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(54) Title: CONCURRENT ELECTROPHYSIOLOGIC AND CEREBRAL BLOOD FLOW NEUROIMAGING

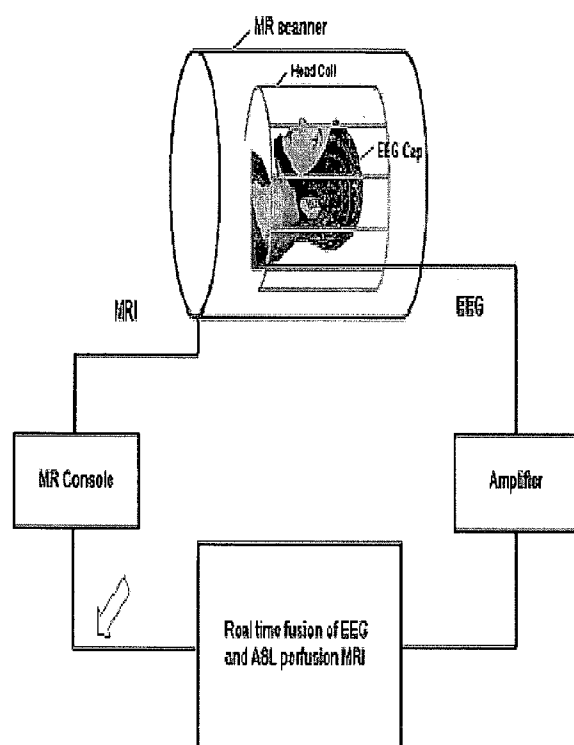


FIGURE 2

(57) Abstract: This invention relates to methods for concurrently recording electrophysiologic signal (EEG) and cerebral blood flow (CBF) signal from human brain. Specifically, the invention relates to methods for noninvasively assessing brain function.



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CONCURRENT ELECTROPHYSIOLOGIC AND CEREBRAL BLOOD FLOW
NEUROIMAGING

FIELD OF INVENTION

[0001] This invention is directed to methods for concurrently recording electrophysiologic signal (EEG) and cerebral blood flow (CBF) signal from human brain. Specifically, the invention relates to methods for noninvasively assessing brain function during a subject's sleep and its utility.

BACKGROUND OF THE INVENTION

[0002] Dynamic neuroimaging of brain function during sleep bears considerable importance in both neuroscientific and clinical fields. For instance, slow wave sleep, characterized by high voltage Delta waves (<4Hz) in EEG, has been demonstrated to be critical for memory consolidation, brain plasticity, learning and recovery of synaptic potential. Brain function can be enhanced during slow wave sleep by applying transcranial electric currents and by sleep medications. Rapid-eye-movement (REM) sleep is commonly known to be associated with dream. To date, however, there has been a large knowledge gap regarding the dynamic changes of brain function across the sleep-wake cycle. Nuclear medicine methods, such as PET, have been the primary approach for mapping brain function during sleep. Once EEG markers of a sleep stage of interest is spotted by researcher, radioisotope (e.g., ^{18}F FDG) is injected into sleeping subjects and radioactivity is measured after a period allowing the tracer to be deposited into the brain (30min for ^{18}F FDG). Such approach is undesirable because of repeated exposure to radioactivity. The fixed acquisition time window (10-30mins) requires subjects' behavioral state remains relatively stable during the whole time period, which is not always satisfied.

[0003] The combination of EEG and functional magnetic resonance imaging (fMRI) offers the potential for multi-model neuroimaging with both high spatial and temporal resolution, which opens the window to a wide range of applications. For instance, simultaneous EEG and (blood-oxygen-level-dependent) BOLD fMRI have been successfully applied for seizure localization in epilepsy patients. However, concurrent EEG/BOLD fMRI cannot be directly applied for sleep research since BOLD fMRI is only able to image transient brain responses elicited by external stimuli and tasks. In addition, removal of the large artifact in EEG signal caused by rapid magnetic gradient switching in BOLD fMRI is challenging, especially performed in real time. Event-related potential (ERP) often has to be extracted from EEG for correlation with BOLD fMRI, whose

magnitude is on the order of one tenth of the original EEG signal, adding further difficulty for signal processing.

[0004] Arterial spin labeling (ASL) perfusion MRI is a noninvasive neuroimaging technique that offers absolute quantification of CBF both at rest and during task activation. ASL is ideally suited for imaging sustained behavioral states due to its long term temporal stability. Concurrent recording of EEG and ASL perfusion fMRI provides several potential advantages. First, resting perfusion can be easily linked to EEG power spectrum during specific behavioral states without the need to perform task activation. Second, ASL scans include inherent magnetic gradient quiet periods (e.g., delay time) with reduced interferences for EEG recording, facilitating real-time noise removal. Third, EEG/ASL studies are less demanding in terms of signal processing, since ERP is generally not required. Finally, EEG/ASL data can be continuously recorded across various stages of the sleep-wake cycle with a temporal resolution of seconds in one scanning session. The acoustic noise level is also much lower in ASL than BOLD fMRI, which is a benefit for sleep neuroimaging.

