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Abstract

Slow waves are the most prominent electroencephalographic (EEG) feature of sleep. These waves arise from the synchronization of slow oscillations in the membrane potentials of millions of neurons. Scalp-level studies have indicated that slow waves are not instantaneous events, but rather they travel across the brain. Previous studies of EEG slow waves were limited by the poor spatial resolution of EEGs and by the difficulty of relating scalp potentials to the activity of the underlying cortex. Here we use high-density EEG (hd-EEG) source modeling to show that individual spontaneous slow waves have distinct cortical origins, propagate uniquely across the cortex, and involve unique subsets of cortical structures. However, when the waves are examined en masse, we find that there are diffuse hot spots of slow wave origins centered on the lateral sulci. Furthermore, slow wave propagation along the anterior-posterior axis of the brain is largely mediated by a cingulate highway. As a group, slow waves are associated with large currents in the medial frontal gyrus, the middle frontal gyrus, the inferior frontal gyrus, the anterior cingulate, the precuneus, and the posterior cingulate. These areas overlap with the major connectional backbone of the cortex and with many parts of the default network.
Source modeling sleep slow waves

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Slow waves are the most prominent electroencephalographic (EEG) feature of sleep. These waves arise from the synchronization of slow oscillations in the membrane potentials of millions of neurons. Scalp-level studies have indicated that slow waves are not instantaneous events, but rather they travel across the brain. Previous studies of EEG slow waves were limited by the poor spatial resolution of EEGs and by the difficulty of relating scalp potentials to the activity of the underlying cortex. Here we use high-density EEG (hd-EEG) source modeling to show that individual spontaneous slow waves have distinct cortical origins, propagate uniquely across the cortex, and involve unique subsets of cortical structures. However, when the waves are examined en masse, we find that there are diffuse hot spots of slow wave origins centered on the lateral sulci. Furthermore, slow wave propagation along the anterior–posterior axis of the brain is largely mediated by a cingulate highway. As a group, slow waves are associated with large currents in the medial frontal gyrus, the middle frontal gyrus, the inferior frontal gyrus, the anterior cingulate, the precuneus, and the posterior cingulate. These areas overlap with the major connectional backbone of the cortex and with many parts of the default network.

The transition from waking to sleep in humans is accompanied by dramatic changes in the electroencephalograph (EEG). The waking EEG is dominated by low-voltage fast activity, while during non-rapid eye movement (NREM) sleep low-frequency components appear in the EEG. During sleep, cortical neurons exhibit a characteristic bistability, oscillating about once every second from a hyperpolarized downstate to a depolarized upstate (1). During the downstate these neurons are almost entirely silent whereas during the upstate neuronal firing rates can be as high as in quiet wakefulness (2). Intracranial recordings of anesthetized cats indicate that the origins of the slow oscillation are cortical and that cortico–cortical connections are necessary for its synchronization (3). Large groups of slowly oscillating neurons synchronize during sleep and the currents produced concomitantly with these changes in membrane potential sum to generate large slow waves in the scalp EEG (4). Increasing evidence suggests that slow waves may mediate some of the functional benefits of sleep, at both the cellular and the systems levels (5–7).

Topographical analyses of slow waves in humans have shown that they have a nonuniform scalp distribution, suggesting that areas of the cortex are differentially involved in slow waves (8, 9). Furthermore, recent analyses have suggested that individual slow waves, rather than being simultaneous events, likely travel throughout the cortex (9). In addition, a growing body of evidence supports the idea that sleep slow waves can be locally regulated (10–12). Therefore, questions remain about the role of specific cortical structures in individual slow waves. Where do slow waves originate? Do they travel through specific pathways or globally invade the cortex? Do all cortical areas participate equally in slow waves?

