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Human Rapid Eye Movement Sleep Shows Local Increases in Low-Frequency Oscillations and Global Decreases in High-Frequency Oscillations Compared to Resting Wakefulness

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Title: Human rapid eye movement sleep shows local increases in low-frequency oscillations and global decreases in high-frequency oscillations compared to resting wakefulness

Abbreviated title: Regional low-frequency activity in human REM sleep

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Abstract

It is often assumed that during rapid eye-movement (REM) sleep the cerebral cortex homogenously shows electroencephalogram activity highly similar to wakefulness. However, to date no studies have compared neural oscillatory activity in human REM sleep to resting wakefulness with high spatial sampling. In the current study, we evaluated high-resolution topographical changes in neural oscillatory power between both early and late naturalistic REM sleep and resting wakefulness in adult humans. All-night recordings with 256-channel high-density electroencephalography (hd-EEG) were collected in healthy volunteers (N=12). Topographic analysis revealed that, compared to wake, both the first and last cycle of REM sleep were associated with increased low-frequency oscillations in local central and occipital regions. In contrast, high frequency activity in both alpha and beta bands (8-20 Hz) was globally decreased during both early and late REM sleep cycles compared to wakefulness. No significant differences in topographic power in any frequency band were observed between REM sleep cycles occurring early and late in the night. We replicated these findings in an independent dataset (N=33). Together our findings show that human REM sleep shows consistent topographical changes in oscillatory power across both early and late sleep cycles compared to resting wakefulness.

64 **Significance statement**

65 In this work we present the first high-resolution topographical study of changes in neural
66 oscillatory power between rapid eye movement (REM) sleep and wakefulness in healthy adult
67 humans. Our results show that REM sleep is characterized by globally reduced high-frequency
68 power as well as increased low-frequency oscillations in local regions of the cerebral cortex,
69 including primary sensory, motor and visual cortices. Our findings are consistent with a recent
70 study using laminar recordings rodents, which found that local slow waves occur during REM
71 sleep in middle/superficial layers (layers 3 and 4) of primary visual, sensory and motor areas.
72 Local low-frequency oscillations in primary sensory and motor cortices could be a potential
73 mechanism for disconnection from the external environment during REM sleep.

74 **Introduction**

75

76 Since its discovery in the 1950s (Aserinsky and Kleitman, 1953), rapid eye movement (REM)
77 sleep has been a source of intrigue for its "paradoxical" similarity with the waking state. As
78 during non-rapid eye movement (NREM) sleep, during REM sleep individuals are in a state of
79 quiescence and remain relatively disconnected from the external environment, as demonstrated
80 by strongly attenuated responsiveness to external stimuli. However, in contrast to NREM, in
81 which the brain shows reduced global metabolism (Braun et al., 1997), prominent EEG slow
82 waves, and widespread bistability of cortical membrane potentials (Steriade et al., 2001), during
83 REM sleep the cortex resumes wake-like global activity levels, primarily caused by neuronal
84 activation through brainstem cholinergic projections (Velazquez-Moctezuma et al., 1991).
85 During REM sleep, neurons fire with a similar overall intensity and desynchronized pattern
86 typical of wakefulness, accompanied by similar global levels of blood flow and metabolic
87 activity (Buchsbaum et al., 1989). Visually the scalp electroencephalogram (EEG) of REM sleep,
88 as visualized in sleep polysomnography, appears similar to wake, exhibiting low-voltage, high
89 frequency activity.