[0005] Neuroimaging of sleep is well suited for concurrent EEG/ASL. Once reliable neuroimaging markers for various sleep stages are identified, the technique can be used for monitoring effects of pharmacological and behavioral manipulations on sleep. Ideally, because EEG and ASL perfusion MRI each provides unique markers for certain neurobiological processes, the fusion of the two technologies is expected to create more reliable neuroimaging markers than each technique alone. EEG/ASL is also expected to have wide applications outside sleep research, including assessing mental state/stress during continuous performance tasks, monitoring neurophysiological effects of drug candidates, and seizure localization etc.

SUMMARY OF THE INVENTION

[0006] In one embodiment, the invention provides a method of neuroimaging brain function of a subject during sleep, comprising the steps of: Concurrently recording electrophysiologic brain signals and cerebral blood flow (CBF) data of the sleeping subject; Reconstructing the cerebral blood flow (CBF) data within time window of interest based on a marker of electrophysiologic brain signals; and Dynamically associating the electrophysiologic brain signals and reconstructed cerebral blood flow (CBF) data, thereby neuroimaging brain function of the subject during sleep.

[0007] In another embodiment, provided herein is a method of diagnosing or providing prognosis of sleep disorders or both in a subject, comprising concurrently neuroimaging brain function of the

subject during sleep using concurrent recording electrophysiologic brain signals and cerebral blood flow (CBF) data; comparing the data with a standard, whereby the standard is taken from a subject or pool of subject previously, correctly diagnosed as having the sleep disorder sought to be diagnosed or for which prognosis is given; and comparing the signals.

[0008] In one embodiment, the invention provides a method of screening an agent for effectiveness as a sleeping aid in a subject, comprising concurrently neuroimaging brain function of the subject during sleep using concurrent recording electrophysiologic brain signals and cerebral blood flow (CBF) data; comparing the data with a standard, whereby the standard is taken from a subject or pool of subject previously exposed to an effective, or ineffective sleeping medication; and comparing the signals.

[0009] In another embodiment, the invention provides a method of screening effects of stress on sleep in a subject, comprising concurrently neuroimaging brain function of the subject during sleep using concurrent recording electrophysiologic brain signals and cerebral blood flow (CBF) data; comparing the data with a standard, whereby the standard is taken from the subject before or after being exposed to the stress whose effect is sought to be screened.

[00010] Other features and advantages of the present invention will become apparent from the following detailed description examples and figures. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[00011] The invention will be better understood from a reading of the following detailed description taken in conjunction with the drawings in which like reference designators are used to designate like elements, and in which:

[00012] **Figure 1** shows concurrent EEG/ASL feasibility study results showing increased CBF in visual cortex during eyes open (EO) vs. eyes closed (EC) states. Increased EEG α power is observed in O1/O2 between EO and EC.

[00013] **Figure 2** shows an embodiment of a system for concurrent fMRI and EEG.

[00014] **Figure 3** shows CBF activation differences between three states.

[00015] **Figure 4** shows EEG spectral analysis of EC (red), EO (green), and MC (yellow) during BOLD fMRI and ASL fMRI scanning.

[00016] **Figure 5** shows diagram of ASL pulse sequences which consist of spin labeling, post-labeling delay time, image acquisition and delay time (TD); also shown are associated acoustic noise level and interferences on EEG recording. The post-labeling delay and TD portions are silent periods in terms of magnetic gradient and acoustic noise, which do not interfere with EEG recording. The labeling period causes mild interferences and mild acoustic noise, while only the imaging acquisition part generates high interferences on EEG and a high acoustic noise level due to the use of rapid imaging sequences such as the echo-planar imaging (EPI).

DETAILED DESCRIPTION OF THE INVENTION

[00017] This invention relates in one embodiment to methods for concurrently recording electrophysiologic signal (EEG) and cerebral blood flow (CBF) signal from human brain. In another embodiment, the invention relates to methods for noninvasively assessing brain function using functional MRI and electroencephalograph (EEG).

[00018] In one embodiment, the method provided herein are used for neuroimaging of sleep. In another embodiment, the methods provided herein are used for investigating the neurobiology of sleep along with the dynamic changes across the sleep-wake cycle. Clinical applications of the methods described herein, are diagnosis and prognosis of sleep disorders, or in another embodiment, testing central effects of sleep medications. In another embodiment, since both EEG and perfusion fMRI provide specific markers for work load, vigilance, stress and drug effects etc, the methods described herein are useful for monitoring continuous performance tasks, CNS responses to pharmacological manipulations, and bio-feedback training.