Although the slow oscillation has been investigated using several different techniques, source modeling of high-density EEG (hd-EEG) sleep slow waves offers a novel way to answer these questions. Scalp-level analyses of EEG sleep slow waves are made difficult by the fact that local potentials can be generated by sources that are distant from the recording electrodes (13). Intracranial recordings are limited in scope and sensitivity; it is impossible to fully sample the large cortical areas thought to be involved in slow waves. Imaging modalities like functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) possess superior spatial resolution to EEG source modeling, but their temporal resolution is insufficient to capture the changes in cortical activity that occur during an individual slow wave (14, 15). Source-level analyses of hd-EEG sleep slow waves, however, offer a considerable advantage in temporal resolution while achieving much higher spatial resolution than traditional scalp recordings, closer to that of other functional imaging methods. Therefore, in this study, we used hd-EEG source modeling to investigate the origin, propagation, and cortical involvement of individual sleep slow waves.

Results

Source Modeling Individual Slow Waves Induced by Transcranial Magnetic Stimulation (TMS) Reliably Produces Maximal Sources Consistent with the Induction Site. In a previous study, we demonstrated that individual pulses of TMS during sleep elicit EEG slow waves that closely resemble spontaneous sleep slow waves (16). For the current study, we capitalized on this phenomenon by first source modeling these evoked slow waves. This allowed us to ascertain whether our source localization method produced consistent results in the case where the locus of the induction of the slow wave was predetermined. Briefly, we recorded EEGs from 15 subjects with a TMS compatible system (Nexstim). After the subjects had transitioned into stage 2 NREM sleep, we applied TMS pulses targeted to midline sensorimotor cortex (Fig. L4). We selected a subject with a minimal TMS artifact and analyzed the TMS-evoked slow waves with several different source modeling methods, including L2 minimum norm with the local autoregressive average (LAURA) (17) constraint, low-resolution electromagnetic tomography (LORETA) (18, 19), standardized low-resolution electromagnetic tomography (sLORETA) (20, 21), and the Bayesian minimum norm (21) [see Methods and SI Text]. To normalize the currents, we selected 5 s of preceding EEG without slow waves, spindles, or artifacts as a baseline (see Methods). Regardless of the algorithm, TMS-triggered slow waves spread through source space in a stereotyped pattern (Fig. 1 B and C). About 120 ms after the TMS pulse, relative current begins to increase in the postcentral gyrus, precuneus, and cingulate gyrus, directly below the site of TMS stimulation on the scalp. Near the negative peak of the potential wave, these sources increase in strength and are joined by relative currents in the anterior and posterior cingulate, lateral parietal, and some temporal areas. As the wave weakens, most activation retreats

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Source Modeling Spontaneous Slow Waves Reveals a Unique Cortical Current Distribution for Each Wave. Having confirmed that our analysis correctly localized the current sources of individual TMS-evoked slow waves, we next examined the source modeled behavior of spontaneous sleep slow waves. Our data indicate that spontaneous sleep slow waves are quite heterogeneous, and therefore the mathematical “average track” is not a clear demonstration of how these waves act. Qualitatively, the “average” sleep slow wave probably begins around the insula, propagates posteriorly along midline structures, and includes large currents in the frontal gyri, anterior cingulate, precuneus, and posterior cingulate. However, because each spontaneous wave is an idiosyncratic event, we systematically characterized individual waves by determining their origin, pattern of propagation, and cortical areas involved.

Spontaneous Slow Waves Originate More Frequently in the Insula and Cingulate Gyrus. For every slow wave, we calculated which voxels were likely to be the origin of that wave (see Methods and SI Text). Examination of the origins of spontaneous waves revealed a consistent pattern across subjects (Fig. 3 A and B and Fig. S1). Although slow waves could originate in either hemisphere, 17 of the top 20 voxels with the most origins were in the left hemisphere. In terms of regional topography, we found a diffuse hot spot of origins centered on the lateral sulcus (including regions of insular, temporal, frontal, and parietal cortices). Approximately 46% of spontaneous slow waves across all subjects included at least one insular voxel in the origin. There was a secondary disjoint hot spot for slow wave origins (~12%) around the medial cingulate gyrus (Fig. 3A). Like the lateral hot spot, the medial cingulate gyrus hot spot also included adjacent portions of the neighboring cortical structures. This secondary origin hot spot was not evident in all subjects (Fig. 3B).

