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BRIEF/TECHNICAL REPORT
NEUROIMAGING PHYSICS/FUNCTIONAL NEUROIMAGING/CT AND MRI TECHNOLOGY

Delta Wave MRI: fMRI Imaging of Electrophysiologic Activity

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ABSTRACT

SUMMARY: We propose a novel application of MR encephalography (MREG) to detect the frequency spectrum of endogenous slow oscillatory brain activity (delta, <4 Hz). MREG offers faster image acquisition than conventional fMRI and superior spatial localization than electroencephalography/magnetoencephalography. MREG was acquired at a 0.1-second temporal resolution in a healthy adult during interleaved wakefulness and sleep to demonstrate its capability for detecting delta-band power changes associated with sleep, previously demonstrated by electroencephalography. For each voxel, the brain activity of MREG signal was used to compute a spectrogram and a whole-brain image of delta-band spectral power. The delta-band power was observed to increase during sleep compared with the awake states using measures from MREG voxelwise spectrograms and sequential whole-brain spatial maps of slow-wave power. This work introduces an MR technique for measuring brain slow-wave activity that is sensitive to changes in the magnitude and frequency of brain activity in sleep.

ABBREVIATIONS: BOLD = blood oxygen level–dependent; EEG = electroencephalography; MEG = magnetoencephalography; MREG = MR encephalography

Conventional fMRI is not used for directly measuring brain electrophysiology because of the relatively low (∼seconds) temporal resolution and a lack of signal sensitivity to the electromagnetic fields that arise directly from neuronal electrical current activity.[1–3] Traditionally, other modalities such as electroencephalography (EEG) and magnetoencephalography (MEG) have provided direct measures of brain electric potentials and magnetic fields with sufficient temporal resolution to detect functionally-relevant neural oscillations ranging from delta (∼1–4 Hz) to γ (>30 Hz) bands. However, EEG and MEG lack the spatial resolution and precise source localization (ie, image formation) intrinsic to MRI techniques such as blood oxygen level–dependent (BOLD) fMRI, as well as requiring dedicated hardware and scanning sessions that need to be subsequently augmented by a separate anatomic MRI for visualization of source estimates. The present work applies MR encephalography (MREG) for detection and observation of endogenous slow brain activity (delta-band, <4 Hz). MREG is a parallel-accelerated, stack of spirals trajectory pulse sequence that provides faster image acquisition (10 frames/second) than conventional fMRI and superior spatial localization than EEG/MEG and thus can be considered "delta wave MRI."[1] The sensitivity of MREG to delta wave activity is illustrated by comparing signal spectra between sleep and awake states, though, in principle, any occurrence of delta wave activity could be similarly imaged.

BOLD MR contrast is dependent on temporal changes in the relative concentrations of oxyhemoglobin and deoxyhemoglobin and relies on the sensitivity of T2*-weighted EPI to local magnetic field homogeneity.[3] However, the event-driven dynamics of oxy- and deoxyhemoglobin levels provide only a secondary, surrogate marker for brain activity and are not necessarily temporally aligned with neuronal activity. Blood exchange at the cortex is controlled by the hemodynamic response mechanism that lags behind neuronal activity and introduces a temporal convolution or smearing to the BOLD signal relative to the underlying brain activity. In traditional "boxcar" and event-related fMRI, the dominant hemodynamic response to a relatively large and sustained brain activity takes approximately 5 seconds to peak.[4] However, recent studies have shown that the hemodynamic response to steady-state brain activity and smaller endogenous oscillations is more localized and rapid than the large and slow hemodynamic response modeled and observed in event-triggered fMRI studies.[5] Fast fMRI is critically enabled to detect slow ongoing neural activity by the existence of a rapid BOLD response, which is akin to the fMRI "negative dip" and uncoupled from the hemodynamic response.[6,7]

The delta wave MRI provides ultrafast whole-brain BOLD imaging which, in turn, translates to detection of higher