[00019] In another embodiment, combination of EEG and fMRI offers the potential for multi-model neuroimaging with both high spatial and temporal resolutions. Accordingly and in one embodiment, provided herein is a method of neuroimaging brain function of a subject during sleep, comprising the steps of: Concurrently recording electrophysiologic brain signals and cerebral blood flow (CBF) data of the sleeping subject; Reconstructing the cerebral blood flow (CBF) data within time window of interest based on a marker of electrophysiologic brain signals; and Dynamically associating the electrophysiologic brain signals and reconstructed cerebral blood flow

(CBF) data, thereby neuroimaging brain function of the subject during sleep. In another embodiment, concurrent EEG and perfusion fMRI is used for tracking gradual state changes in brain function (e.g. sleep), with characteristic markers in both hemodynamics and neurophysiology.

[00020] In one embodiment, electrophysiologic brain signals are recorded using electroencephalography (EEG). An "electroencephalogram" or "EEG" refers in one embodiment, to an outward indication of electrical activity from the most superficial layers of the cerebral cortex, usually recorded from electrodes on the scalp. This activity is the result of the rhythmic discharging of neurons under the electrode. In another embodiment, the EEG signal provides information about the frequency and amplitude of the neuronal electrical activity and its temporal variation, or in another embodiment, of electrophysiologic brain signals. In one embodiment the EEG frequency spectrum comprises signals in a 2 to 80 Hz range, with most activity between about 2 and 15 Hz.

[00021] In one embodiment, there are two methods for analyzing the EEG, i.e., a linear analysis method such as a Fourier transform and a nonlinear analysis method such as a correlation dimension estimation. The Fourier transform can obtain the information for a specific frequency component such as α -wave (8-13 Hz) and β -wave (14-30 Hz) extensively studied. The correlation dimension estimation is used to determine whether or not EEG time series are chaos signals.

[00022] In one embodiment, a particular MRI technology, termed arterial spin labeling (ASL) perfusion MRI, is used to measure dynamic variations in cerebral blood flow during sleep. In one embodiment, the term MRI refers to magnetic resonance imaging. Magnetic resonance imaging refers in one embodiment to a technique for magnetically exciting nuclear spins of a subject placed in a static magnetic field by applying a radio-frequency signal with the Larmor frequency, and obtaining images using FID (free-induction decay) signals or echo signals induced with the excitation. One category of the magnetic resonance imaging is ASL (Arterial Spin Labeling) imaging. This imaging provides perfusion (tissue blood) images in which blood vessels and microcirculation of a subject are reflected, without injecting contrast medium into the subject, i.e., non-invasively. In one embodiment, the ASL method used in the methods described herein, includes a "continuous ASL (CASL) technique" or a "pulsed ASL (PASL) technique" or a "pseudo-continuous ASL technique". CASL technique refers in one embodiment, to a way of applying a largely continuous adiabatic RF wave, while in another embodiment, PASL technique refers to the application of a pulsed adiabatic RF wave that can easily be practiced by a clinical

MRI system. In another embodiment, pseudo-continuous ASL technique refers to the application of a train of pulsed RF wave to simulate the effect of CASL.

[00023] In one embodiment, cerebral blood flow (CBF) is measured directly by using arterial blood water as an endogenous contrast agent. In one embodiment, perfusion MRI used in the methods as described herein, is ideal for imaging a sustained behavioral state, such as sleep in another embodiment with excellent reproducibility over long-term time periods and minimal sensitivity to magnetic-field inhomogeneity effects, that involves the function of deep brain structures.

[00024] In one embodiment, the brain regions used in the methods for tracking gradual state changes in brain function (e.g. sleep) with characteristic markers in both hemodynamics and neurophysiology are the right prefrontal cortex (RPFC), left prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex (ACC), insula, putamen, amygdala, striatum, nucleus accumbens (NA) and hippocampus or a combination thereof. In another embodiment, the prefrontal cortex, dorsal striatum, and medial temporal lobe are involved in task completion under condition of sleep deprivation and are the brain regions monitored using the methods provided herein.

[00025] In one embodiment, concurrent recording of EEG and ASL perfusion MRI involves the use of MRI compatible EEG systems during perfusion MRI scanning. In another embodiment, subjects wear an electrode cap made of non-magnetic material, and the EEG signal is conducted through fiberoptic cables or carbon fibers to amplifiers outside the MRI scan room. Amplified EEG signal is stored in one embodiment and displayed in real time in another embodiment, by a PC workstation.

