles, the centrally computed f_{c201}(C,k) is with dots and occipital f_{c201}(O,k) with asterisk. Visual RKS curves are shown for comparison. Deepest sleep or greatest neural synchronization was reached frontally and lightest occipitally in both cases. The developed measures quantifying anteroposterior sleep depth differences (in TST, presented later) were ΔDS(Fp-C)% and Δ_{C-Fp} of 23.6% and 0.58 Hz in this control subject and 16.1% and 0.38 Hz in this apnea patient, respectively, showing typical values in both groups (as seen in Tables II and III).

Then, corresponding average differences in anteroposterior sleep depth measures during the night were determined, denoted as Δ_{C-Fp}, Δ_{O-C}, Δr_{C-Fp}, Δr_{O-C}. Positive values of Δ_{C-Fp} or Δr_{C-Fp} indicated that sleep depth measures showed deeper sleep frontopolarly than centrally, for example.

Analysis (B), Anteroposterior Differences in Deep Sleep Percentages

First, a quantity called Deep Sleep percentage (DS%) was extracted indicating percentage of the all-night recording containing deeper sleep depth than the threshold λ_{DS}. Deep Sleep percentage determined on the basis of central sleep depth measure $f_{c201}(C,k)$ is denoted as DS(C)%. This quantity was derived as follows. The letter L denotes TIB or TST in seconds. First, an intermediate quantity was set to zero: deep_sleep[1:L] = 0. The time index k was run through the all-night recording at one-second steps and

if $f_{c201}(C,k) < \lambda_{DS}$
then deep_sleep[k] was set to 1

Then DS(C)% was obtained as 100% · (number of seconds with deep_sleep[k] = 1 divided by L). Identically, by using the same threshold λ_{DS}, the deep sleep percentages were computed also based on frontopolar and occipital sleep depth measures $f_{c201}(Fp,k)$ and $f_{c201}(O,k)$, which are denoted as DS(C)% and DS(O)%. Finally, a measure of anteroposterior sleep depth difference between frontal and central positions, denoted as ΔDS(Fp-C)%, was obtained directly as DS(Fp)%-DS(C)% and in the same manner ΔDS(C-O)% was obtained as DS(C)%-DS(O)% for each recording. Positive value of ΔDS(Fp-C)% indicated that the frontal sleep depth measure was deeper than λ_{DS} for a longer time than central sleep depth measure.

The Mann–Whitney U test was used to compare independent variables. The significance level $p < 0.05$ was utilized in statistical tests.

RESULTS

The sleep parameter values are given in Table I. The sleep efficiency indexes ranged from 75.6 to 98.0% and from 74.4 to 94.4% in control subjects and apnea patients, respectively. There were no other statistical differences in sleep stage percentages than the apnea patients having a higher amount of sleep stage 2.

The results of analysis (A) are seen in Table II. The average simultaneous differences in sleep depth measures between the central and frontopolar brain regions (Δ_{C-Fp}) were statistically significantly higher in control subjects than apnea

Table I. Sleep Parameters in Groups of Control Subjects and Apnea Patients

	Control subjects median (range)	Apnea patients median (range)	
TIB	8 h 0 min (6 h 57 min-8 h0 min)	8 h 0 min (7 h13 min-8 h0 min)	n.s.
SEI%	89.1 (75.6–98.0)	89.7 (74.4–94.2)	n.s.
SREM%	21.2 (13.9–33.4)	18.9 (12.4–30.4)	n.s.
S1%	8.8 (1.8–17.1)	7.3 (4.2–12.5)	n.s.
S2%	56.2 (43.0–70.8)	63.6 (41.9–74.2)	$p = 0.024$
S3%	9.7 (1.7–13.0)	8.4 (0.1–13.1)	n.s.
S4%	3.4 (0–14.4)	1.5 (0–13.5)	n.s.
SWS% (S4 + S4)	13.1 (1.7–25.1)	9.6 (0.1–26.6)	n.s.

Note. Percentages of stages S1, S2, S3, S4 and SREM, referred to total sleep time, TST. SEI% = TST/TIB. Mann-Whitney U test was used in statistical analysis between groups.

