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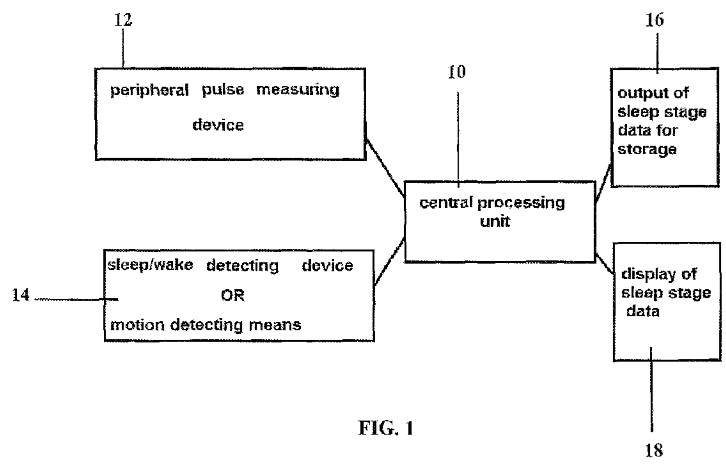

FIG. 1

(57) Abstract: A method and apparatus for detecting and distinguishing epochs of deep-sleep from epochs of light-sleep of a subject by sensing by a peripheral pulse signal related to the systemic circulation of the subject, preferably a peripheral arterial tone (PAT) sensor for sensing pulsatile arterial volume changes in a digit (e.g., a finger) of the subject reflecting sympathetic tone variations; analyzing the sensed pulse signals for determining therefrom a number of features, particularly seven specific variables in each of two time periods; and utilizing the results of the analysis for determining whether the epoch detected is a light-sleep epoch or a deep-sleep epoch.

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NON–INVASIVE METHOD AND APPARATUS FOR DETERMINING LIGHT–SLEEP AND DEEP–SLEEP STAGES

RELATED APPLICATION

The present application includes subject matter described in US Provisional Application No. 61/071,127 filed April 14, 2008, claims its priority date, and incorporates by reference the complete disclosure therein.

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to a method and apparatus for non–invasively determining light–sleep and deep–sleep stages by sensing peripheral pulse signals related to the systemic circulation of the subject. The invention is particularly useful when utilizing a peripheral arterial tone (PAT) sensor, such as disclosed in U.S. Patent Application No. 10/195,464, filed July 16, 2002, U.S. Patent Application No. 10/471,580, filed September 12,2003, and U.S. Patent Application No. 10/520,273, filed January 18, 2005, all assigned to the same assignee as the present application, the descriptions of which are incorporated herein by reference, and the invention is therefore described below with respect to such sensors.

To facilitate understanding the following description, there are set forth below the meanings of a number of acronyms frequently used therein.

REM	rapid eye movement (sleep stage)
NREM	non–rapid eye movement (sleep stage)
PAT	peripheral arterial tone (signal)
AMP	PAT signal amplitude
EEG	electroencephalogram – electrical currents associated with the brain
EMG	electromyogram – electrical currents associated with muscles
EOG	electrooculography – measuring the resting potential of the retina
ANS	automatic nervous system
OSA	obstructive sleep apnea
OSAS	obstructive sleep apnea syndrome
RDI	respiratory disturbance index
PSG	Polysomnography
IPP	inter–pulse period (heart–rate)

DFA	detrended fluctuation analysis
VLF	peak of the very low frequency spectral density
LF	peak of the low frequency spectral density
ULF	peak of the ultra–low frequency spectral density
HF	peak of the high frequency spectral density
Spec Ratio	ratio of LF to HF
NF	neighboring filter
ROC	Receiver Operating Characteristic (curve)
AASM	American Academy of Sleep Medicine

Detecting various sleep–state conditions, particularly sleep–wake status and REM sleep stages versus NREM sleep stages, is commonly used in the determination of various medical conditions, particularly obstructive sleep conditions such as OSA, and REM related apnea. At the present time, detecting the various the sleep–state conditions is commonly done by PSG in a sleep laboratory equipped with specialized instruments for sensing various conditions, particularly the EEG signal, and utilizing the results of the sensed conditions for determining the sleep state. The above–cited U.S. Patent Application Serial No. 10/195,464 filed July 16, 2002 utilizes an external probe applied to peripheral body location, such as a digit (finger or toe) of the individual, for detecting peripheral pulse signals related to the systemic circulation of the subject. The preferred embodiment therein disclosed utilizes a PAT probe for detecting changes in the peripheral vascular bed volume of the subject. Likewise, the above–cited U.S. Patent Application Serial No. 10/520,273, filed January 18, 2005, utilizes an external probe capable of being applied at virtually any body site of the individual, for detecting peripheral pulse signals related to the systemic circulation of the subject.

The present invention is directed particularly to detecting and distinguishing epochs of deep–sleep from epochs of light–sleep using a probe applied to the individual for sensing peripheral pulse signals related to the systemic circulation of the subject, which can be used for unattended ambulatory sleep monitoring, not requiring the sensors (e.g., EEG sensors) or other specialized instruments provided in a sleep laboratory.

The invention is particularly effective when using a PAT probe described in the above–cited U.S. Applications, Serial Nos. 10/195,464, 10/471,580, and

10/520,273, for detecting changes in the peripheral vascular bed volume of the individual, and is therefore described below particularly with respect to the use of such sensors. For the sake of brevity, the construction and operation of such PAT sensors are not described herein, but are available in the above–cited US Application Serial No. 10/195,464, 10/471,580, and 10/520,273, incorporated herein by reference for this purpose. While the invention preferably uses such a PAT sensor, it will be appreciated that the invention could use other sensors for sensing peripheral pulse signals. A number of such other sensors are well known to the art. These include, but are not restricted to; skin optical density or skin surface–reflectivity devices, optical plethysmographs, (also known as photo–plethysmograps), Doppler ultrasound devices, laser Doppler device, pulse oximeters, segmental plethysmographs, circumferential strain gauge devices, isotope washout techniques, thermal washout techniques, electromagnetic techniques, Hall effect sensors, and the like for sensing peripheral pulse signal related to the systemic circulation of the subject.

Non–Rapid Eye Movement (NREM) sleep was traditionally classified into four stages, where stage 1 was defined as drowsiness (just falling asleep); stage 2 as light–sleep, and stages 3 and 4 as deep sleep, which is considered the more refreshing sleep. Both Stages 1 and 2 NREM sleep, classified as light–sleep, are characterized by theta EEG activity. In stage 1 NREM sleep, there may be slow vertical eye rolling while stage 2 of NREM sleep is characterized by sleep spindles and/or K complexes, no eye movements and reduced EMG activity. Stages 3 and 4 NREM sleep, classified as deep sleep, are characterized by delta EEG activity (which is the reason for the common term describing these stages as slow–wave sleep), no eye movements (although the EOG channels commonly show EEG artifacts), and even further diminished EMG activity (Lavie et al., 2002; Rechtschaffen and Kales, 1968). Given the more restorative nature of deep sleep, and the common findings of increased deep sleep following sleep deprivation or treatment for sleep disorders, it is of substantial clinical importance to distinguish between light–sleep and deep–sleep stages.

Recently, the AASM Visual Scoring Task Force re–examined these rules and came up with a new terminology for sleep stages. Since no evidence was found to justify dividing slow wave sleep into two stages, i.e. stages 3 and 4 of NREM sleep, it was proposed to combine these into a single stage of deep sleep (Silber et al., 2007) However, despite coming up with new scoring criteria, as with its predecessor (Rechtschaffen & Kales,1968) the activity of the autonomic nervous system (ANS) still does not play a major role in scoring sleep stages, despite increasing evidence for substantial and differential activities of this system in the various sleep stages. In other words, regardless of the EEG changes measured via surface electrodes, light and deep sleep seem to differ by autonomic activations manifested predominantly as higher and more stable parasympathetic activity in deep sleep than light NREM sleep (Dvir et al., 2002; Herscovici et al., 2007; Lavie et al., 2000; Narkiewicz et al., 1998; Penzel et al., 2000; Penzel et al., 2003; Penzel et al., 2004; Pressman and Fry, 1989; Villa et al., 2000; Virtanen et al., 2007). Thus, ANS such as heart rate, heart rate variability or peripheral arterial tone may be of significant importance in evaluating the quality of NREM sleep.