Previous analysis of surface EEG slow waves suggested that many waves originated from the anteromedial part of the scalp, often laterally, while a second group of waves originated centromedially (9). To compare our results with those measured from the scalp, we separated waves into 2 groups on the basis of whether they had at least 1 probabilistic origin voxel in the left insula but not the cingulate gyrus (or vice versa). We then calculated the origins of the surface EEG waves (see Methods) in each group (Fig. 3C). We found that the relative current waves that originated in the left insula most often manifested on the scalp as potential waves that began at the left anterior portion of the scalp. Relative current waves that originated in the cingulate gyrus typically manifested on the scalp as potential waves with centromedial origins.

Spontaneous Slow Waves Stereotypically Propagate Along Certain Paths. For each slow wave, we used the timing of the relative current maxima in each voxel to map how the wave propagated across the cortex (see Methods and SI Text). We found that each slow wave travels uniquely across the cortex (see individual example in Fig. 4A). The propagation speed in source space ranged from 0.4 to 6.3 m/s. The average speed was ~2.2 m/s, was remarkably consistent across subjects (ranging from 2.0 to 2.3 m/s), and was roughly in agreement with previous estimations from EEG and computer simulations (9, 23). Visual inspection of the streamlines for the spontaneous slow waves for each subject suggested the existence of a mesial slow wave highway oriented along the anterior–posterior axis (Fig. 4B and Fig. S2): regardless of where they originated, waves that traveled along the anterior–posterior axis usually did so along the mesial aspect of the cortex.

To determine what structures were included in this mesial slow wave highway, we calculated the number of streamlines that passed through each voxel (Fig. 4C and D and Fig. S2). As expected given the origin results, there were high densities of streamlines in the insula. However, the highest density of streamlines was in the anterior portions of the cingulate. There were also high densities of streamlines in the posterior cingulate and precuneus. These mesial streamlines are not merely the result of the waves originating in the cingulate gyrus because more slow waves propagate through the other wave starts in the left hemisphere near the insula, invades the cingulate gyrus, and then migrates through the right temporal lobe. The results were qualitatively similar for other source modeling algorithms. Our data indicate that spontaneous sleep slow waves are quite heterogeneous, and therefore the mathematical “average track” is not a clear demonstration of how these waves act. Qualitatively, the “average” sleep slow wave probably begins around the insula, propagates posteriorly along midline structures, and includes large currents in the frontal gyri, anterior cingulate, precuneus, and posterior cingulate. However, because each spontaneous wave is an idiosyncratic event, we systematically characterized individual waves by determining their origin, pattern of propagation, and cortical areas involved.
cingulate gyrus than originate there (paired t test, $P < 0.005$). Therefore, many waves originate elsewhere and then propagate to or through the cingulate cortex, confirming the existence of a mesial highway. To a lesser extent this highway also incorporates dorsal midline structures such as the paracentral lobule.

Propagation along the highway could occur in either direction, but most often traveling occurred from front to back. For each voxel, we also examined the average direction of all streamlines that passed through and calculated in what dimension the average direction vectors were anisotropic. In the highway, the largest group of voxels was anisotropic along the anterior–posterior axis (43.4%, standard deviation 7.0%) with the average direction vector heading posteriorly for each subject. There was comparatively less movement along the anterior–posterior axis in the lateral aspect of the cortex. The percentage of anisotropic voxels in the highway was significantly larger than in the rest of the brain (26.1%, standard deviation 1.8%, paired t test, $P < 0.005$). Furthermore, waves travel about the same distance along the highway whether they are moving anteriorly (4.0 dipoles/wave) or posteriorly (3.6 dipoles/wave, paired t test, $P > 0.3$). Waves that moved anteriorly on the highway tended to have more posterior origins than waves that moved posteriorly, but this difference was not statistically significant.