[00026] In another embodiment, perfusion fMRI scanning utilizes ASL sequences (including pulsed in one embodiment, or continuous and pseudo-continuous ASL in other embodiments, or their combination), which is comprised of four portions for spin labeling, post-labeling delay time, image acquisition and delay time. A relatively long repetition time ($TR > 4s$) is used in one embodiment, to ensure at least 50% of scan time is free of magnetic gradient artifact. The ASL sequence transmits a TTL pulse every measurement (TR) to the EEG workstation to synchronize the data stream in two modalities. If real time analysis of ASL data is required in one embodiment, the acquired perfusion MRI series is transferred from the MR host computer to the EEG workstation through network links on the fly.

[00027] For sleep research, the acoustic noise of ASL image acquisition can be further reduced by several approaches. These approaches include adjusting the gradient-readout frequency to avoid the resonance frequencies of gradient coil vibrations, the use of quiet gradient coils and silent MR pulse sequences. Due to the relatively long scan time for sleep research, the ASL sequences can further correct head motion in real time by incorporating techniques such as prospective acquisition correction.

[00028] In one embodiment, physiological data that can be concurrently measured include heart rate, blood pressure, respiration rate, temperature, PaCO₂, PaO₂, and galvanic skin response (GSR).

[00029] In one embodiment, for the purpose of reconstruction of CBF data within time window of interest based on EEG markers, perfusion MRI series are loaded in one embodiment onto a common software platform together with EEG during post-processing or in real time in another embodiment. In one embodiment, MRI and EEG data are temporally aligned according to TTL markers. Initial MRI data processes include exclusion of spurious spikes in one embodiment, or motion correction and spatial smoothing or their combination in other embodiments. In another embodiment, the user defines the time window of interest by evaluating continuous EEG data (e.g., REM) in certain embodiments, or according to other pre-selected triggers. In another embodiment, mean quantitative CBF maps of the defined time window are automatically generated (using ASL perfusion models), displayed and stored for further analysis. The software is flexible enough to generate CBF maps for each time period, or to integrate over several discrete time windows, or to provide difference CBF maps between two periods. In another embodiment ASL data is acquired through the use specific EEG markers as trigger to initiate ASL perfusion MRI scanning.

[00030] In another embodiment, within the defined time window, dynamic association of EEG and perfusion image series are carried out. In one embodiment, EEG power spectrum provides indices of slow and fast components (e.g. Delta vs. Beta) as a function of time, which are used in another embodiment as covariates in correlation analysis of the perfusion time series. In another embodiment, perfusion time series in specific brain regions are used as covariates in correlation analysis of the EEG time series.

[00031] In one embodiment, the step of reconstruction of CBF data within time window of interest based on EEG markers in the methods of neuroimaging brain function of a subject during sleep is preceded by a step of removing noise of EEG data in real time. In one embodiment, since

>50% EEG is free of MRI artifact, EEG periods presenting gradient artifacts are masked. In another embodiment, the cardio-ballistic noise in EEG caused by involuntary subject movements is minimized by online regression with EKG signal. The processed EEG signals have sufficient quality in one embodiment, for spotting characteristic marks for behavioral states (e.g., Delta wave, K complexes for slow wave sleep). In one embodiment, online noise removal is performed to further reduce the gradient artifacts during MRI scanning. In another embodiment, reducing the gradient artifacts during MRI scanning according to the methods provided herein, requires pre-scanning to generate a template of time-locked gradient induced EEG artifact, followed by subtracting this noise template from real time EEG data using statistical methods, such as principle component analysis in one embodiment, or least-squares based fitting and cluster analysis in other embodiments.

[00032] In one embodiment, brain regions demonstrating CBF changes in ASL perfusion MRI can be used as hypothesized foci of neural activation. Simulated EEG data based on these detected activation loci (seeds) can be generated and compared with the observed EEG signals, providing a means to validate the neural network model associated with a specific behavioral state. In another embodiment, both EEG and ASL data can be correlated with behavioral performance and physiological signals such as heart rate, blood pressure etc.

[00033] In one embodiment, the concurrently collected EEG/ASL data using the methods provided herein is displayed to subjects in real time as bio-feedback, while subjects are required to self-manipulate blood flow and electrophysiologic signals.

[00034] The term "subject" refers in one embodiment to a mammal including a human in need of therapy for, or susceptible to, a condition or its sequelae. The subject may include dogs, cats, pigs, cows, sheep, goats, horses, rats, and mice and humans. The term "subject" does not exclude an individual that is normal in all respects.

[00035] The following examples are presented in order to more fully illustrate the preferred embodiments of the invention. They should in no way be construed, however, as limiting the broad scope of the invention.

EXAMPLES

Materials and Methods:

Concurrent recording of EEG and ASL perfusion MRI

[00036] This step involves the use of MRI compatible EEG systems during perfusion MRI scanning. Subjects wear an electrode cap made of non-magnetic material, and the EEG signal is conducted through fiberoptic cables or carbon fibers to amplifiers outside the MRI scan room. Amplified EEG signal is then stored and displayed in real time by a PC workstation. EEG sampling rate can be kept within 5kHz because of the low interference from ASL sequences.