The Watch–PAT 100 (WP100 or WP200 further version of the same system) is an ambulatory sleep recorder, which is based predominantly on recordings of the peripheral arterial tone (PAT) signal and pulse rate (two important outputs of the autonomic nervous system), actigraphy and pulse oximetry (Bar et al, 2004, Penzel et al, 2004, Pillar et al 2003). It has been shown to accurately detect sleep vs. wakefulness (Hedner et al., 2004), as well as to detect REM sleep (Dvir et al., 2002; Herscovici et al., 2007; Lavie et al., 2000). Given the well established changes of the autonomic nervous system characteristics in patients with obstructive sleep apnea (Aydin et al., 2004; Brooks et al., 1999; Jo et al., 2005; Narkiewicz et al., 1998; Narkiewicz and Somers, 1997; Penzel et al., 2000; Penzel et al., 2003; Pepin et al., 1994), the WP100 has been tested on both normal subjects and patients with OSA (Bar et al., 2003; Dvir et al., 2002; Hedner et al., 2004; Herscovici et al., 2007; Lavie et al., 2000; Penzel et al., 2004; Pillar et al., 2003). However, the ability to distinguish between light–sleep and deep sleep based on autonomic nervous system (ANS) outputs monitored by the WP100 has not been examined.

Deep sleep has been shown to be associated with increased parasympathetic activity (projected in heart rate and heart rate variability), and more regular and stable heart rate (Berlad et al., 1993; Bonnet and Arand, 1997; Brandenberger et al., 2005; Burgess et al., 1999; Busek et al., 2005; Elsenbruch et al., 1999; Ferri et al., 2000; Kirby and Verrier, 1989; Kodama et al., 1998; Liguori et al., 2000; Monti et al., 2002; Negoescu and Csiki, 1989; Noll et al., 1994; Okada et al., 1991; Penzel et al., 2003; Pressman and Fry, 1989; Somers et al., 1993; Takeuchi et al., 1994; Trinder et al., 2001; Villa et al., 2000). Therefore it would be highly desirable to develop an algorithm which will allow detecting and distinguishing light from deep sleep solely based on a sensor for sensing a peripheral pulse signal related to the systemic circulation of a subject. A PAT probe is particularly useful for the this purpose since the vascular tone and the pulse rate both are channels of the PAT probe in the WP100. This would allow for testing the hypothesis that autonomic nervous system output changes are sleep–stage dependent. As mentioned, other sensors for sensing peripheral pulse signals could be used to this end.

OBJECTS AND BRIEF SUMMARY OF THE PRESENT INVENTION

An object of the present invention is to provide a method, and also apparatus, for detecting and distinguishing epochs of deep–sleep from epochs of light–sleep which could be used for unattended ambulatory sleep monitoring of a subject outside of a sleep laboratory and not requiring the special equipment, such as an EEG sensor, usually available only in sleep laboratories.

According to a broad aspect of the present invention, there is provided a method of detecting and distinguishing epochs of deep sleep from epochs of light–sleep of a subject, comprising: (a) sensing from the subject, for the period of the epoch, a peripheral pulse signal related to the systemic circulation of the subject; (b) analyzing the sensed peripheral pulse signal for determining therefrom one or more variables that are derived from the following features where each feature can provide 2 variables – one is an amplitude variable and the other is a heart rate variable (altogether up to 14 variables) : (1) the mean amplitude and heart rate of the sensed peripheral pulse signal; (2) a scaling coefficient of a detrended fluctuation analysis (DFA) of the amplitude and heart–rate of the sensed peripheral pulse signal; (3) the peak of the low frequency spectral density (LF) of the amplitude and heart rate of the sensed peripheral pulse signal; (4) the peak of the very–low frequency spectral density (VLF) of the amplitude and heart rate of the sensed peripheral pulse signal,(5) the peak of the ultra–low frequency spectral density (ULF) of the amplitude and heart rate of the sensed peripheral pulse signal; (6) the peak of the high frequency spectral density (HF) of the amplitude and heart rate of the sensed peripheral pulse signal; and (7) the ratio of LF to HF (Spectral Ratio) of the amplitude and heart rate; and (c) utilizing the result of the foregoing analysis to determine whether the epoch detected is a light–sleep epoch or a deep–sleep epoch.

In the preferred embodiment of the invention described below, all the above variables determined by the analyzing operation are utilized to determine whether the epoch detected is a light–sleep or deep–sleep epoch. Also in that embodiment, the sensed peripheral pulse signals are sensed by a PAT sensor applied to a digit of the subject.

Further, in the described preferred embodiment, there are a plurality of the epochs each of a period of seconds within a sliding window of minutes. The peripheral pulse signal is sensed from the subject during each of two time periods. Each peripheral pulse signal is analyzed as set forth in operation (b) for each time period, and the results of such analyses are utilized to determine whether each epoch is a light–sleep epoch or a deep–sleep epoch.

According to a further aspect of the present invention, there is provided apparatus for detecting and distinguishing epochs of deep sleep from epochs of light–sleep of a subject, comprising: (a) a sensor for sensing from the subject, for the period of the epoch, a peripheral pulse signal related to the systemic circulation of the subject;

(b) a processor for analyzing the sensed peripheral pulse signal for determining therefrom one or more variables that are derived from the following features where each feature can provide 2 variables – one is an amplitude variable and the other is a heart rate variable (altogether up to 14 variables) : (1) the mean amplitude and heart rate of the sensed peripheral pulse signal or the (2) a scaling coefficient of a detrended fluctuation analysis (DFA) of the amplitude and heart–rate of the sensed peripheral pulse signal; (3) the peak of the low frequency spectral density (LF) of the amplitude and heart rate of the sensed peripheral pulse signal; (4) the peak of the very–low frequency spectral density (VLF) of the amplitude and heart rate of the sensed peripheral pulse signal,(5) the peak of the ultra–low frequency spectral density (ULF) of the amplitude and heart rate of the sensed peripheral pulse signal; (6) the peak of the high frequency spectral density (HF) of the amplitude and heart rate of the sensed peripheral pulse signal; and (7) the ratio of LF to HF (Spectral Ratio) of the amplitude and heart rate;

As indicated above, in the preferred embodiment described below, the sensor is a PAT sensor for application to a digit of the subject, and all the features determined by the analyzing operation are utilized to determine whether the epoch detected is a light–sleep epoch or a deep–sleep epoch.

The method and apparatus of the present invention, particularly when used with the method and apparatus described in the above–cited Patent Application Serial

No. 10/195,464, can be utilized for detecting all the sleep stages without the need of special sensors (e.g., EEG sensors) or other special equipment normally available in a sleep laboratory, and therefore can be used for unattended ambulatory sleep monitoring. This capability of the present invention has been favorably tested by a study comparing the results produced by the method and apparatus of the present invention with the results produced in a conventional sleep laboratory, as will be described more particularly below.

Further features and advantages of the invention will be apparent from the description below.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings, wherein:

Fig. 1 is a block diagram illustrating the main components of one form of apparatus constructed in accordance with the present invention;

Fig. 2 is a flowchart showing the manner in which data is processed to determine sleep stages according to the preferred embodiment of the invention described herein;

Fig. 3 illustrates histograms of separations for the variables that demonstrate the best separation (after NF);

Fig. 4 is a diagram illustrating the weighted sum distribution without NF;

Fig. 5 is a diagram illustrating the weighted sum distribution with NF;

Fig. 6 is a diagram illustrating agreement for mild (1), moderate (2), and severe (3) OSA training set;

Fig. 7 is a diagram illustrating the Bland Altman plot, of the percent deep sleep stage detection (PSG first algorithm) for the training set;

Fig. 8 is a diagram illustrating the agreement for mild (1), moderate (2), and severe (3) OSA validation sets; and

Fig. 9 is a Bland Altman plot of error in percent deep sleep stage detection (PSG versus algorithm developed herein) for the validation set.

It is to be understood that the foregoing drawings, and the description below, are provided primarily for purposes of facilitating understanding the conceptual aspects of the invention and possible embodiments thereof, including what is presently considered to be a preferred embodiment. In the interest of clarity and brevity, no attempt is made to provide more details than necessary to enable one skilled in the art, using routine skill and design, to understand and practice the described invention. It is to be further understood that the embodiment described is for purposes of example only, and that the invention is capable of being embodied in other forms and applications than described herein.

DESCRIPTION OF A PREFERRED EMBODIMENT OF THE INVENTION

Fig. 1 is a block diagram illustrating the main components of one form of apparatus constructed in accordance with the present invention; and Fig. 2 is a flowchart showing the manner in which data is obtained and processed to determine sleep stages according to the described embodiment of the invention.

Thus, as shown in Fig. 1, the apparatus includes a central processing unit, generally designated 10, having one input from a peripheral pulse measurement device 12 and another input from a sleep/wake detecting device or motion detecting devices 14. This information is processed by the central processing unit 10 to produce a data output 16 representing the sleep stage data for storage, and a display output 18 for displaying the sleep stage data.

Input device 12 is a sensor for sensing a peripheral pulse signal from the subject related to the systemic circulation of the subject. The peripheral pulse measuring device 12 may be any known device for detecting such signals, but preferably is a PAT probe applied to a digit (finger or toe) of the subject for measuring the peripheral arterial tone and the pulse rate of the subject. Many such PAT sensors are known in the art, for example as described in the above–cited U.S. Patent Applications 10/195,464, 10/471,580, and 10/520,273, incorporated herein by reference and assigned to the same assignee as the present application.