**Spontaneous Slow Waves Preferentially Involve a Subset of Brain Areas and Avoid Others.** We next examined the amount of current produced by different cortical areas during a slow wave. For each voxel, we defined the involvement in that voxel for each individual slow wave as the average relative current during a 100 ms window centered on the negative peak of the EEG slow wave (see SI Text).

This analysis revealed that certain brain structures are more involved than others by sleep slow waves. Relative current hot spots included the precuneus, the cingulate gyrus, the posterior cingulate, the anterior cingulate, and left and to a lesser extent right frontal structures including the middle frontal gyri, the medial frontal gyri, the inferior frontal gyri, and the insula (Fig. 5 and Fig. S1). This result could not be inferred from the voltage topography alone (Fig. S3). While there was some variation between subjects (Fig. 5B), on the whole, the left middle, medial, and inferior frontal gyri were
more involved than the right middle, medial, and inferior frontal gyri (paired t test, \( P < 0.05 \)). There was also a subset of areas that typically showed weak involvement. This subset included some sensory areas (such as the postcentral gyrus, visual cortex, and association areas) and the inferior parietal lobe, the middle temporal gyrus, and regions that were electrotonically distant from the recording electrodes (such as the uncus, hippocampus, and fusiform gyrus) (Fig. 5).

**Discussion** Slow waves are the most prominent electrophysiological feature of NREM sleep. In this paper, we first validated our source modeling results by analyzing slow waves evoked by TMS. We found that each of these waves has a stereotyped source topography with the largest relative currents under the site of stimulation. We then source modeled individual spontaneous slow waves and determined that each corresponds to a unique relative current distribution. While individual slow waves could originate from a wide variety of cortical locations, as a group, there was some indication that some areas were more likely to be origins, namely the insula and, to a lesser extent, the cingulate gyrus. Slow waves often travel along the anterior–posterior axis via the cingulate cortices. In addition, slow waves preferentially involve several cortical areas including the inferior frontal gyrus, the medial frontal gyrus, the middle frontal gyrus, the insula, the anterior cingulate gyrus, the posterior cingulate, and the precuneus. Slow waves for the most part avoid the visual and sensory cortices and the fusiform gyrus.

**Source Modeling hd-EEG Is Uniquely Suited to Studying Individual Slow Waves.** While other neuroimaging techniques like PET and fMRI offer superior spatial resolution, source modeling of hd-EEG is uniquely suited to the analysis of slow waves. First, the superior time resolution of EEG permits tracking the evolution of individual slow waves. Furthermore, although source modeling typically restricts the space to cortical sources, evidence from several different modalities suggests that the sleep slow oscillations do indeed originate in, travel across, and are maintained by the cortex. Isolated cortical slabs undergo slow oscillations, suggesting that the cortex is sufficient for the generation of slow waves (24, 25). Disrupting thalamo–cortical connections leaves the slow oscillation intact while damaging cortico–cortical connections disrupts the synchronization of the slow oscillation (3). Additionally, TMS does not directly reach subcortical structures (26), yet it can reliably elicit slow waves (15). Spreading upstates have been observed in multiple-electrode single-unit recordings of cortical neurons during slow wave oscillations in anesthesia (27). The possibility of a subcortical basis for EEG slow waves is also discounted by the fact that cortical decreases in regional cerebral blood flow during NREM sleep are correlated with EEG delta power and are independent of thalamic activity (28). Furthermore, the variability between individual spontaneous EEG slow waves suggests that a single subcortical substrate is unlikely (9).