Perfusion fMRI scanning utilizes ASL sequences (including pulsed, continuous and pseudo-continuous ASL), which generally comprise of three portions for spin labeling, delay time and image acquisition. A relatively long repetition time ($TR > 4s$) is used to ensure at least 50% of scan time is free of magnetic gradient artifact. The ASL sequence transmits a TTL pulse every measurement (TR) to the EEG workstation to synchronize the data stream in two modalities. If real time analysis of ASL data is required, the acquired perfusion MRI series need to be transferred from the MR host computer to the EEG workstation through network links on the fly.

For sleep research, the acoustic noise of ASL image acquisition can be further reduced by several approaches. These approaches include adjusting the EPI-readout frequency to avoid the resonance frequencies of gradient coil vibrations, the use of quiet gradient coils and silent MR pulse sequences. Due to the relatively long scan time for sleep research, the ASL sequences can further correct head motion in real time by incorporating techniques such as prospective acquisition correction. Additional physiological data that can be concurrently measured include heart rate, blood pressure, respiration rate, temperature, $PaCO_2$, PaO_2 , and galvanic skin response (GSR).

Real time noise removal of EEG data

[00037] Because >50% EEG is free of MRI artifact, the simplest approach is just to mask out those EEG periods presenting gradient artifacts. The cardio-ballistic noise in EEG caused by involuntary subject movements is minimized by online regression with EKG signal. These processed EEG signals have sufficient quality for spotting characteristic marks for behavioral states (e.g., Delta wave, K complexes for slow wave sleep). If required, online noise removal can be performed to further reduce the gradient artifacts during MRI scanning. This step requires pre-scanning to generate a template of time-locked gradient induced EEG artifact, and then subtract this noise template from real time EEG data using principle component analysis or least-squares based fitting.

Reconstruction of CBF data within time window of interest based on EEG markers

[00038] The perfusion MRI series are loaded onto a common software platform together with EEG during post-processing or in real time. The MRI and EEG data are temporally aligned according to TTL markers. Initial MRI data processes include exclusion of spurious spikes, motion correction and spatial smoothing. The user then can define the time window of interest by evaluating continuous EEG data (e.g., REM). Mean quantitative CBF maps of the defined time window can be automatically generated (using ASL perfusion models), displayed and stored for further analysis. The software is flexible enough to generate CBF maps for each time period, or to integrate over several discrete time windows, or to provide difference CBF maps between two periods. An alternative approach to acquire ASL data is to use specific EEG markers as trigger to initiate ASL perfusion MRI scanning.

Dynamic association of EEG and CBF data

Within the defined time window, dynamic association of EEG and perfusion image series can be further carried out. EEG power spectrum provides indices of slow and fast components (e.g. Delta vs. Beta) as a function of time, which are used as covariates in correlation analysis of the perfusion time series. Vice versa, perfusion time series in specific brain regions are used as covariates in correlation analysis of the EEG time series. Further, brain regions demonstrating CBF changes in ASL perfusion MRI can be used as hypothesized foci of neural activation. Simulated EEG data based on these detected activation loci (seeds) can be generated and compared with the observed EEG signals, providing a means to validate the neural network model associated with a specific behavioral state. Both EEG and ASL data can be correlated with behavioral performance and physiological signals such as heart rate, blood pressure etc.

Bio-feedback of real time EEG and CBF data (optional)

[00039] The EEG/ASL data can be displayed to subjects in real time as bio-feedback, while subjects are required to self-manipulate blood flow and electrophysiologic signals

Example 1:

[00040] Five subjects (4 male, age 23-27 years) were scanned on a Siemens 3.0T Trio scanner, using the standard volume head coil. EEG data were simultaneously recorded using a 64-channel Neuroscan MagLink System. BOLD images were acquired during the two resting states of

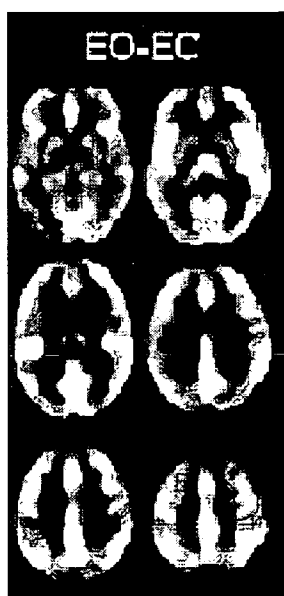
eyes closed (EC) and eyes open (EO) with a typical gradient echo EPI sequence [60 acquisitions, 25 slices, 4mm thk/interleave, TR: 3s (1.5s image acquisition and 1.5s interval), TE: 30 ms, FOV: $22 \times 22 \text{ cm}^2$, Matrix: 64×64]. Perfusion images were acquired during EC, EO and a mental calculation (MC) task of serial subtraction (eyes closed), using an amplitude-modulated continuous ASL technique [60 acquisitions, 12 slices, 6mm thk/1.5mm sp, TR: 5s (2s labeling, 1s delay, 0.5s image acquisition and 1.5s interval), TE: 17 ms, FOV: $22 \times 22 \text{ cm}^2$, Matrix: 64×64]. SCAN 4.5 (Neuroscan) was used to analyze the interleaved EEG data recorded during the scan interval of BOLD fMRI and during the delay time of CASL perfusion fMRI, during which no EPI induced noise was present. Perfusion fMRI data were analyzed by SPM99. For each subject, raw EPI images were corrected for head motion, followed by pair-wise subtraction of label and control acquisitions and conversion to quantitative cerebral blood flow (CBF) images based on the single-compartment perfusion model. Voxel-wise population comparisons were then conducted on CBF images. Areas of significant activation were identified for uncorrected P value smaller than 0.05 and cluster size larger than 30 voxels (voxel size $2 \times 2 \times 2 \text{ mm}^3$).