90 While it is often stated that neural oscillatory activity during REM sleep is homogenously
91 wake-like, REM sleep notably also includes lower frequency waveforms, such as "sawtooth"
92 waves (2-5 Hz waves with a serrated or sawtooth appearance) (Sato et al., 1997). Furthermore,
93 recent work has measured brain activity in local regions of cortex during REM sleep using
94 laminar recordings in rodents and found that slow waves, a hallmark of NREM sleep, also occur
95 during REM sleep in localized cortical regions and layers. Specifically, slow waves were
96 observed in primary sensory and motor areas (V1, S1 and M1), but not in secondary visual and

97 motor areas (V2 and M2) or retrosplenial cortex (Funk et al., 2016). Furthermore, this slow wave
98 activity occurred mainly in layer 3 and layer 4, the latter being the main target of relay thalamic
99 inputs to the cortex. As slow waves during NREM sleep are associated with sensory
100 disconnection and higher arousal thresholds (Neckelmann and Ursin, 1993; Ermis et al., 2010),
101 the authors suggested that slow waves in middle/superficial cortical layers of primary cortical
102 regions could partly account for the sensory disconnection that occurs during REM sleep despite
103 the global wake-like activation of the cortex.

104 The current study had three primary aims. The first aim was to examine narrow-band changes
105 in topographical EEG patterns in naturalistic REM sleep compared to wakefulness in healthy
106 adult humans with high spatial resolution, which, to our knowledge, has not yet been
107 investigated. The second aim was to contrast spatially localized topographical changes in
108 oscillatory power between REM sleep cycles occurring early and late in the night, in order to test
109 whether neural activation patterns in REM sleep show differences across sleep cycles. Finally,
110 following the results of Funk et al. (2016), the third aim was to examine the spatial distribution
111 of changes in low-frequency oscillations during REM sleep compared to resting wakefulness
112 both on the scalp and on the cortical surface in humans. We examined EEG topographical
113 changes during both the first and last cycle of REM sleep in order to compare REM sleep cycles
114 with the largest temporal interval (and highest *a priori* potential to show differences). We used
115 high-density electroencephalography (hd-EEG; 256 channels) coupled with registration to
116 individual cortical anatomy assessed with magnetic resonance imaging (MRI), as this method
117 enables high temporal and spatial resolution and allows for analysis of neural oscillatory activity
118 on the cortical surface.
119

Materials and methods

Participants. Twelve participants (6 females, age = 42 ± 12 (mean ± SD), range 27-59) were randomly selected from a healthy control group participating in a larger sleep research study being conducted at the University of Wisconsin – Madison. Signed informed consent was obtained from all participants before the experiment, and ethical approval for the study was obtained from the University of Wisconsin – Madison Institutional Review Board. All participants were free of significant neurological conditions as well as sleep-related breathing or movement disorders as verified by polysomnography. Specifically, all participants had an Apnea–Hypopnea Index (AHI) less than 10 events per hour and a Periodic Limb Movement Arousal index during sleep (PLMSAI) with less than 15 events per hour of sleep.

Procedure. Participants completed an all-night high-density electroencephalography (hd-EEG) recording with simultaneous sleep polysomnography (PSG). Participants arrived at the sleep laboratory between 18:00 and 20:00. Hd-EEG and PSG setup lasted approximately 2 hours. Baseline wake recordings consisted of 6 minutes of quiet resting wakefulness with eyes closed in a seated upright posture. Participants were instructed to close their eyes, to refrain from moving and to relax while staying awake. Participants went to sleep within one hour of their most consistently reported bedtime and were allowed to sleep undisturbed until their usual self-reported waking time.