The sleep/wake detecting device 14 may be a conventional Actigraph probe applied to the wrist, or to any other part of the patient's body surface if some adaptation to the initial algorithm is made and if the same sensitivity to movement is kept. Alternatively, it may be a motion detecting device, such as an accelerometer–type sensor, applied to the subject for detecting body movements.

The central processing unit 10 processes the data inputted by input units 12 and 14 according to the algorithm described below, particularly with respect to the flowchart of Fig. 3, to produce a data output 16 of the sleep stage data for storage or other processing control, and also a display output 18 of the sleep stage data.

The flowchart illustrated in Fig. 3, describing the algorithm of the central processing unit 10, receives the peripheral pulse signal sensed from the subject related to the system circulation of the subject, analyzes the peripheral pulse signal sensed for determining therefrom a number of features as described below and as illustrated in Fig. 3, and utilizes the results of the analysis to determine the probability that a specific sleep epoch is a deep–sleep or a light–sleep epoch. All the variables and their conditional probabilities are computed within a five–minute sliding window, as shown at 20, advanced by 30 second epochs, as shown at 22.

As further shown in Fig. 3, a set of 14 normalized variables in both the frequency and time domains (7 in each domain) are derived from features of the PAT signal amplitude (AMP) time series and the heart–rate, i.e. inter–pulse (IPP), time series as indicated by block 24. All the variables are scaled to their mean value so that they could be interpreted as a conditional probability. From each of the time series, a set of seven similar types of variables are derived, making it total of 14 variables, as indicated by blocks 1–16 in Fig. 3. Each such set of seven variables includes: (1) scaling coefficients of detrended fluctuation analysis (DFA) as indicated by block 26; (2) the mean value (AMP in block 30)(heart rate in block 32); (3) the peak of the low frequency spectral density (LF) (block 34); (4) the peak of the very low frequency spectral density (VLF); (5) the peak of the ultra–low frequency spectral density (ULF) (block 36); (6) the peak of the high frequency spectral density (HF) (block 38); and (7) the ratio of LF to HF (Spec Ratio) (blocks 28, 40, 42).

The central processing unit 10 further utilizes the results of the foregoing analyses to determine whether each 30–second epoch within the 5–minute slotting window is probably a light–sleep epoch or a deep–sleep epoch.

As said before, each such type of variable is derived from each of the two time series. The frequency ranges, corresponding to the respiratory, baro–receptor, thermoregulation and hormonal ranges, are 0.4 — 0.15 Hz (HF), 0.15 — 0.04 Hz (LF), 0.04 — 0.015 Hz (VLF) and 0.015 — 0.005 Hz (ULF) (Burgess et al 2004).

To combine and weigh each of the features we performed a 2 step algorithm. The first step was to filter each of the features by defining a ± 5 minutes window around each epoch, allowing for smoothing around the epoch under consideration. This filter is defined as a Neighboring Filter (NF). The second step was done by choosing weightings that minimize the differences between the PSG staging and the

PAT derived staging. Each feature was examined for the degree to which it differentiates between light and deep sleep, prior and after the filtering.

The total probability equation can be written as follows:

$$Y_{est}(n) = \sum_{j-1}^{14} \sum_{k=10}^{10} W_{jk} * X_j(n+k) \qquad \text{Eq. (1)}$$

Where:

$Y_{est}(n)$ is the Probability of an epoch n to be a deep sleep epoch;

Xj(n) is the value of each one of the 14 variables at epoch n;

and W_{jk} is the 21 filter coefficient of each k variables

The weights are computed analytically to minimize the error in the identification process. The minimization criteria and weights computation method can be express by the following equation:

$$W_{jk} = Min(\sum_{n-1}^{N} Y_{est\_n} - Y_{actual\_n})^2 \qquad \text{Eq. (2)}$$

Where Y_{actual} is “1” if the n epoch is deep, and “0” otherwise.

The least squares error between the stage estimates Y_{est} and the PSG stages Y_{actual} (a vector of length N corresponding to the PSG sleep stage of each epoch),

Optimization was performed on a training set of 49 sleep studies. Rather than optimizing each estimator (W_{jk}) separately, the algorithm uses a single level of optimization wherein a linear classifier acts on an enlarged variable set composed of 20 epochs for every variable.

TESTING THE DESCRIBED EMBODIMENT

Subjects

For purposes of testing the described embodiment, a study was conducted in which the study group consisted of two separate sets: A training set, used to develop the algorithm, and a separate validation set, used to validate the algorithms. The raining set consisted of 49 adult patients (27 males) referred to the Technion Sleep Disorders Center for evaluation of presumed obstructive sleep apnea syndrome (OSAS), and an additional 6 young healthy volunteers (3 males) without any complaints of sleep disruption, daytime sleepiness, or snoring, recruited via advertisements in the Faculty of Medicine of the Technion, Haifa. The healthy volunteers were free of any disease and were on no medications. The exclusion criteria for the suspected OSAS patients were: permanent pacemaker, non–sinus cardiac arrhythmias, peripheral vasculopathy or neuropathy, severe lung disease, S/P Bilateral cervical or thoracic sympathectomy, finger deformity that precluded adequate sensor application, use of alpha–adrenergic receptor blockers (24 hours washout period required), alcohol or drug abuse during the last 3 years.

The validation set consisted of 44 adult OSAS patients (30 males), and 10 young healthy volunteers (8 males) recruited in the same manner as the training set and according to the same inclusion and exclusion criteria. The study was approved by the Rambam Medical Center committee for studies in human subjects, and patients signed an informed consent form prior to participation.

The training and validation groups did not differ statistically in RDI, age, BMI Desaturation index, mean SAO2 values, arousal index percent of Deep Sleep percent of REM sleep and total sleep time (see Table 1).

	Training Set (N=49)	**Validation Set (N=44)**	**P Value**
Mean RDI	26.9 ±19.09	34.0 ± 30.28	NS
Mean Age	44.7 ±13.58	43.5 ± 14.67	NS
Mean BMI	27.4 ±5.31	28.7 ± 6.23	NS
Mean arousal index	33. ± 22	26.6 ± 14.	NS
Mean deep %	21 ±9	20.9 ± 10	NS
Mean REM %	21 ±7	19.4 ± 6	NS
Total Sleep time [min.]	351 ± 49	357 ± 61	NS
mean SaO2	86 ±19	84 ± 21	NS
De–saturation index	22 ±23	21 ± 23	NS
Sleep efficiency	0.83 ±11	0.84 ± 15	NS

Protocol

All participants underwent a whole night polysomnography (PSG, Embla system, Flaga HF, Iceland) with simultaneous recordings of the Watch–PAT (WP) device (Itamar–Medical LTD, Caesarea, Israel). The PSG and the WP were synchronized using a continuous synchronization bi–level signal generated by the WP and recorded on both devices. The 2 sets of signals (the one from the PSG and the one from the WP) were then synchronized to compensate differences in internal clock of the 2 systems. The final error in synchronization time does not exceed 20 sec. By the end of the recording, the two data files (in PSG and in Watch–PAT) included the same synchronization signal and could thus be aligned exactly off line for head to head comparisons.

Prior to the study, patients completed a sleep questionnaire including physical data (e.g. weight and height), general health condition and medical history, medication usage, and sleep habits. Lights off were no later than midnight, and lights on at 06:00 AM. The mean start time of the test was 11 PM± 30min and the end of the test was 6:00± 45min and the mean duration was 7.99 ± 42 min

The WP was attached to the forearm of the dominant hand of the patient. The PAT probe was mounted on the index finger and the oximetry probe on the adjacent finger. Recording started with lights off and continued in a synchronized mode till lights on. The data quality of both the WP and the PSG were quite good and the signals recorded were valid for about 90% of the study.

The PSG files were scored for Apnea–Hypopnea index using Chicago criteria. Data was blindly double scored for stages to assess inter–scorer variability. The kappa coefficient for the stages double scoring was 0.83 –which is considered "Almost perfect agreement" according to Landis and Koch (1977).

<u>In–Laboratory WP recording</u>

The WP device has been previously described, (Bar et al., 2003; Hedner et al., 2004; Margel et al., 2003; Penzel et al., 2004; Penzel et al., 2004; Pillar et al., 2003). Briefly, it consists of a battery–powered, wrist–mounted recording device and software for post–acquisition viewing and analysis of the recorded PAT data, which are derived from a specialized finger probe which records the arterial pulse. It records 4 signals: PAT signal (arterial pulse wave amplitude), pulse rate derived from the PAT signal, oxyhemoglobin saturation, and wrist activity (derived from an accelerometer). The WP device contains a rechargeable power supply, preliminary signal conditioning hardware, 100 Hz data acquisition, and data storage on a removable compact flash disk.