[00041] Fig. 3 illustrates the CBF differences between the three states overlaid on the mean CBF images from all five subjects. High quality perfusion images were obtained in each subject, with a mean global CBF value of 43.6 ml/100g/min. Consistent with the neuroimaging literature, perfusion fMRI revealed greater visual activation for EO than EC, and greater frontal and parietal activations for MC than EC. Fig. 4 illustrates the differences between the three states from EEG spectral analysis. Consistent with the EEG literature, EEG revealed greater alpha component (8-11Hz) in posterior brain for EC than EO, greater delta (1-3.5Hz) and theta components (3.5-6Hz) in frontal areas for MC than EC

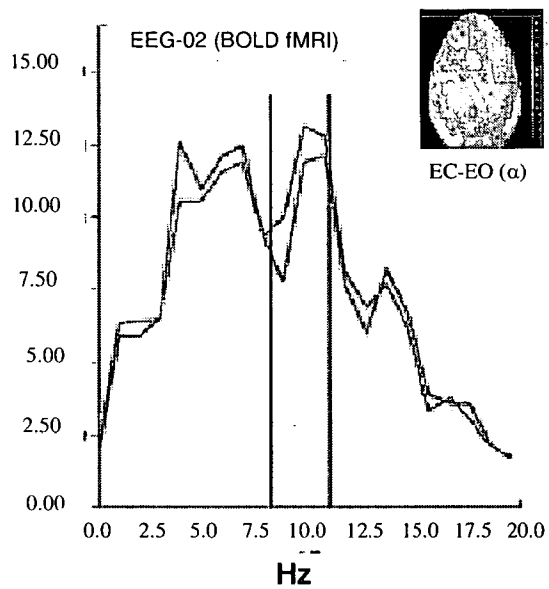
[00042] Having described preferred embodiments of the invention with reference to the accompanying drawings, it is to be understood that the invention is not limited to the precise embodiments, and that various changes and modifications may be effected therein by those skilled in the art without departing from the scope or spirit of the invention as defined in the appended claims.

What is claimed is:

1. A method of neuroimaging brain function of a subject during sleep, comprising the steps of:
 - a. Concurrently recording electrophysiologic brain signals and cerebral blood flow (CBF) data of the sleeping subject;
 - b. Reconstructing the cerebral blood flow (CBF) data within time window of interest based on a marker of electrophysiologic brain signals; and
 - c. Dynamically associating the electrophysiologic brain signals and reconstructed cerebral blood flow (CBF) data, thereby neuroimaging brain function of the subject during sleep
2. The method of claim 1, whereby recording electrophysiologic brain signals is carried out using an electroencephalography. (EEG)
3. The method of claim 1, whereby recording cerebral blood flow (CBF) data is carried out using perfusion magnetic resonance imaging (MRI) scanning.
4. The method of claim 3, whereby perfusion magnetic resonance imaging (MRI) scanning utilizes an arterial spin labeling (ASL) sequence.
5. The method of claim 4, whereby the arterial spin labeling (ASL) sequence is pulsed, continuous, pseudo-continuous ASL, or a combination thereof.
6. The method of claim 2, whereby the step of reconstructing is preceded by a step of removing noise of EEG data in real time.
7. The method of claim 2, whereby the step of reconstructing the cerebral blood flow (CBF) data within time window of interest comprises aligning the cerebral blood flow (CBF) data and electrophysiologic brain signals according to a transistor-transistor-logic (TTL) marker, wherein the TTL marker is generated by the MRI system and captured by EEG.