142 *Hd-EEG and PSG sleep recordings.* Sleep recordings were made at the Wisconsin Institute for
143 Sleep and Consciousness (University of Wisconsin-Madison) sleep laboratory. Hd-EEG
144 recordings were collected using a 256-channel dense array geodesic sensor net (GSN; Electrical
145 Geodesics, Inc., Eugene, Ore.) with a sampling rate of 500 Hz and online referencing to the
146 vertex (CZ). Simultaneous polysomnography (anterior tibialis, chin electromyogram (EMG),
147 electrocardiogram (EKG), pulse oximetry, pulse oximetry and respiratory inductance) was
148 recorded in parallel by Respironics Alice5 software (Philips Respironics, Murrysville, PA). Sleep
149 staging was performed offline using standard criteria of the American Academy of Sleep
150 Medicine (AASM) (Iber et al., 2007). From the all-night hd-EEG recordings, data segments
151 corresponding to the complete first and last cycle of REM sleep for each participant were
152 selected for further analysis. REM sleep epochs were further divided in tonic and phasic epochs,
153 with phasic REM sleep visually classified by a trained technician as any epochs that contained
154 rapid eye movements and/or myoclonic twitches.
155
156 *Hd-EEG processing.* Hd-EEG data analysis was conducted with MATLAB (Mathworks Inc.,
157 Natick, MA, USA) using the EEGLAB v13 toolbox (Delorme and Makeig, 2004) and custom
158 scripts. EEG data were bandpass filtered from 1 to 30 Hz using a two-way least-squares FIR
159 filter. Data segments and channels containing artifactual activity were visually identified and
160 removed. Consistent with previous studies using 256-channel GSN sensor arrays, electrodes on
161 the face and outer ring of the sensor net were eliminated entirely for all participants due to
162 excessive artifacts, yielding a final scalp montage of 185 channels (e.g., Castelnovo et al., 2016).
163 EEG data were denoised using the Extended Infomax ICA algorithm (Lee et al., 1999). ICA
164 components with specific activity patterns and component maps characteristic of artifactual

activity (ocular, cardiographic and myogenic) were visually identified and removed (Jung et al., 2000). Finally, bad channels were interpolated using spherical splines and EEG signals were referenced to the average of all electrodes.

Hd-EEG spectral analysis. Spectral power density was computed using Welch's modified periodogram method (*pwelch* function in Matlab) in 2-s Hamming windows (50% overlap) to decompose EEG time series signals into frequency bands of interest. We analyzed average power spectral density (PSD) in the delta (1-4 Hz), theta (4-7 Hz), alpha (8-12 Hz) and beta (12-20 Hz) frequency bands. Sawtooth waves were visually detected and met the criteria established in Sato et al. (1997): 1) frequency between 2 and 5 Hz, 2) amplitude between 20 and 100 μV, and 3) three or more consecutive waves. We performed a follow-up analysis in which we evaluated whether there was a region-specific correlation between pre-REM delta power and REM delta power to examine whether regions that showed relatively high delta during NREM preceding REM sleep also showed relatively high delta during REM sleep. To conduct this analysis, we first extracted the last 5 minutes of NREM sleep before REM sleep onset. Then, for each REM and NREM sleep data segment separately, we then computed the z-score normalized delta power across the scalp and calculated the Pearson correlation coefficient across all participants at each channel.

MRI acquisition. High-resolution T1-weighted anatomical scans were acquired on a GE 3.0 Tesla MRI scanner prior to the overnight sleep recording (BRAVO; TR = 6.70 ms; TE = 2.93 ms; TI = 450 ms; flip angle = 12°; FOV = 256 mm; acquisition voxel size = 1×1×1 mm).

188 *Source localization.* Source modeling was performed using Brainstorm software (Tadel et al.,
189 2011) using cortical reconstructions of individual T1 MRI scans processed using the FreeSurfer
190 pipeline (Fischl et al., 1999; Fischl et al., 2004; Han et al., 2006; Jovicich et al., 2006; Fischl,
191 2012). A symmetric Boundary Element Model (BEM) of the head having three realistic layers
192 (scalp, inner skull, outer skull) (Kybic et al., 2005; Gramfort et al., 2010) and a standard
193 coregistered set of electrode positions were used to construct the forward model. The inverse
194 matrix was computed using the Minimum Norm with sources constrained to be perpendicular to
195 the cortical surface. Spectral power density was computed in source space using Welch's
196 modified periodogram method in 2-s Hamming windows (50% overlap). From the source PSD,
197 we extracted the magnitude of the complex PSD for further analysis. For group-level whole-
198 brain source analysis, the magnitude of the source PSD was then smoothed at the individual level
199 using a 5 mm full width half max (FWHM) kernel and normalized to the anatomical Montreal
200 Neurological Institute (MNI) atlas.
201
202 *Statistical analysis.* Statistical comparisons for sensor and source topographical analysis were
203 made within-subjects and used two-sided paired *t*-tests between behavioral states. Group level
204 analyses on average power values were performed separately for each frequency band. At the
205 scalp level, we corrected for multiple comparisons using a nonparametric cluster based
206 permutation test (statistical nonparametric mapping (SNPM)) (Nichols and Holmes, 2002), with
207 a cluster forming threshold of t=3.12, corresponding to an uncorrected alpha level of p=0.01.
208 Statistics on cortical sources were computed using the GLM framework implemented in SPM12
209 (Wellcome Trust Department of Imaging Neuroscience, University College London). Whole-
210 cortex analyses were conducted, correcting for multiple comparisons using topological cluster