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frequency brain oscillations. Conventional echo-planar fMRI acquires whole-brain volumes at a rate of approximately 2–3 seconds per volume (with an approximate sampling frequency of 0.33–0.5 Hz and a Nyquist bandwidth of 0.17–0.25 Hz). The delta wave MRI uses a single-shot "stack of spirals" trajectory, as well as image acquisition acceleration, to acquire whole-brain volumes at a much faster rate of ~0.1 seconds per volume.[1,8,9] This sampling rate of 10 Hz enables detection of fluctuating signals (brain oscillations) up to 5 Hz in accordance with the Nyquist limit. As discussed above, if one assumes that the hemodynamic response to natural and slow brain oscillations is rapid, the hemodynamic response will not be substantially smoothed or convolved relative to the underlying brain activity. Unlike in conventional fMRI, which has a large, slow hemodynamic response, in this study, the delta wave MRI BOLD signal is thus directly examined without the need to remove or deconvolve the hemodynamic response function.

We present a method for using ultrafast MR encephalography to measure and visualize a spectrogram of electrophysiologic brain activity in the ~1–4 Hz band: delta wave MRI. Although this activity is referred to as "slow" on an electrophysiologic scale, it is much faster than the typical BOLD fMRI sensitivity. The subject's sleep state is used to illustrate the sensitivity of the technique to changes in brain activity because the delta band activity is well-known to increase during sleep.[2,10] The framework of using an ultrafast delta wave MRI to detect alterations to low-frequency band brain activity is expected to have applications in multiple conditions and diseases that cause pathologic slow (delta) wave activity, including traumatic brain injury, stroke, brain tumor, epilepsy, Alzheimer's disease, and Parkinson's disease.

MATERIALS AND METHODS

An overview of the method framework is shown in Fig 1. Briefly, ultrafast MREG is acquired at a 0.1-second temporal resolution and reconstructed. The MREG reconstruction is a 4D volume comprising 3 spatial dimensions and a temporal dimension, analogous to conventional fMRI 4D volumes. Spatial resolution is comparable with typical fMRI paradigms (~3 mm). At each spatial location (voxel), the brain activity waveform and/or power spectrum may be extracted and computed. Frequency and spatial information may be combined to create an image of spectral power across the brain.