Table II. Outcome of Analysis A, Simultaneous Anteroposterior Difference in Sleep Depth Measure

	Measure	Control subjects median (25%, 75% percentiles)	Apnea patients median (25%, 75% percentiles)	
TIB	Δ_{C-Fp}	0.56 Hz (0.46, 0.66)	0.37 Hz (0.30-0.43)	$p = 0.003$
	Δ_{O-C}	0.35 Hz (0.26, 0.46)	0.37 Hz (0.25, 0.47)	n.s.
	Δr_{C-Fp}	13.1% (11.4, 15.9)	8.8% (6.2–10.3)	$p = 0.001$
	Δr_{O-C}	9.5% (6.4, 10.2)	8.5% (5.4–11.1)	n.s.
TST	Δ_{C-Fp}	0.54 Hz (0.39, 0.63)	0.33 Hz (0.24–0.38)	$p = 0.003$
	Δ_{O-C}	0.35 Hz (0.23, 0.46)	0.35 Hz (0.25, 0.49)	n.s.
	Δr_{C-Fp}	12.7% (10.0, 14.7)	8.4% (6.0–9.7)	$p = 0.002$
	Δr_{O-C}	9.4% (6.3, 10.2)	8.5% (5.4–12.3)	n.s.

Note. The figures were determined using absolute values of differences (Δ_{C-Fp}, Δ_{O-C}) and as related to central sleep depth (Δr_{C-Fp}, Δr_{O-C}) providing percentage values. The analyses were done for TIB and TST. Mann-Whitney U test was used in statistical analyses between the groups. The control subjects showed larger differences between the frontopolar and central sleep depth measures than the apnea patients.

patients ($p = 0.003$, in TIB and TST). The corresponding average relative differences (Δr_{C-Fp}) were also statistically significantly larger in control subjects than in apnea patients ($p = 0.001$ and $p = 0.002$, in TIB and TST, respectively). There were no statistically significant differences in average differences in sleep depth measures between occipital and central regions (Δ_{O-C} and Δr_{O-C}).

In analysis (B), threshold values λ_{DS} from 4.0 down to 2.0 Hz were applied in steps of 0.1 Hz. With values of 3.0 Hz and below there were statistically significant differences between the control subjects and apnea patients between the frontopolar and central Deep Sleep percentages ΔDS(Fp-C)%. The p-values were 0.011, 0.007 and 0.021 for λ_{DS} of 3.0, 2.9 and 2.8 Hz, respectively (in TST). With even smaller values of λ_{DS} more and more values started to be zeros as there was no such deep sleep in all recordings.

The outcome with the threshold λ_{DS} set to 2.9 Hz is visualized in Table III. The differences between frontopolar and central Deep Sleep percentages ΔDS(Fp-C)% were statistically significantly higher in the control subjects than in the apnea patients ($p = 0.006$ and $p = 0.007$, in TIB and TST, respectively). The values of ΔDS(C–O)% showed no statistically significant differences between the groups.

Table III. Outcome of Analysis B

	Measure	Control subjects median (25%, 75% percentiles)	Apnea patients median (25%, 75% percentiles)	
TIB	ΔDS(Fp-C)%	14.3% (9.8, 15.2)	7.6% (2.7, 12.1)	$p = 0.006$
	ΔDS(C-O)%	3.1% (0, 6.8)	1.1% (0, 3.3)	n.s.
TST	ΔDS(Fp-C)%	14.6% (9.4, 19.6)	8.1% (1.9, 11.9)	$p = 0.007$
	ΔDS(C-O)%	3.7% (0, 7.0)	1.2% (0, 3.6)	n.s.

Note. The anteroposterior differences in Deep Sleep percentages. The figures are given including TIB and TST. DS% computed from different locations with the threshold $\lambda_{DS} =$ 2.9 Hz. Mann-Whitney U test was used in statistical analyses between the groups.

DISCUSSION

The focus of the present work was to quantify the differences in the frontopolar, central and occipital sleep depth measures at each time instant during the night (analysis A) and in part of the deep sleep (analysis B). The developed measures were able to show that control subjects had larger fronto-central differences in sleep depth measures than the apnea patients.