false-discovery rate (FDR) on the cortical surface. Cluster-size tests were used to test for significant regions using a cluster-forming threshold of p=0.01 and a cluster size threshold of p<0.05 (cluster corrected). Follow-up ROI analysis was performed to examine delta power in primary sensory and motor cortices (S1, M1 and V1). As we had a clear directional hypothesis, one-tailed tests were used for all ROI comparisons. S1, M1 and V1 ROIs were constructed in FreeSurfer using a template derived from histology of postmortem human brains and warped to individual anatomy based on cortical folding patterns (Zilles et al., 2002; Toga et al., 2006; Amunts et al., 2007; Fischl et al., 2007).

Replication study and comparison to NREM low-frequency oscillations. We repeated our topographical analysis in a separate retrospective group of participants in order to evaluate the replicability of results obtained from our primary analysis. As the dataset for Study 2 was larger and already contained preprocessed data for the whole night, we also used this dataset to perform a follow-up analysis comparing low-frequency oscillatory activity in REM and NREM sleep. Processed EEG/PSG sleep data from thirty-three participants (23 females, age = 49 ± 10 (mean ± SD), range 27-64) were randomly selected from a dataset of a healthy control group participating in a sleep research study being conducted at the University of Wisconsin – Madison. All participants had an Apnea–Hypopnea Index (AHI) with less than 10 events per hour and a Periodic Limb Movement Arousal index during sleep (PLMSAI) with less than 15 or more events per hour of sleep. Data acquisition procedures were identical to those described above and included all-night hd-EEG/PSG recordings and baseline waking recordings. EEG data were bandpass filtered from 0.5 to 100 Hz for wake recordings and 1 to 40 Hz for sleep recordings. We analyzed average power spectral density (PSD) in delta (1-4 Hz), theta (4-7 Hz), alpha (8-12

Hz) and beta (12.5-20 Hz) bands, correcting for multiple comparisons using SNPM (cluster forming threshold of t=3.49). EEG processing and spectral analyses were identical to the methods described above. As no anatomical data (MRI) was available for these participants, we did not analyze cortical sources.

Results

Global power analysis. Sleep architecture variables, including minutes in each sleep stage for individual participants as well as group mean values, are shown in Table 1. Global power (power spectral density averaged across all EEG sensors) in the delta band was significantly higher in the first cycle of REM sleep (p=0.04) and marginally higher in the last cycle of REM sleep (p=0.08) compared to wakefulness (Table 2, Figure 1a). No significant differences between states in global power in the theta band were observed ($p\geq$0.35), while decreased global alpha and beta were observed in both the first and last REM sleep cycle compared to wakefulness (all $p\leq$0.01; Table 2, Figure 1a). No significant differences in global power were observed between the first and last cycle of REM sleep (all $p\geq$0.09; Table 2, Figure 1a).

Hd-EEG topographical analysis. Visual inspection of hd-EEG timeseries revealed that oscillatory activity during REM sleep showed a mixture of both high-frequency, low amplitude desynchronized patterns as well as low-frequency activity (Figure 1b). Low-frequency activity was predominantly seen in central and occipital scalp regions. Visually, this low-frequency activity appeared as a mixture of different types of waves, including bursts of so-called

"sawtooth" waves as well as slower oscillations, which were at times superimposed with high-frequency activity. Topographic spectral analysis revealed that compared to wakefulness both the first and last cycle of REM sleep was associated with increased delta power in both a central (first cycle: p=0.003, cluster corrected; last cycle: p=0.003, cluster corrected) and occipital (first cycle: p=0.02, cluster corrected; last cycle: p=0.03, cluster corrected) electrode cluster (Figure 1c, left panel). No significant topographical differences in delta power were observed between the first and last cycle of REM sleep (Figure 1c, left panel, right column).