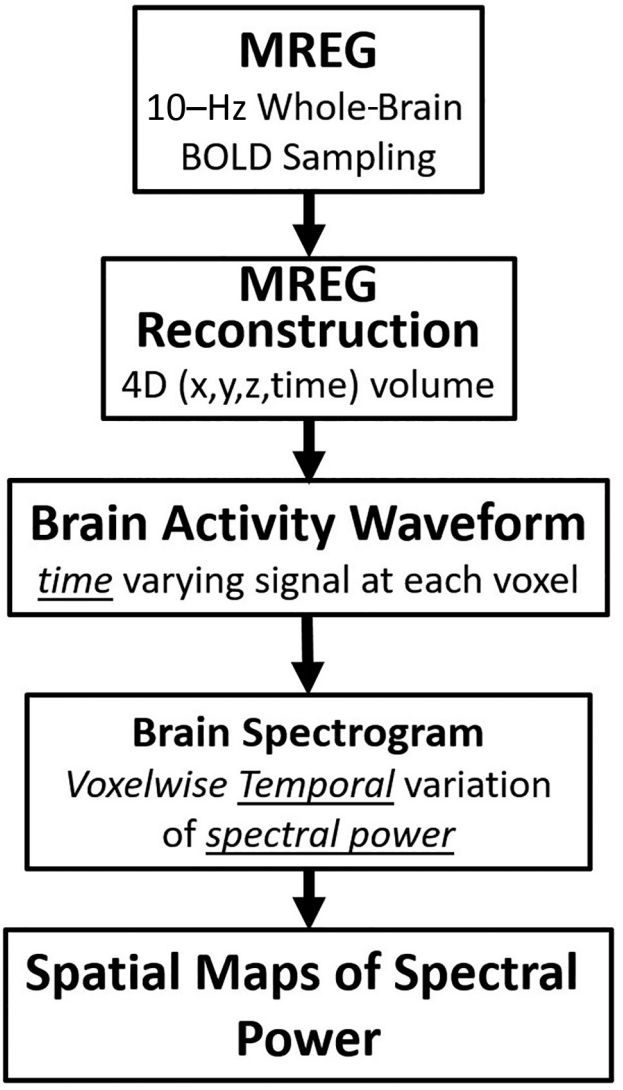

FIG 1. Overview of the MR slow-wave detection method using MREG. MREG reconstruction is performed as a postprocessing step before time course, spectral, and spectrogram computations. The spectral power of each voxel in the brain may be visualized as an image, a delta wave MRI.

MRI Acquisition

The MR acquisition was performed on a 3T Magnetom Prisma scanner (Version VE11C; Siemens) with a 32-channel radiofrequency head coil, TR of 100 ms, TE of 20 ms, 15° flip angle, 64 × 64 × 64 matrix, field of view of 192 × 192 × 192 mm, and 3-mm isotropic resolution. The stack of spirals MREG pulse sequence was a C2P Package, Version 2.3, authored by Assländer et al[11] and was acquired through a research agreement with Siemens Healthineers.

A healthy adult subject (male, 56 years of age) was continuously scanned with the MREG sequence for 45 minutes during wakefulness and sleep. To ease the computational demands of reconstruction, the MREG sequence was limited to 3.5 minutes and repeated 13 times consecutively during the subject's MR examination, for approximately 45 minutes. The scanner was set to automatically proceed to the next MREG sequence to limit the nonscan time gap between sequences. The subject was instructed to lie motionless in the scanner and fall asleep. Following the MREG acquisition, the subject reported being aware of approximately 3–4 sequence noise "gaps" (~15 minutes) before falling asleep. Approximately 35 minutes after onset, the subject was awakened and scanning was continued for another 10 minutes with the subject awake. Thus, an extended boxcar of awake/drowsy – sleep – awake was achieved with ~15:20:10 minute blocks.

Reconstruction

Non-Cartesian data from each of the 13 MREG scans was reconstructed independently using an iterative regularization Matlab (MathWorks) reconstruction algorithm provided with the MREG sequence, yielding a 4D image matrix with dimensions V = [x, y, z, t], where *x, y, z* are the spatial dimensions and *t* is the time

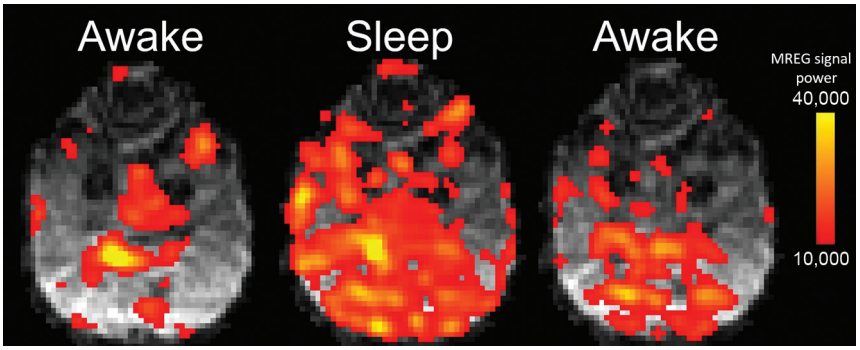

FIG 2. Spatial distribution of delta power. The spatial distribution of delta power is visualized across the brain during the initial awake period, the sleep period, and the final awake period. Full delta-band power between 0.2 and 4 Hz was averaged during a 50-second period for every voxel in the brain and is expressed in arbitrarily scaled units related to MREG BOLD signal intensity. The delta power is highest during sleep and is generally strongest in the brain periphery and sulcal regions, consistent with cortical tissue. This contrast in delta power is apparent from the relatively short 50-second measurement period.