<u>In–Laboratory Polysomnography</u>

All subjects underwent a standard in–laboratory overnight PSG. Recorded signals included: EEG (C4–A1, C3–A2, O2–A1 and O1–A2), EOG, sub–mental and bilateral tibial EMG, ECG, airflow (nasal pressure and thermistor), chest and abdominal motion (piezo bands), oxyhemoglobin saturation, positive airway pressure, and body position. All physiological data were collected and stored on the digital polysomnography system (Embla, Flaga, Reykjavik, Iceland). PSG recordings were scored manually, with the scorer being blinded to the PAT signals. Sleep was blindly staged on the PSG according to standard R&K criteria and applying the updated AASM Visual Scoring Task Force criterion to combine the stages 3 and 4 into one deep sleep stage (Rechtschaffen and Kales, 1968; Silber et al., 2007).

PAT Algorithms Description

The WP system is already equipped with a set of algorithms, well described in the literature, detecting Sleep, Wake, and REM states using actigraphy and PAT signal, with an epoch by epoch high resolution performance (Hedner et al., 2004, Herscovici et all 2007). The newly developed algorithm described in the current study is intended to further separate the non–REM epochs, and classify them into deep or light–sleep epochs. The actigraph is used to differentiate between sleep and wake periods only and not used for differentiation within the sleep periods between REM, deep and light–sleep stages and neither is the oximeter.

A set of 14 normalized variables in both the frequency and time domains were derived from the PAT signal amplitude (AMP) time series and the Heart Rate, i.e. inter–pulse period (IPP) time series (seven from each time series), and utilized to determine whether a particular epoch detected was probably a light–sleep epoch or a deep–sleep epoch in the manner described above with respect to Equations (1) and (2). All the variables and their conditional probabilities were computed within a 5 minute sliding window advanced by 30 seconds epochs.

Analysis method

The algorithm accuracy was assessed by applying the weighted coefficient computed from the training set to the validation set.

The PAT studies were analyzed using the Actigraph algorithm to separate the sleep and wake periods using previously described algorithms (Hedner et al, 2004) . The REM periods were detected using the previously described REM algorithm (Herscovici et al., 2007). The Non–REM periods were then separated into deep and light–sleep periods using the newly developed algorithm. The oximetry measurement is not used to differentiate between deep and light neither the actigraph. The comparison was done based on a 30sec epoch by epoch comparison. Comparisons of performance in different OSA severity groups were made to show that the algorithm is not impaired by OSA severity effects on the PAT signal. The Algorithm performance was evaluated for each RDI group stratified by mild (0–20), moderate (20–40), and severe (more than 40).

The total sensitivity specificity and agreement were measured using the whole 27,597 (20,555 Light–sleep and 7,042 Deep sleep) from the PSG epochs for training and 24,383(18,320 Light–sleep and 6063 Deep Sleep) epochs for validation. Mean values of sensitivity specificity and agreement based on per subject value were also computed as well as Kappa Cohen agreement

RESULTS

Training Data Set

Fig. 2 shows the normalized histogram of the 8 major contributive variables with the relative separation of each.

In Fig. 2, the histograms of separations for the variables demonstrate the best separations (after NF). The best separation is given in the upper left panel and decreases clockwise. The dark shaded region represents complete separation of deep sleep. The lighter shaded region represents complete separation of light–sleep and the un–shaded area in between represents un–separation (overlap of the two). The value on top of the graph represents the un–separated area relative to deep sleep complete separation area (a lower ratio means better separation).

	Group 1 RDI<20	Group2 20<RDI<40	Group 3 RDI>40
Sensitivity[%]	61±26	55±23	72±32
Specificity[%]	89±10	87±13	87±6
Agreement[%]	82±7	78±13	85±6

Table 2 - sensitivity specificity and agreement mean values by subject for the three groups

Fig. 4 shows the combined histogram of all the variables (14 variables) for the combined data of all the patients for deep and light–sleep, and illustrates the separation without filtration, and Fig. 5 shows the separation including the NF. The filtered data improves the separation between stages by 2% in sensitivity and 8% in specificity. Without filters the sensitivity/specificity is 72% and 77 % respectively (threshold –0.325). By adding the filter, the sensitivity and specificity increase to 74 % and 85% when choosing the threshold at the intersection point (threshold –.2).

The last step is to choose a threshold for the clinical application. The threshold was chosen in order to bring up the total specificity on an ROC curve to approximately 90%. (Threshold 0.1) The one chosen yields in the training set sensitivity, specificity and agreement values of 66%, 89 % and 82% respectively for the whole training set. The per subject mean values of the sensitivity specificity and agreement were (63%± 89% ± 0.83±) respectively for the whole training set the Kappa Cohen coefficient was 0.52 (moderate agreement). mean value of Kappa averaging patients in each group is (0.52± 0.17, 0.56±0.20 and 0.55± 0.28) for light, moderate and severe RDI groups respectively.

Fig. 6 shows the total agreement of all the training set stratified to RDI categories. It can be seen that there is no substantial difference between the severe, mild and moderate OSA patient groups. The Bland Altman plot shown in Fig. 7 shows no offset and no systemic error in the results.

Validation Data Set

In order to asses the accuracy of the algorithm it was tested on a separate validation set of 44 studies, reflecting a broad range of sleep apnea severity. The whole validation set shows 65%, 87 % and 80% sensitivity specificity and agreement values respectively. The mean value of sensitivity specificity and agreement of all the patients is 56% 87% and 81 respectively. The total sensitivity, specificity, and agreement values for the training set were very similar at 66%, 89% and 82% respectively. The correlation of percent of deep sleep over the night with the PSG was $R=0.51$ ($P<0.05$) for the whole validation set. The per subject mean values of the sensitivity specificity and agreement were (56%± 87% ± 0.81±) respectively for the whole validation set the Kappa Cohen coefficient was 0.57 (moderate agreement). Mean value of Kappa averaging patients in each group is (0.46± 0.19, 0.42±0.1 and 0.54± 0.3) for light, moderate and severe RDI groups respectively.

Fig. 8 shows the total agreement of all the training set stratified to RDI categories. It can be seen that there is no substantial difference between the severe, mild and moderate OSA patient groups

Fig. 9 shows the Bland Altman plot of the percent deep sleep for the validation set. There is no systemic error in percent deep sleep.

The above evaluations show that the described algorithm which is based on the PAT signal, or other known peripheral pulse signal, is capable of detecting light and deep sleep stages. Used together with previously known algorithms to detect sleep/wake, non–REM and REM sleep, e.g., as described in their prior patents cited above, it is believed that the present inventive method and apparatus, enable a comprehensive sleep stage assessment to be provided without the special equipment, such as EEG sensors, normally available only in sleep laboratories.

While the invention has been described with respect to one preferred embodiment, it will be appreciated that this is set forth merely for purposes of example, and that many variations, modifications and other applications of the invention may be made.

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What is claimed is:

1. A method of detecting and distinguishing epochs of deep–sleep from epochs of light–sleep of a subject, comprising:

(a) sensing from the subject, for the period of the epoch, a peripheral pulse signal at a body site of the subject related to the systemic circulation of the subject;

(b) analyzing the sensed peripheral pulse signal for determining therefrom one or more of the following variables:

(1) the mean amplitude and heart rate of the sensed peripheral pulse signal;

(2) a scaling coefficient of a detrended fluctuation analysis (DFA) of the amplitude and heart–rate of the sensed peripheral pulse signal;

(3) the peak of the low frequency spectral density (LF) of the amplitude and heart rate of the sensed peripheral pulse signal;

(4) the peak of the very–low frequency spectral density (VLF);

(5) the peak of the ultra–low frequency spectral density (ULF) of the sensed peripheral pulse signal;

(6) the peak of the high frequency spectral density (HF) of the sensed peripheral pulse signal; and

(7) the ratio of LF to HF (Spectral Ratio);

(c) and utilizing the result of the foregoing analysis to determine whether the epoch detected is a light–sleep epoch or a deep–sleep epoch.

2. The method according to Claim 1, wherein all said variables determined by the analyzing operation are utilized to determine whether the epoch detected is a light–sleep epoch or a deep–sleep epoch.

3. The method according to Claim 2, wherein said sensed peripheral pulse signal is sensed by a peripheral arterial tone (PAT) sensor applied to a digit of the subject.

4. The method according to Claim 1, wherein another sensor for sensing whether the subject is asleep is applied to the subject.

5. The method according to Claim 1, wherein there are a plurality of said epochs each of a period of seconds within a sliding window of minutes.

6. The method according to Claim 1, wherein there are a plurality of said epochs each of a period of about 30 seconds within a sliding window of about five minutes.

7. The method according to Claim 2, wherein said peripheral pulse signal is sensed from the subject during each of two time periods; and wherein each peripheral pulse signal is analyzed as set forth in operation (b) for each time period, and the results of such analyses are utilized to determine whether each epoch is a light–sleep epoch or a deep–sleep epoch.