We performed a follow-up analysis comparing REM sleep delta power in the first and last segment of each REM cycle (1st vs. last 3rd). No significant clusters were observed (all $p\geq$0.19), suggesting that the increased low-frequency power in REM sleep was not attributable to a transitory period of NREM mixture at the beginning of the REM sleep cycle. We next analyzed differences in low-frequency oscillations during phasic and tonic REM sleep (see *Methods*). Because no differences were observed between the first and last REM sleep cycle, we collapsed phasic and tonic REM sleep across both the first and last cycle for this analysis. Compared to wakefulness, both phasic and tonic REM sleep had increased delta power in central (phasic: p=0.001, cluster corrected; tonic: p=0.004, cluster corrected) and occipital (phasic: p=0.03, cluster corrected; tonic: p=0.02, cluster corrected) regions (Figure 1c, right panel). No significant differences were observed between phasic and tonic REM sleep in low-frequency oscillations (Figure 1c, right panel).

To analyze differences in REM sleep slow oscillations between REM sleep and wakefulness independently of sawtooth waves, we evaluated differences in low-frequency oscillations between REM sleep and wake after removing REM sleep data segments containing sawtooth wave bursts in either of the central or occipital electrode clusters identified above (see *Methods:*

Hd-EEG spectral analysis). We again observed increased delta power in both central (first cycle: p=0.003, cluster corrected; last cycle: p=0.003, cluster corrected) and occipital (first cycle: p=0.02, cluster corrected; last cycle: p=0.03, cluster corrected) clusters. Additionally, we repeated our spectral analysis for slow oscillations ≤2 Hz and observed that REM sleep showed increased power in the same central and occipital regions for both the first cycle of REM (central cluster: p=0.002, occipital cluster: p=0.01 cluster corrected) and the last cycle of REM (central cluster: p=0.006, occipital cluster: p=0.03, cluster corrected) compared to wakefulness. Finally, we evaluated whether regions that showed relatively high delta power during REM sleep also showed relatively high delta power in the NREM sleep segment immediately preceding the REM cycle (see *Methods: Hd-EEG spectral analysis*). We found that normalized delta power across the scalp during REM sleep was significantly correlated with normalized delta power during NREM sleep, which peaked over similar central and occipital scalp regions (p<0.05; data not shown).

Decreases in alpha (first cycle: p=0.003, last cycle: p=0.003, cluster corrected) and beta (first cycle: p=0.006, last cycle: p=0.003, cluster corrected) band power were observed in REM sleep compared to wakefulness, but these differences were observed globally and did not localize to specific scalp regions (Figure 2, left and middle panels). No significant differences were observed between REM sleep and wakefulness in the theta band (Figure 2). No significant differences in topographic power were observed between the first and last cycle of REM sleep in theta, alpha or beta frequency bands (Figure 2, right panel). Alpha and beta band power was globally reduced in both phasic and tonic REM sleep compared to wakefulness (all p<0.01, cluster corrected).