dimension.[12] The image matrix for each MREG segment was truncated to remove the first 60 time points corresponding to 6 seconds (~2–3 T1s) before steady-state stabilization of the MR signal. Reconstructed MREG image matrices were then concatenated along the time domain, yielding a single 4D image matrix for the entire (45 minute) scan. The data set was motion-corrected with 6 *df* using the FMRIB Linear Image Registration Tool (FLIRT; http://www.fmrib.ox.ac.uk/). From the 4D image matrix, any individual position in space $r = [r_x, r_y, r_z]$ could be enumerated to create a time course signal $s(r,t) = V[r_x, r_y, r_z, t]$. An MREG time course s(r,t) could thus be selected from any voxel in the brain. The MREG time courses were then high-pass filtered with a Butterworth filter and a cutoff frequency of 0.01 Hz to remove ultralow frequency activity and DC offset. Spectrograms from 50-second frames were then computed for the MREG time course of each voxel using the spectrogram function from the SciPy package in python (https://scipy.org/citing-scipy/), which computes consecutive Fourier transforms.

RESULTS

Figure 2 shows that the spatial distribution of delta power may be visualized across the brain. The full delta-band power between 0.2 and 4 Hz was averaged during a 50-second period for every voxel in the brain during the initial awake period, the sleep period, and the final awake period. Power is expressed in arbitrary units related to BOLD signal intensity. The peak delta power was localized primarily in the brain periphery and sulcal regions, consistent with cortical tissue. During the sleep state, the delta power was observed to be elevated in cortical regions throughout the cerebrum.

Figure 3*A* shows the whole-brain voxelwise *t*-statistic map of the slow-wave (0.2–4 Hz) power difference between sleep and awake. The delta-band power was contrasted with a Student *t* test for an asymmetric boxcar of 250 seconds awake, 500 seconds sleep, and 250 seconds sleep. The asymmetric boxcar-design contrast limits the impact of linear signal drift during the experiment. The time and frequency domain of MREG waveforms of a single temporal cortex voxel are shown in Fig 3*B*–*E*. The red arrows along the time axis represent the approximate time period when the subject was asleep. While the exact time the subject transitioned into sleep is unknown, the subject stopped reporting being awake about 10–15 minutes into the scan (and was thus presumed asleep). The subject was abruptly awakened at the time indicated by the vertical red arrow.

An example of the time domain MREG waveform of the temporal cortex voxel (sampling frequency, 10 Hz) is shown across the entire experiment in Fig 3*B*. A distinct change in waveform amplitude and signal appearance is seen during the period of sleep. The associated spectrograms of slow-wave power across time (0.2–4 Hz and Fig 3*C*, *-D*) show an increase in power during the sleep period compared with the awake periods at the beginning and end of the recording. The spectrogram visualizes changing power in specific frequency bands during the recording, also referred to as the "spectrotemporal neural dynamics." Elevated power during sleep is observed at 0.25 Hz in addition to elevated power in frequencies above 1 Hz.

DISCUSSION

We have demonstrated the utility of combining the ultrafast MREG BOLD acquisition with spectrally selective filtering to detect and localize selected electrophysiologic brain activity using MRI. Specifically, we have demonstrated the feasibility of selecting and imaging power in the delta frequency band (~0.1–4 Hz). Spatial foci and temporal dynamics can be probed, revealing, in this demonstration, the time course and spectral patterns of wakefulness and sleep.

This application of ultrafast MREG in combination with the assumption of a rapid hemodynamic response opens the possibility of MR imaging delta waves. The 10-Hz BOLD sampling afforded by the MREG pulse sequence mathematically opens the possibility of measuring oscillations up to 5 Hz, capturing the electrophysiologically-termed "delta" band. High-frequency oscillatory activity above the delta band is not captured; thus, measured delta activity could not be normalized to broadband activity, and only absolute (not relative) delta power is reported.