8. The method according to Claim 7, wherein the results of such analyses are utilized to determine whether each detected epoch is a light–sleep epoch or a deep–sleep epoch according to the following equation:

$$Y_{est}(n) = \sum_{j-1}^{14} \sum_{k=10}^{10} W_{jk} * X_j(n+k)$$

where:

$Y_{est}(n)$ is the Probability of an epoch n to be a deep sleep epoch;

Xj(n) is the value of each one of the 14 variables at epoch n; and

W_{jk} is the 21 filter coefficient of each k features

9. The method according to Claim 1 wherein said detecting and distinguishing epochs of deep–sleep from epochs of light–sleep of a subject are used, together with known algorithms to detect sleep/wake, non–REM and REM sleep stages, to provide a comprehensive sleep stage assessment.

10. Apparatus for detecting and distinguishing epochs of deep–sleep from epochs of light–sleep of a subject, comprising:

(a) a sensor for sensing from the subject, for the period of the epoch, a peripheral pulse signal related to the systemic circulation of the subject;

(b) a processor for analyzing the sensed peripheral pulse signal for determining therefrom one or more of the following variables:

(1) the mean amplitude and heart rate of the sensed peripheral pulse signal;

(2) a scaling coefficient of a detrended fluctuation analysis (DFA) of the amplitude and heart–rate of the sensed peripheral pulse signal;

(3) the peak of the low frequency spectral density (LF) of the amplitude and heart rate of the sensed peripheral pulse signal;

(4) the peak of the very–low frequency spectral density (VLF);

(6) the peak of the ultra–low frequency spectral density (ULF) of the amplitude and heart rate of the sensed peripheral pulse signal;

(7) the peak of the high frequency spectral density (HF) of the amplitude and heart rate of the sensed peripheral pulse signal; and

(8) the ratio of LF to HF (Spectral Ratio) of the amplitude and heart rate;

(c) said processor also utilizing the result of the foregoing analysis to determine whether the epoch detected is a light–sleep epoch or a deep–sleep epoch.

11. The apparatus according to Claim 10, wherein said sensor is a peripheral arterial tone (PAT) sensor for application to a digit of the subject.

12. The apparatus according to Claim 10, wherein said processor utilizes all said variables determined by the analyzing operation to determine whether the epoch detected is a light–sleep epoch or a deep–sleep epoch.

13. The apparatus according to Claim 10, wherein said apparatus further includes another sensor for application to the subject for sensing whether the subject is asleep.

14. The apparatus according to Claim 10, wherein said processor: analyzes the sensed peripheral pulse signals during a plurality of said epochs, each of a period of seconds, within a sliding window of minutes; performs said analysis on each of the sensed peripheral pulse signals; and utilizes the results of such analyses to determine whether the epoch detected is a light–sleep epoch or a deep–sleep epoch.

15. The apparatus according to Claim 10, wherein said sensor senses the peripheral pulse signal in a plurality of said epochs, each of a period of about 30 seconds, within a sliding window of about five minutes.

16. The apparatus according to Claim 10, wherein said sensor senses the peripheral pulse signal during each of two time periods; and wherein said processor analyses each peripheral pulse signal for each time period, and utilizes the results of such analyses to determine whether each epoch is a light–sleep epoch or a deep–sleep epoch.

17. The apparatus according to Claim 15, wherein said processor determines whether the peripheral pulse signals analyzed indicate a light–sleep epoch or a deep–sleep epoch according to the following equation:

$$Y_{est}(n) = \sum_{j-1}^{14} \sum_{k=10}^{10} W_{jk} * X_j(n+k)$$

where:

$Y_{est}(n)$ is the Probability of an epoch n to be a deep sleep epoch;

Xj(n) is the value of each one of the 14 variables at epoch n; and

W_{jk} is the 21 filter coefficient of each k variables.

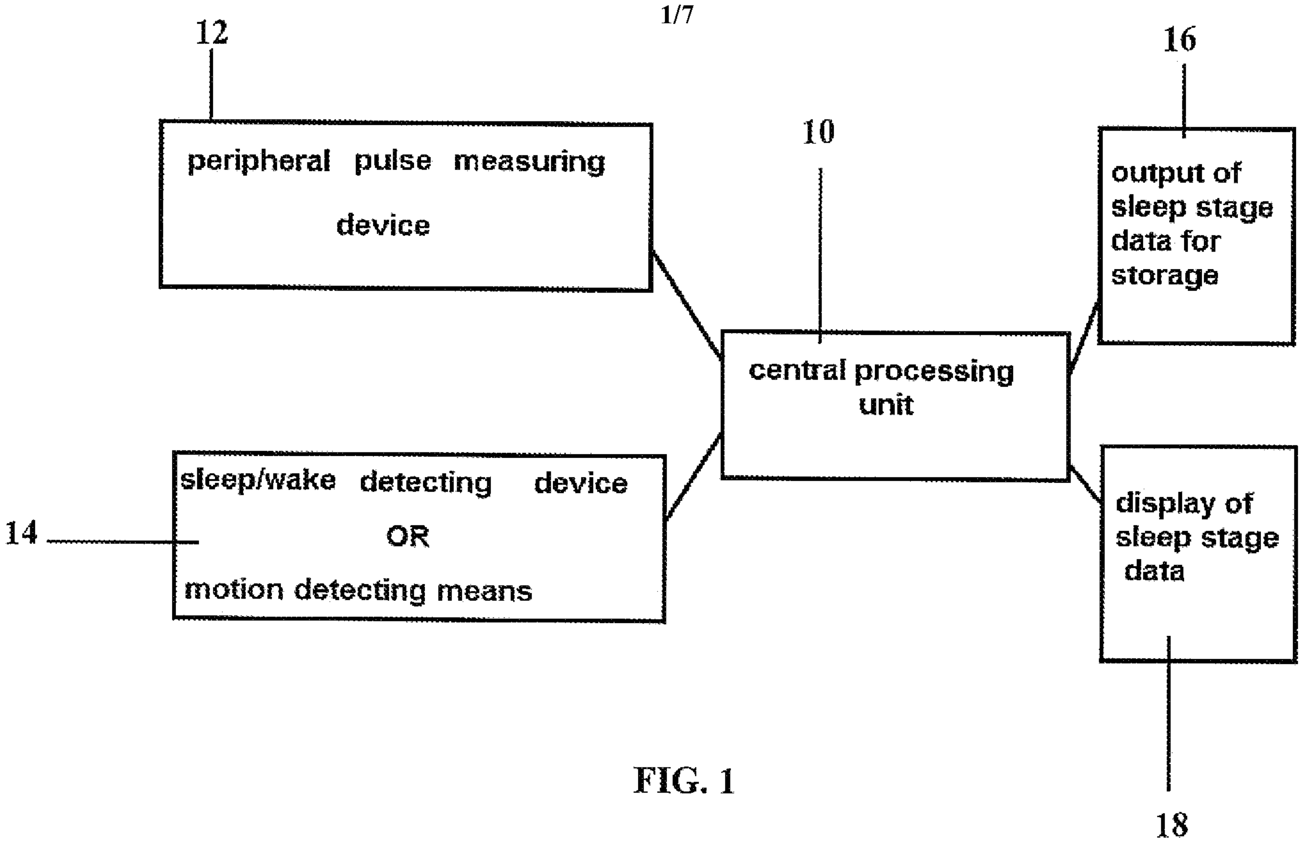

12
peripheral pulse measuring device
10
central processing unit
16
output of sleep stage data for storage
14
sleep/wake detecting device
OR
motion detecting means
display of sleep stage data
18