303 *Cortical source analysis.* We followed-up the local topographical increase in delta power in
304 REM sleep by examining differences in low-frequency power at the cortical level. Compared to
305 wakefulness, both the first and last cycle of REM sleep were associated with increased source
306 delta power in a cluster including the right precentral gyrus, postcentral gyrus, posterior
307 cingulate cortex (PCC) and supramarginal gyrus (SMG) (p<0.0001, cluster corrected), a cluster
308 including the left precentral gyrus, postcentral gyrus, posterior cingulate cortex (PCC)
309 (p<0.0001, cluster corrected) and the parietal operculum (first cycle: p=0.02, last cycle: p=0.01,
310 cluster corrected; Figure 3a, Table 2). No significant differences in power were observed
311 between the first and last REM sleep cycle at the source level for any frequency band. We also
312 performed a follow-up region-of-interest (ROI) analysis on primary sensory and motor cortices
313 (S1, M1, V1) in both the first and last REM sleep cycle compared to wakefulness. Compared to
314 wakefulness, increased delta power was observed in S1 (first cycle: p=0.0005; last cycle:
315 p=0.001) and M1 (first cycle: p=0.0005; last cycle: p=0.0005) and marginally increased in V1
316 (first cycle: p=0.05; last cycle: p=0.10, all one-tailed two-sample t-tests). In contrast, delta power
317 was not increased in associative cortices of the inferior parietal lobule (IPL) (first cycle: p=0.83,
318 last cycle: p=0.85), anterior cingulate cortex (ACC) (first cycle: p=0.81, last cycle: p=0.86) or
319 orbitofrontal cortex (OFC) (first cycle: p=0.96, last cycle: p=0.97; Figure 3b).
320
321 *Replication study and comparison to NREM*. We next evaluated whether our topographic results
322 could be replicated in a separate larger group of control participants (N=33) from a different
323 sleep study conducted in our laboratory (see *Methods: Replication study*). We again observed
324 that compared to wakefulness REM sleep was associated with increased delta power in both
325 central (p=0.008, cluster corrected) and occipital regions (p=0.02, cluster corrected), as well as

increased theta in an occipital cluster (p=0.02, cluster corrected), while alpha (p<0.0001, cluster corrected) and beta (p=0.0003, cluster corrected) were globally decreased (Figure 4a). Together these data replicate our topographical results with an independent and larger sample.

Finally, we evaluated how delta power in REM sleep compared to delta power in NREM sleep. Replicating previous findings (e.g., (Riedner et al., 2007), we observed that delta power in NREM sleep was most prominent in prefrontal regions (Fig 4b). This contrasted with the topography of low-frequency oscillations in REM sleep, which, as noted above, showed peaks over middle central and occipital electrodes (Fig 4b). NREM sleep displayed globally increased delta power compared to REM sleep (p=0.02, cluster corrected; Fig 4b). On average REM sleep showed lower delta power as compared to NREM sleep in both the central and occipital electrode clusters, with REM sleep exhibiting 24.4% of NREM delta power in the central cluster and 26.5% of NREM delta power in the occipital cluster.

Discussion

To the best of our knowledge, the current study is the first to examine topographical EEG patterns in human REM sleep with high spatial resolution and the first to directly contrast spatially localized topographical changes in power in naturalistic REM sleep with wakefulness in healthy adults. Our results show that, compared to wake, both the first and last cycles and both phasic and tonic periods of human REM sleep are characterized by increased low-frequency oscillations in local central and occipital regions. In contrast, high frequency activity in both alpha and beta bands (8-20 Hz) was globally decreased during both early and late REM sleep

cycles compared to wakefulness. No significant differences in local topographic power in any frequency band were observed between REM sleep cycles occurring early and late in the night. Together these findings show that human REM sleep shows topographical changes in oscillatory power compared to resting wakefulness that are consistent across both early and late REM sleep cycles.

Our results for low-frequency oscillations are consistent with a recent study in rodents, which observed low-frequency activity during REM sleep in primary sensory and motor areas (V1, S1 and M1) (Funk et al., 2016). Our results are also consistent with existing human EEG studies, although as noted no previous study has evaluated neural oscillatory activity in human REM sleep with high spatial sampling. In one of the few studies directly comparing EEG power in REM sleep to wakefulness, increased power in the 1-6 Hz range in REM sleep was observed, though spatially localized effects were not observed in the 12 channel EEG montage (Corsi-Cabrera et al. (2006). Using slightly improved spatial resolution with a 27-channel montage, Tinguely et al. (2006) observed maximum power in 1-6 Hz frequency bands in REM sleep, but local differences in absolute power were not evaluated across states. Another study compared REM sleep with other sleep stages at central electrodes (C3 and C4) and found a higher incidence of delta during REM sleep compared to stage 1 sleep and a lower incidence of delta activity during REM sleep compared to NREM sleep (Armitage, 1995).