Our interpretation of the MREG signal dynamics is enabled by the key assumption of a hemodynamic response matched to the time scale of the delta-band neuronal firing, based on a body of literature describing the ability of fMRI to detect activity faster than would be possible if the hemodynamic response were as slow as 5 seconds.[5,6,13] The approximate 0.25-Hz peak has been shown in EEG and conventional fMRI to be associated with sleep spindles, as well as the more well-known "slow-waves" (1–4 Hz) characteristic of "slow-wave sleep."[10,14] This more naturalistic and ongoing brain activity does not elicit a large hemodynamic response, but rather a short-lived increase in deoxyhemoglobin akin to the negative BOLD dip described in conventional fMRI.[7,15] Either the local perfusion changes are small or possibly

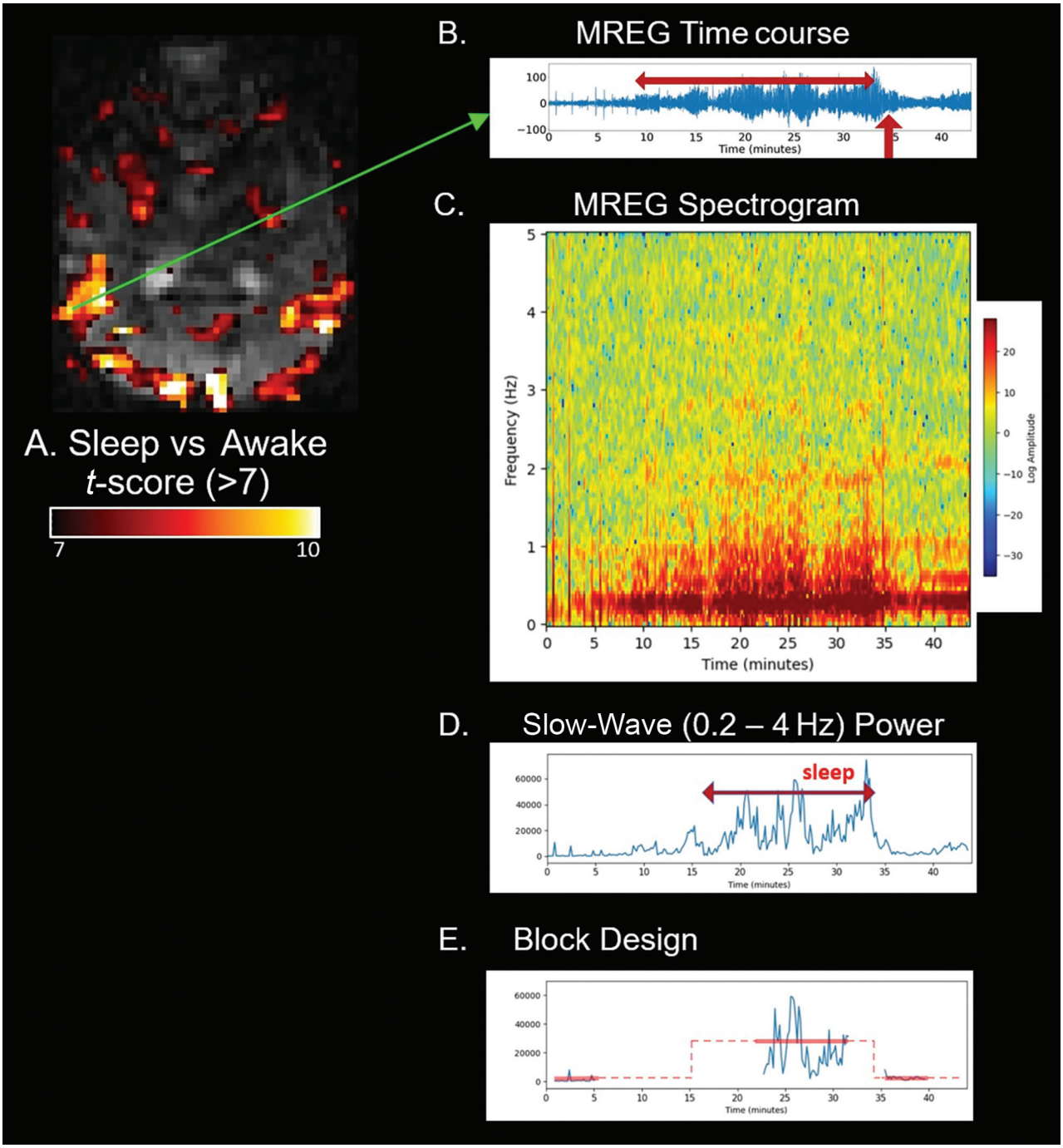

FIG 3. The MREG time course and spectra in an example of a single voxel. *A*, The *t*-score map shows brain regions with increased slow-wave (0.2–4 Hz) MREG activity during sleep. The *t*-score map is derived from an fMRI-style Student *t* test, with an asymmetric boxcar design: 250 seconds awake, 500 seconds asleep, and 250 seconds awake. *B*, A single voxel from the right temporal cortex was selected to demonstrate the spectral-temporal data that may be computed and visualized. The MREG BOLD signal time course is displayed after filtering out ultralow frequencies. The approximate time period of sleep is indicated by the *horizontal arrow*. The *vertical arrow* indicates the known time point when the subject was awakened. The time course amplitude is noticeably higher during the period of sleep. *C*, The corresponding spectrogram shows the full temporal-spectral data for the selected voxel. The delta-band sleep power is elevated. *D*, The temporal evolution of the slow-wave power is computed by integrating over the specified frequency rows in the spectrogram of 3*C*. *E*, The boxcar model (red) and overlaid delta power (blue) of awake, sleep, and awake periods. Solid red segments of the boxcar (250, 500, and 250 seconds) indicate high-confidence awake and sleep periods, which are used in the whole brain *t* test of delta power. *Dashed red periods* are not included in the *t* test.

the perfusion remains constant and provides a continual supply of oxyhemoglobin, which rapidly displaces deoxyhemoglobin.