FIG. 1

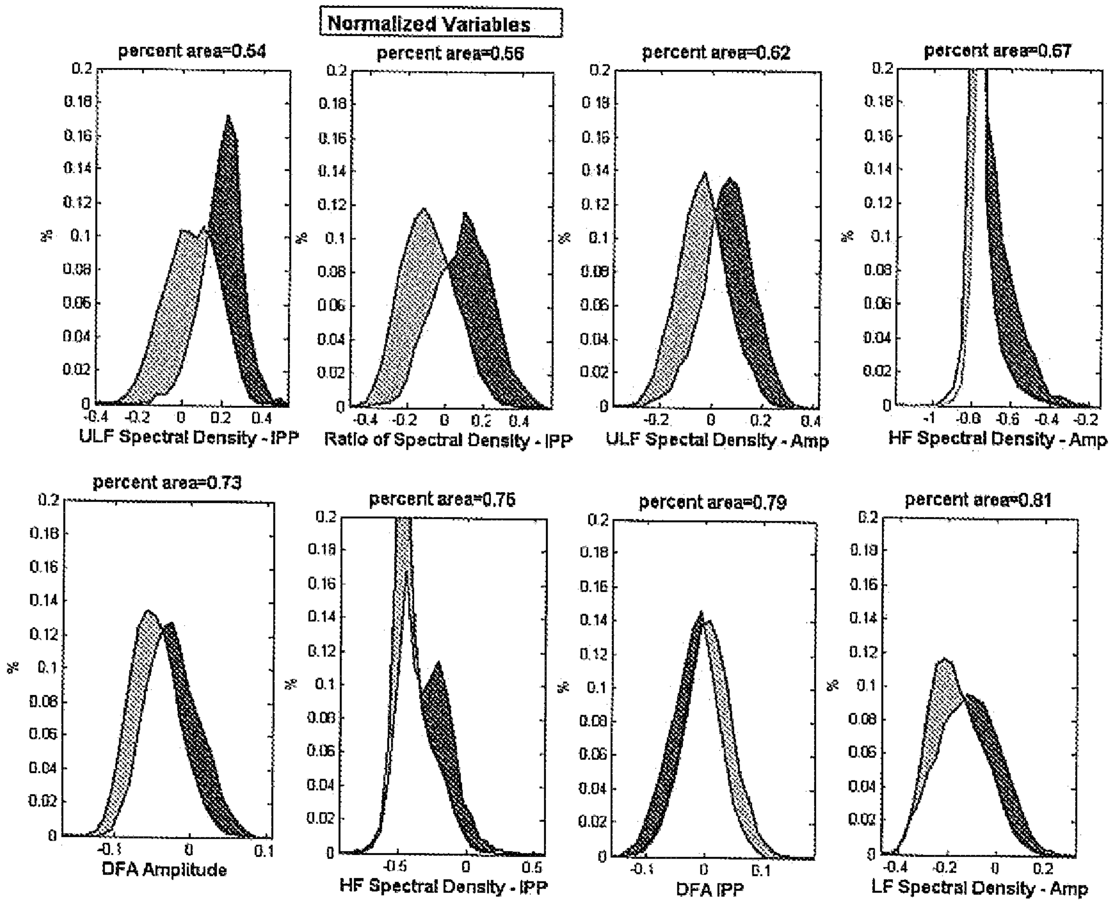

Normalized Variables
percent area=0.54
ULF Spectral Density - IPP
percent area=0.56
Ratio of Spectral Density - IPP
percent area=0.62
ULF Spectal Density - Amp
percent area=0.67
HF Spectral Density - Amp
percent area=0.73
DFA Amplitude
percent area=0.76
HF Spectral Density - IPP
percent area=0.79
DFA IPP
percent area=0.81
LF Spectral Density - Amp

FIG. 2

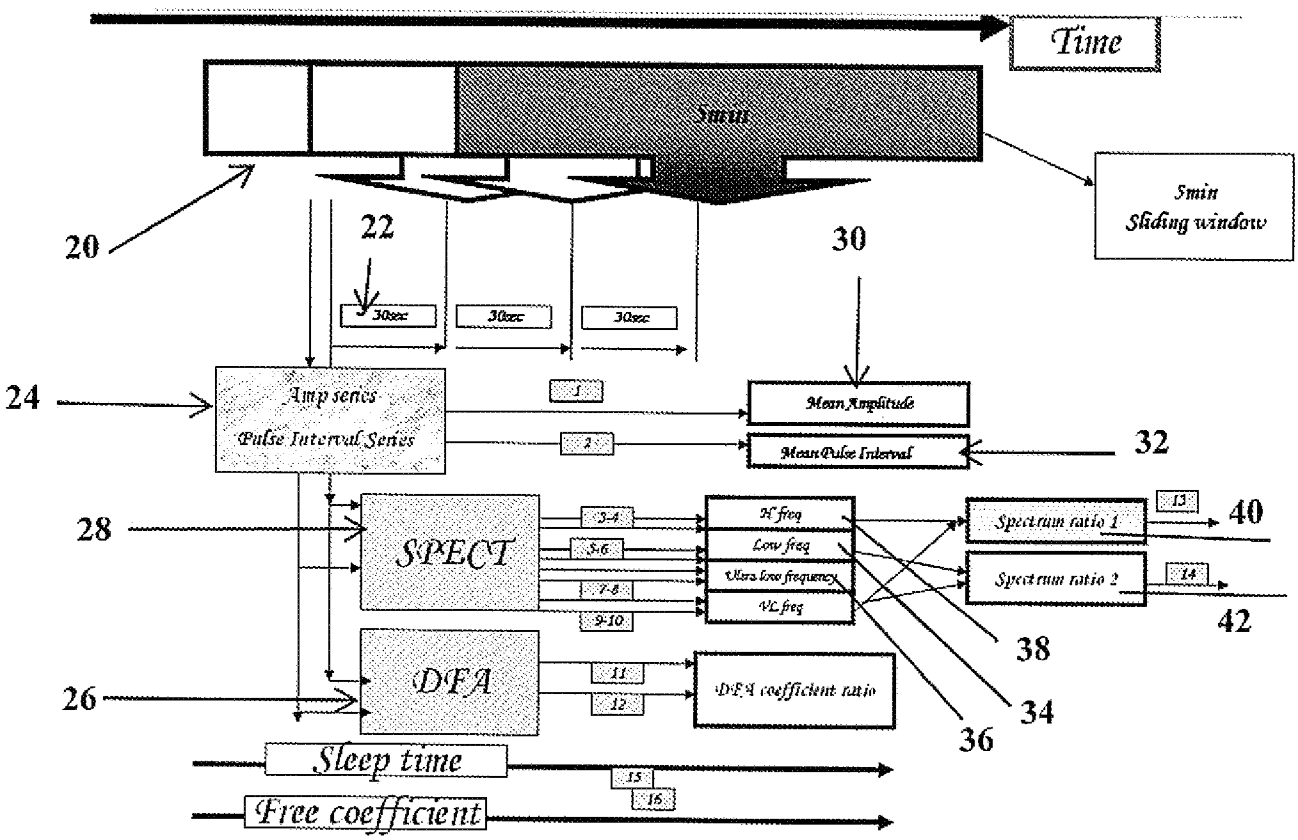

Time
5min
5min
Sliding window
20
22
30
30sec
30sec
30sec
24
Amp series
Pulse Interval Series
1
2
Mean Amplitude
Mean Pulse Interval
32
28
SPECT
3-4
5-6
7-8
9-10
H freq
Low freq
Ultra low frequency
VL freq
Spectrum ratio 1
Spectrum ratio 2
13
14
40
42
38
34
36
26
DFA
11
12
DFA coefficient ratio
Sleep time
Free coefficient
15
16

FIG. 3

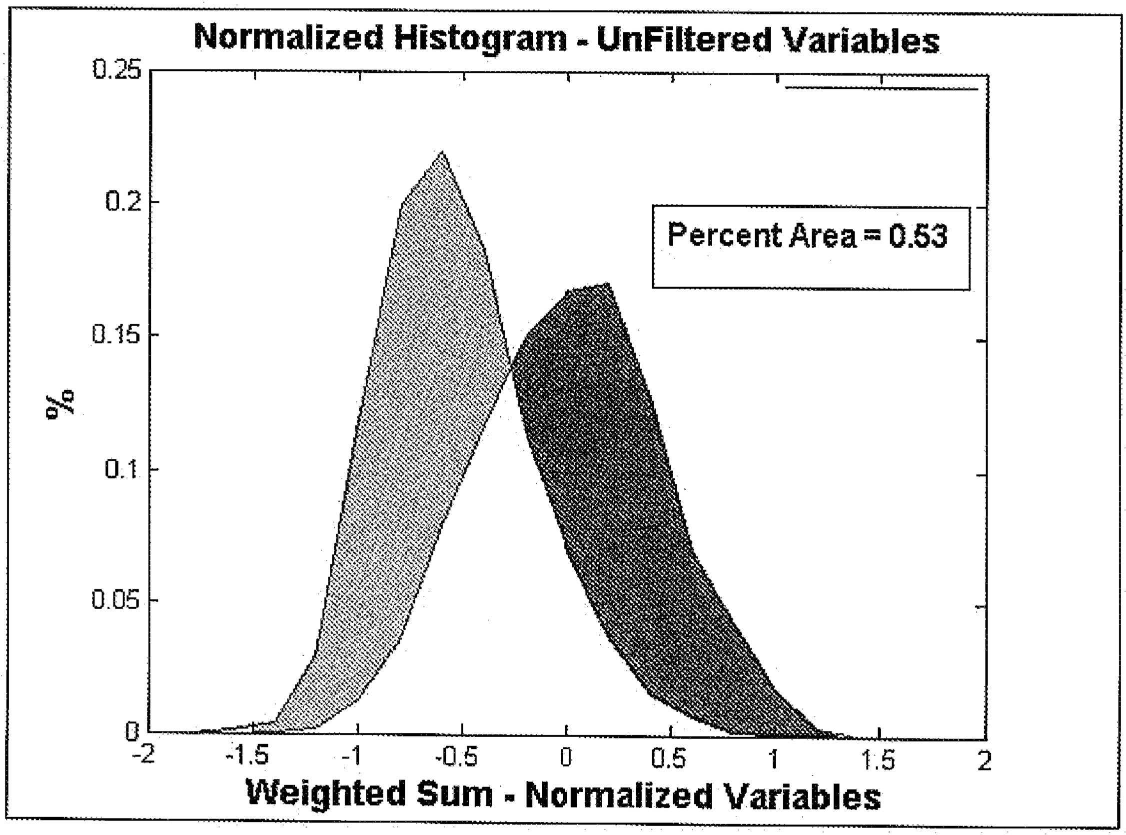

Normalized Histogram - UnFiltered Variables
0.25
0.2
0.15
0.1
0.05
0
%
Percent Area = 0.53
-2
-1.5
-1
-0.5
0
0.5
1
1.5
2
Weighted Sum - Normalized Variables