Synchronization measures of sleep depth, like mean frequency and entropy, have previously been studied and found capable in sleep depth quantification.[17,18,22,23] The present study provided further experience on sleep depth quantification based on mean frequency measure of EEG frequency band of 0.5–12.5 Hz extracted with 5-s FFT windowing. This mean frequency measure quantified sleep depth well, which can also be seen in Fig. 1. (Naturally also other details would be possible, for instance a longer 10-s FFT window would result somewhat more averaging already inside the window.) The raw sleep depth measures were smoothed to allow as reliable analysis as possible. A moving 201-s median filter was used to remove sudden transient changes possible caused by EEG arousals or other events, even short periods of wakefulness. Also the effect of artifacts, stemming for example from eye movements, were mostly rejected this way. There are no eye movements in NREM sleep stages S3–S4 and they are few in normal S2. The remaining variation was reduced by combining the symmetric channels between the brain hemispheres. All these steps were done so that the rather slowly changing baseline of sleep depth could be obtained as reliably as possible in the three sleep depth measures $f_{c201}(\mathrm{Fp},k)$, $f_{c201}(\mathrm{C},k)$ and $f_{c201}(\mathrm{O},k)$. The presented analyses were additionally repeated using 101 and 31-s median filtering and still the outcomes remained consistent.

The control subjects showed statistically significant larger absolute and relative differences between frontopolar and central sleep depth measures ($\Delta_{\mathrm{C-Fp}}$, $\Delta \mathrm{r}_{\mathrm{C-Fp}}$) than apnea patients (analysis A). In should be noted that in both groups these values were positive indicating deeper frontal sleep depth as compared to central sleep depth. The average differences between occipital and central regions ($\Delta_{\mathrm{O-C}}$ and $\Delta \mathrm{r}_{\mathrm{O-C}}$) were also positive, indicating deeper central sleep depth as compared to occipital sleep depth, but there were no differences between the groups.

The values of anteroposterior differences in Deep Sleep percentages ΔDS(Fp-C)% were statistically significantly higher in the control subjects than in the apnea patients (analysis B). Also these values were positive indicating that frontal sleep depth measure was deeper than λ_{DS} for a longer time than central sleep depth measure, both in control subjects and apnea patients. The values of ΔDS(C–O)% were also positive showing with no statistically significant differences, however.

The results of the present work are in line with a previous finding that the amplitude of delta waves is highest frontally in normal sleep and therefore frontal delta waves can show deep sleep at the same time as delta waves in central leads are too low to be scored as deep sleep.[34] Also in other work it has been presented that slow waves can be higher in the frontal EEG leads than in the central leads.[35,36,37] Recently it was found with visual analysis that apnea patients have less high amplitude

frontal delta activity than healthy subjects.[38,39] These outcomes might demonstrate the importance of the frontal brain lobe in human sleep. For example, visual sleep stage scoring with central EEG derivation does not necessarily differentiate between healthy subjects and sleep apnea patients.[3,4,5] It might be that sleep disorder caused by apneas disturbs the sleep process more in the frontal lobe inhibiting synchronization producing neuronal mechanisms.

To the best knowledge of the authors topographic differences in whole-night sleep EEG in sleep apnea patients have not previously been described. Usually only central leads have been used. Therefore information about the state of the frontal lobes during sleep has not been acquired. There is, however, evidence that sleep might be particularly important for the proper function of the frontal lobes. Recent experimental studies report impaired performance due to fragmented or restricted sleep on tasks of frontal lobe function (for review please see).[40] In addition, quite recently a significant relationship between frontal sleep EEG and performance tasks was presented.[41]

Spatial differences in slowly changing sleep depth are difficult to quantify by visual analysis of the EEG. Therefore automatic analysis seems very useful in this task. Based on the outcome of the present work it might be suggested that the higher the developed parameter values Δ_{C-Fp}, Δr_{C-Fp} and ΔDS(Fp-C)% are, the more refreshing the sleep is, as these values were reduced in apnea patients. It would be interesting to monitor them to see if these measures improve with apnea treatment.

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