Alterations to delta waves (~1–4 Hz) are known to be hallmarks of anomalous brain activity in a variety of neurologic and pathologic conditions. We hypothesize that the presently-demonstrated delta wave MRI method can identify and monitor the spatial localization of pathologic neural spectrotemporal features. Clinical opportunities are based on the following known observations:

Elevated resting-state delta-band activity is a common observation across conditions in which neuronal deafferentation or degenerative damage has occurred with trauma, stroke, edema, Alzheimer's disease, or tumor infiltration.[16,17] Specifically, MEG methods have also been demonstrated to be sensitive to enhanced and localizable slow-wave activity in traumatic brain injury.[18] However, the spatial resolution of MEG is limited and reliant on a separate MRI examination to perform subject-specific source localization. A technique such as delta wave MRI provides inherent spatial localization along with the required spectral sensitivity and potentially reduces the need for an additional imaging test for patients already undergoing MRI.

This single-subject study applying MREG to detect delta wave activity has several limitations. Data from additional subjects are necessary to determine intersubject variance in sensitivity to delta power. Non-neuronal physiologic noise sources may contribute to activity in the delta frequency band. Future characterization, possibly in combination with respiration, cardiac, and/or simultaneous EEG monitoring of sleep status, will enable spectral notch filtering, should a particularly dominant artifact source be identified. Multiple MREG sequences were concatenated, potentially introducing discontinuity artifacts in the spectra. Future studies will address this issue by acquiring continuous MREG recordings for longer durations.

CONCLUSIONS

The demonstrated MR technique for measuring brain slow wave activity is sensitive to changes in the magnitude and frequency of brain activity in sleep. It is expected that these methods can be extended to study a variety of pathologies. The technique of delta wave MRI (or more broadly "frequency-selective brainwave MRI") will potentially prove efficacious in the diagnosis, prognosis, and monitoring of therapeutic interventions in a range of neurologic conditions, characterized by delta-band (slow-wave) oscillopathy.

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Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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