FIG. 4

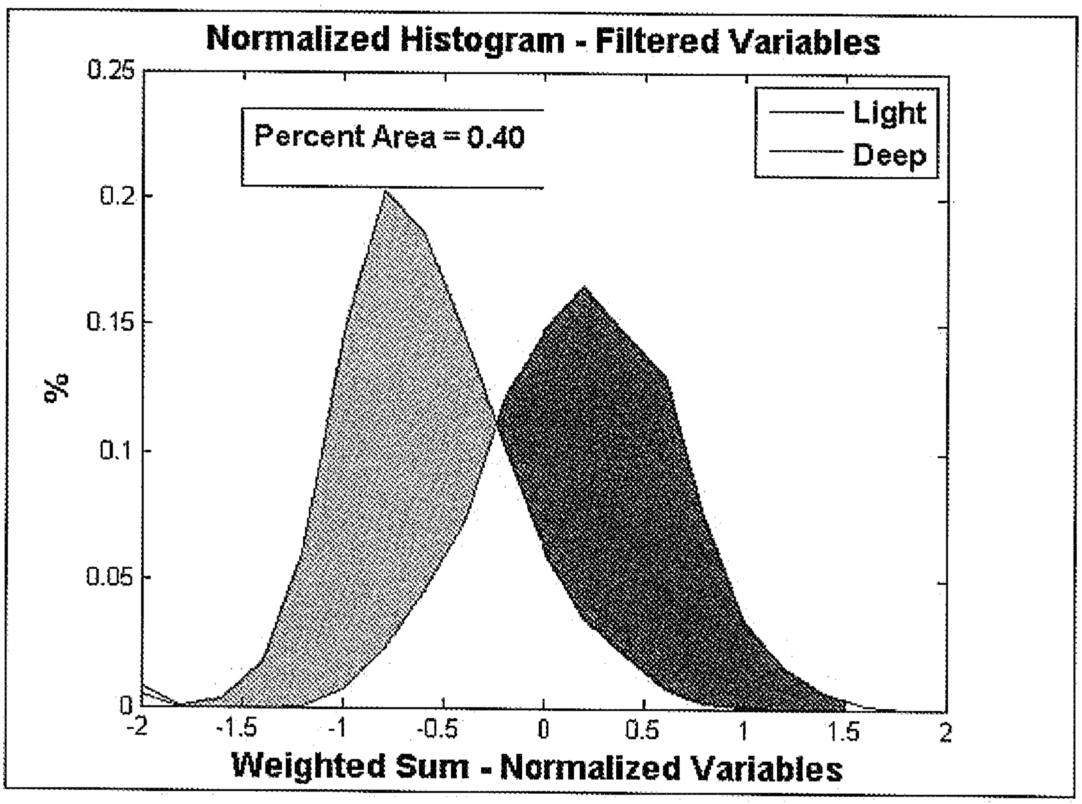

Normalized Histogram - Filtered Variables
Percent Area = 0.40
Light
Deep
%
0.25
0.2
0.15
0.1
0.05
0
-2
-1.5
-1
-0.5
0
0.5
1
1.5
2
Weighted Sum - Normalized Variables

FIG. 5

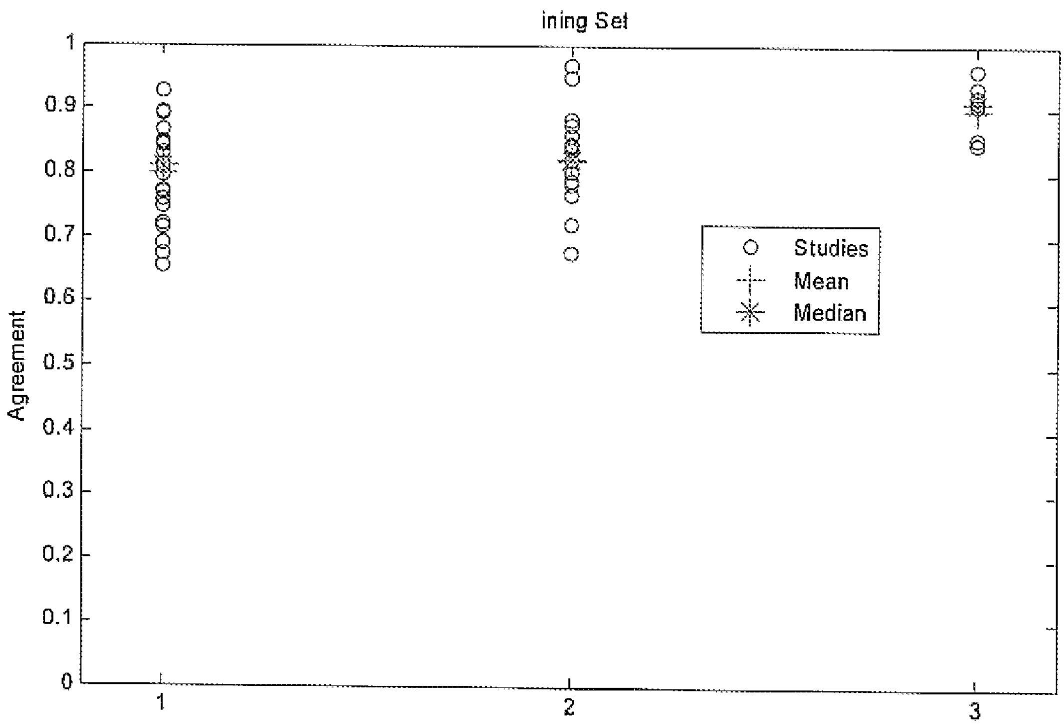
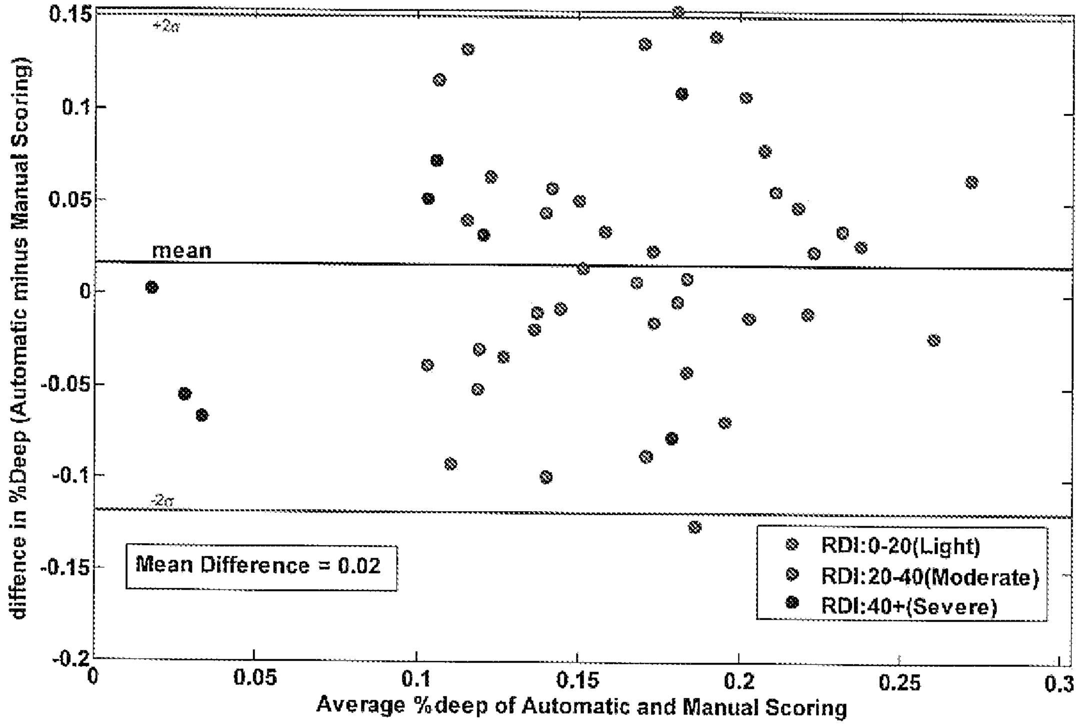

ining Set
Studies
Mean
Median
Agreement
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1
2
3
RDI groups: 0-20, 20-40,40+