Perfusion



EEG

FIGURE 1

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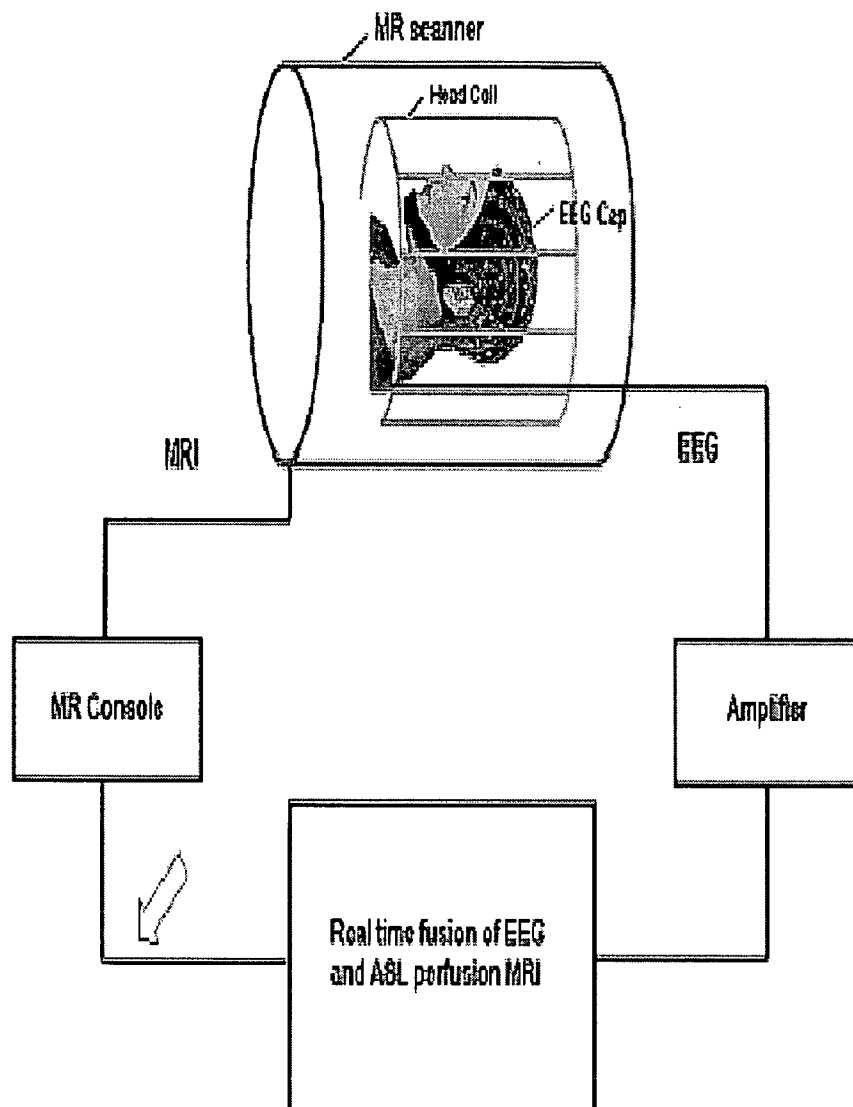