While the above evidence suggests that source modeling is particularly well suited to describing slow waves, there are several caveats. First, despite improvements in source modeling, there is the
We found that slow waves were associated with large relative currents in the middle frontal, medial frontal, and inferior frontal cortices, as well as the anterior cingulate, cingulate, insula, posterior cingulate, and precuneus. By contrast, sensory areas, such as the postcentral and occipital gyri, did not contribute much current to slow waves. This result is in agreement with previous PET studies, suggesting that decreases in regional metabolism during NREM sleep occur in the anterior cingulate, insula, medial frontal cortex, and precuneus (28, 45, 46). There was also considerable overlap between areas that were consistently not involved in slow waves and areas that showed increases in regional metabolism. It is unclear why different brain areas are differentially involved in slow waves. It may be that only certain areas of the brain possess the necessary dendritic geometry to produce such large scalp potentials (13). However, increasing evidence suggests that sleep plays an important role in brain plasticity and that it can be locally regulated (11, 47, 48). Therefore, one intriguing possibility is that during waking primary sensory areas may undergo less plasticity than the higher-order cortical areas and therefore may be less involved in slow waves.

Sleep Slow Waves Propagate Across the Default Network. Slow waves preferentially propagate along the anterior–posterior axis through the cingulate gyrus and neighboring structures. This slow wave highway may act to functionally connect anterior high-involvement areas (the anterior cingulate, middle frontal gyri, and inferior frontal gyri) with posterior high-involvement areas (the precuneus, the posterior cingulate). Diffusion spectrum imaging (DSI) has revealed that an anatomical backbone of fibers runs along the anterior–posterior axis (49). The overlap between the highly interconnected regions making up the backbone and the cortical areas that are highly traveled by slow waves is striking. This suggests that a functional role of the connectional backbone revealed by DSI may be to mediate the propagation of sleep slow waves between distinct cortical areas. Perhaps the repeated occurrence of downstates in this connectivity backbone (49) may contribute to the disruption of information transmission within the cerebral cortex that accompanies deep stages of NREM sleep (50). The areas showing maximal involvement in slow waves also show considerable overlap with the default network, consistent with recently published event-related fMRI data, triggered on the negative peak of spontaneous slow waves (15). This functional network was first identified as a set of brain regions active during rest that undergo task-dependent decreases in activity as measured by fMRI and PET (51, 52). Subsequent observations revealed that this network exhibits correlations in spontaneous BOLD signal (53, 54) that persist into sleep (55). The overlap between default network structures and the areas maximally involved by sleep slow waves is intriguing, considering that this network has been implicated in monitoring the external environment, social cognition, and memory (51, 56) and that it can be altered by sleep deprivation (57).

Methods

Subjects and Recordings. Six male subjects (ages 24–35, 3 right-handed) participated in the spontaneous sleep portion of the study. All participants gave written informed consent, and the experiment was approved by the University of Wisconsin Human Subjects Committee. HD-EEG (Geodesic, 256 electrodes) was recorded across an entire night of sleep. EEG recordings were sampled at 500 Hz. Noisy channels were replaced with splines interpolations using NetStation software (EGI). The EEG was visually scored for sleep stages (20-s epochs) on the basis of standard criteria (58). Artifacts were rejected on the basis of an automated threshold-crossing detection algorithm. Subjects who had TMS also had T1 weighted MRIs (resolution 0.5 mm) acquired with a 3T GE Signa scanner.

Transcranial Magnetic Stimulation Data. The data for the TMS-evoked slow waves were collected from a single male subject (age 21) as part of a previous study (16). In this prior study, we used a 60-channel TMS-compatible EEG net (Nexstim) to record the response to TMS in 15 sleeping males (ages 21–36). Stimulation of the sensorimotor cortex at 65% of maximal stimulator output
was restricted to 2447 cortical voxels (7 mm3) that were each assigned to a gyrus based on the Montreal Neurological Institute probabilistic atlas. All inverse modeling was performed using GeOSource (EGI). Relative current was determined by dividing the inverse model of each slow wave by the average inverse model of several (average = 4.5) seconds of quiet waking data from the same subject during the same recording. For TMS, the baseline period was stage 2 sleep dominated by low-voltage fast activity; there were no spontaneous slow waves, 1. Steriade M, Nunez A, Aizik M (1993) A novel slow (<1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. J Neurosci 13(8):3252–3265.