FIG. 6



0.15
0.1
0.05
0
-0.05
-0.1
-0.15
-0.2
+2σ
mean
-2σ
Mean Difference = 0.02
RDI:0-20(Light)
RDI:20-40(Moderate)
RDI:40+(Severe)
diffence in %Deep (Automatic minus Manual Scoring)
0
0.05
0.1
0.15
0.2
0.25
0.3
Average %deep of Automatic and Manual Scoring

FIG. 7

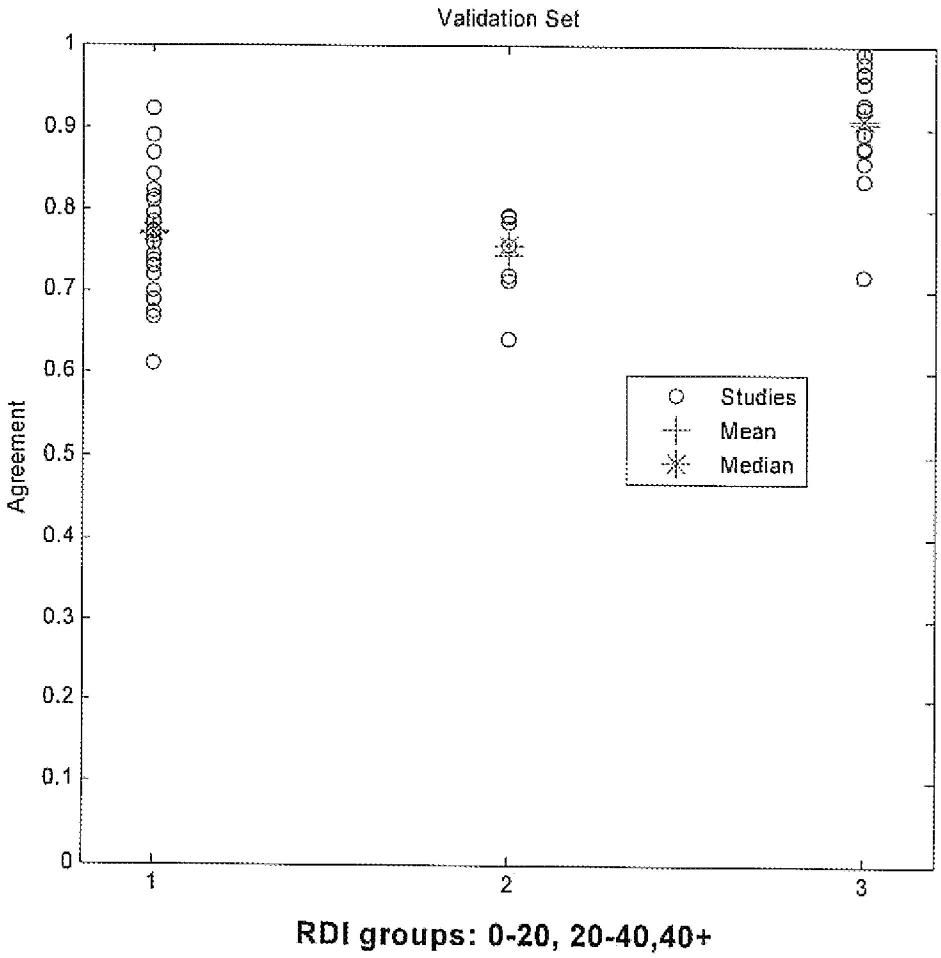

Validation Set
Agreement
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1
2
3
Studies
Mean
Median
RDI groups: 0-20, 20-40,40+

FIG. 8

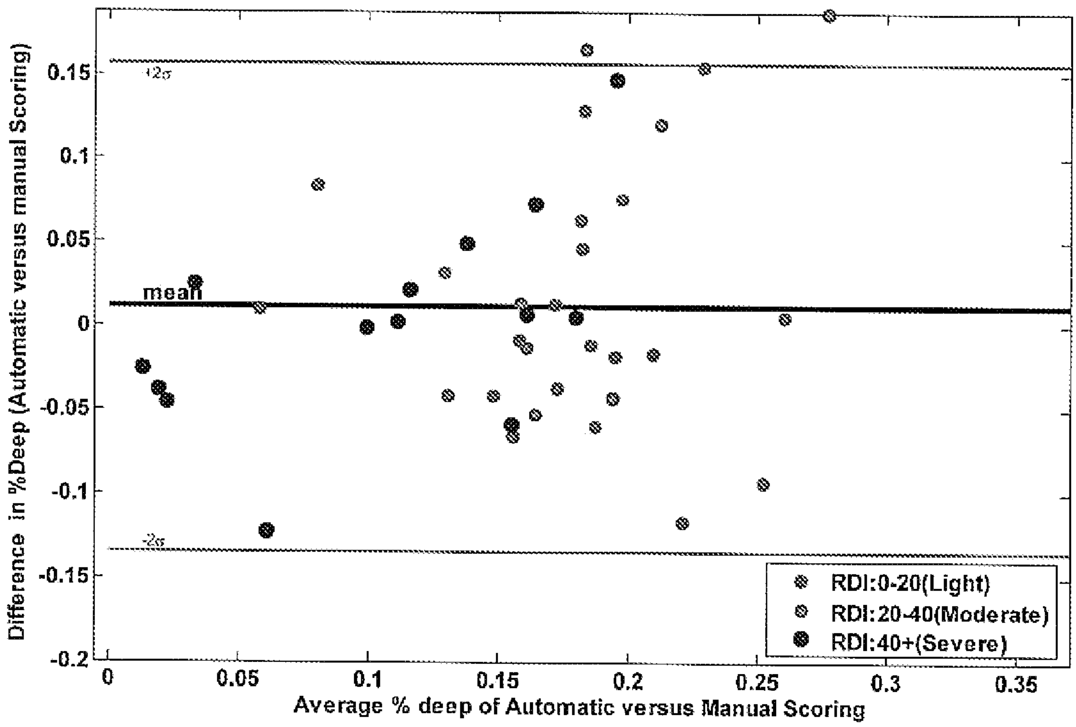

0.15
0.1
0.05
0
-0.05
-0.1
-0.15
-0.2
+2σ
mean
-2σ
Difference in %Deep (Automatic versus manual Scoring)
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
Average % deep of Automatic versus Manual Scoring
RDI:0-20(Light)
RDI:20-40(Moderate)
RDI:40+(Severe)

FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 09/51535

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61B 5/02 (2009.01)
USPC - 600/301, 322, 384, 595
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61B 5/02 (2009.01)
USPC: 600/301, 322, 384, 595

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
600/300, 311, 323-324
A61B 5/103 (2009.01

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic Databases Searched: PubWEST; Google; Google Scholar;
Search Terms Used: light, deep, sleep, analyze, analysis, peripheral, tone, pulse, arterial, equation, algorithm, LF, HF, VLF, ULF

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2003/0004423 A1 (Lavie et al) 02 January 2003 (02.01.2003); Fig. 1; para[0014], [0042], [0091], [0113], [0116]	1-17
Y	"Signal Processing Methods for Heart Rate Variability Analysis" (Clifford) 2002 (2002), Department of Engineering Science, University of Oxford; Entire document, especially, pg. 25, 37, 138, 151, 192-200	1-17

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 September 2009 (18.09.2009)	30 SEP 2009

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

patsnap

专利名称(译)	用于确定轻度睡眠和深度睡眠阶段的非侵入性方法和设备

公开(公告)号	EP2276398A1	公开(公告)日	2011-01-26
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申请(专利权)人(译)	伊塔马尔MEDICAL LTD.
当前申请(专利权)人(译)	伊塔马尔MEDICAL LTD.
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发明人	HERSCOVICI-COHEN, SARAH SHEFFY, JACOB
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优先权	61/071127 2008-04-14 US
其他公开文献	EP2276398B1 EP2276398A4
外部链接	Espacenet

摘要(译)

一种用于通过感测与受试者的全身循环相关的外周脉冲信号来检测和区分深度睡眠的时期与受试者的轻度睡眠的时期的方法和装置，优选地用于感测脉动的外围动脉张力（PAT）传感器。动脉体积以反映交感神经张力变化的受试者的手指（例如手指）变化;分析所感测的脉冲信号以由此确定多个特征，特别是在两个时间段的每一个中的七个特定变量;并利用分析结果确定检测到的时期是轻度睡眠时期还是深度睡眠时期。