FIGURE 2

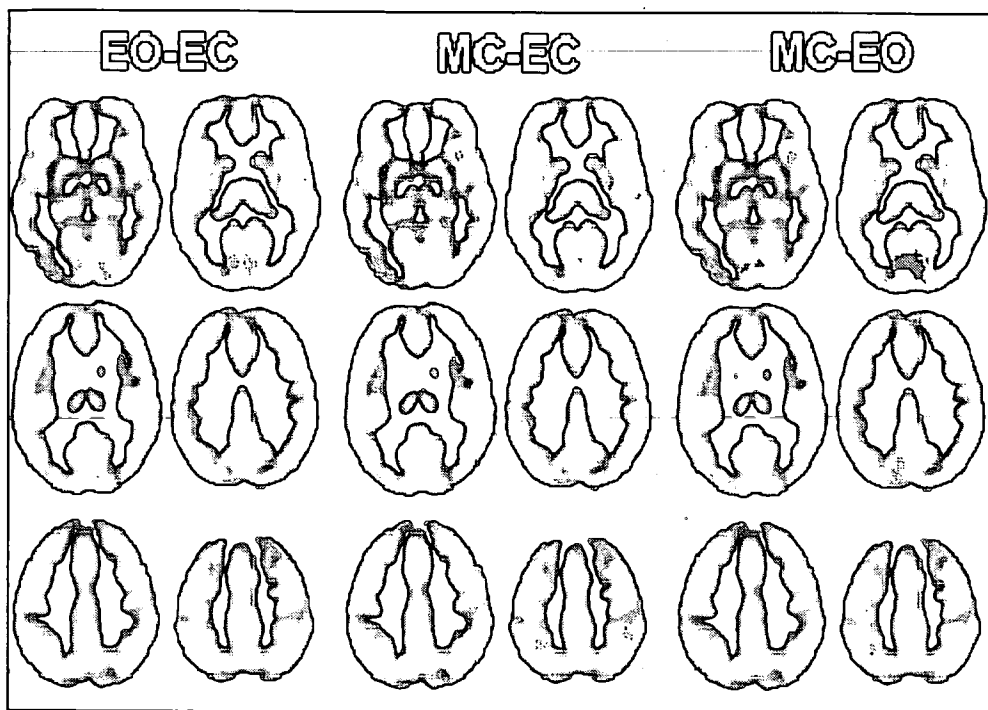


FIGURE 3

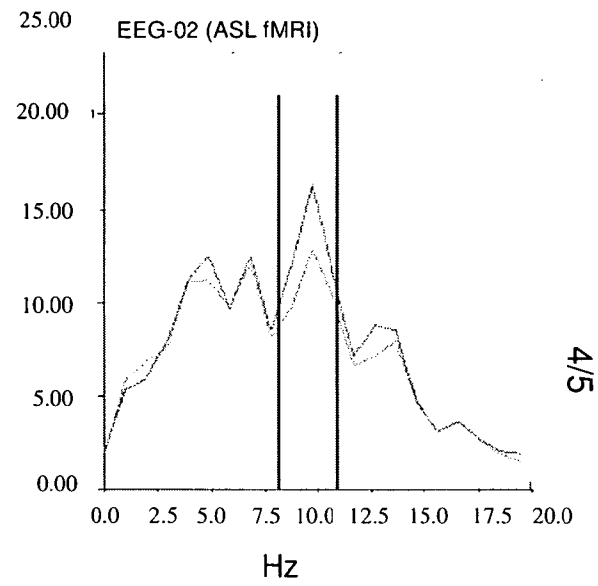
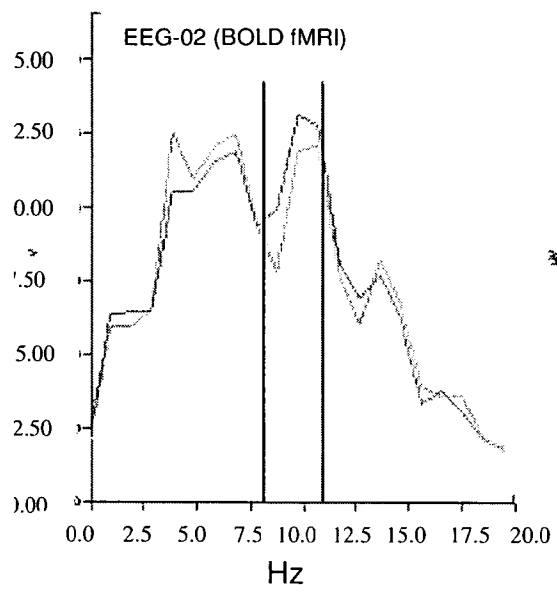


FIGURE 4

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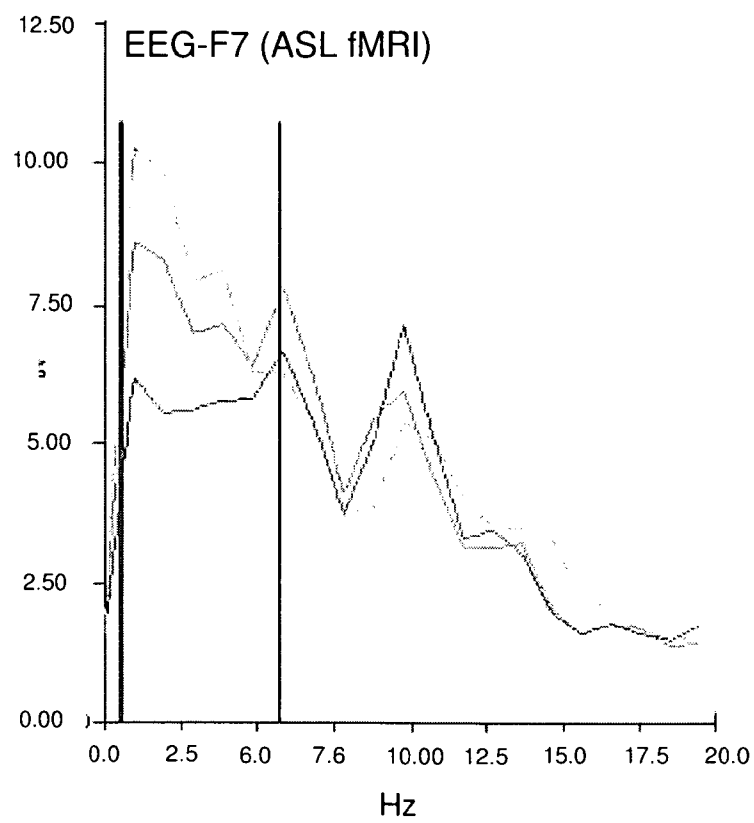


FIGURE 4 (continued)