Extracellular recordings have revealed that motor cortex is activated during REM sleep (Steriade and Hobson, 1976), and cortical responses to transcranial magnetic stimulation (TMS) administered on the motor cortex are preserved or even increased during REM sleep compared to wakefulness (Hess et al., 1987). Increased regional cerebral blood flow (rCBF) has also been observed in motor cortices during REM sleep in response to learning (Laureys et al., 2001).

Similarly, functional neuroimaging (PET and rCBF) studies have also found that visual cortices are active during REM sleep, though the evidence for activation of primary visual cortex is mixed (Maquet et al., 1990; Madsen et al., 1991; Braun et al., 1997). Our results do not contradict these findings. Indeed, it is possible that activation of these areas could coexist with local increases in low-frequency oscillations, particularly if this activity is layer-specific, as it is in rodents (Funk et al., 2016).

Intracranial recordings have shown that slow waves during NREM sleep are often spatially restricted, involving only a subset of cortical regions (Murphy et al., 2009; Nir et al., 2011). Furthermore, local slow wave activity has also been observed during waking in both humans and rodents (Vyazovskiy et al., 2011; Bernardi et al., 2015). The current findings are consistent with the local nature of low-frequency oscillations observed in other behavioral states. The mechanisms for the generation of local low-frequency oscillations during REM sleep, however, are not currently understood. Intriguingly, acetylcholine has been found to specifically hyperpolarize layer 4 spiny neurons (Eggermann and Feldmeyer, 2009). If local low-frequency oscillations in primary sensory and primary motor cortices during REM sleep occur mostly in layer 4, as suggested by Funk et al. (2016), it is therefore possible that high levels of acetylcholine during REM sleep could facilitate bistability between ON and OFF periods in these regions. It is also possible that thalamic nuclei could contribute to bistable dynamics in these regions, as thalamic neurons entrain cortical slow waves during NREM sleep (David et al., 2013). While several studies have found that thalamic nuclei show tonic depolarization during REM sleep (e.g., (Hirsch et al., 1983), low-frequency activity has been unexpectedly observed in intracranial recordings of pulvinar nuclei during REM sleep (Magnin et al., 2004). Overall, more research will be needed to determine the thalamic, cortical and neuromodulatory mechanisms by

which local low-frequency oscillations are generated during REM sleep. Additionally, in future research it will be important to evaluate whether this activity is coupled to sleep homeostasis, as is slow wave activity during NREM (Borb and Achermann, 1999; Riedner et al., 2007). Our finding that the low-frequency activity during NREM sleep preceding REM sleep and during REM sleep are correlated may provide some preliminary evidence for regulation by similar homeostatic mechanisms, though further research is needed to address this important question.

As noted above, a potential functional implication of local low-frequency oscillations in primary sensory and motor cortices is that this activity could partly account for the sensory disconnection that occurs during REM sleep, which has remained a mystery (Nir and Tononi, 2010). At the current time a mechanistic role for local slow oscillations during REM sleep in sensory disconnection remains speculative. However, there is some evidence for a role of slow oscillations in sensory disconnection during NREM sleep. For instance, slow waves during NREM sleep are associated with higher arousal thresholds (Neckelmann and Ursin, 1993; Ermis et al., 2010). Furthermore, given that bistability between ON and OFF periods impairs cortical information transmission (Massimini et al., 2005; Pigorini et al., 2015), slow wave activity is a plausible mechanism for gating transmission of sensory information to the cortex, particularly when such activity occurs in primary sensory regions. However, an alternative interpretation is that low-frequency oscillations during REM sleep is the result rather than the cause of sensory disconnection, or fulfills another functional role entirely. Sensory disconnection is not always completely blocked during REM sleep and at times auditory and visual stimuli can be perceived, often though incorporation into dream imagery, even while individuals remain asleep (Nir and Tononi, 2010). An intriguing direction for future work would therefore be to directly investigate the role of local low-frequency oscillations in sensory disconnection during REM sleep by

testing the relationship between the presence of slow oscillations in primary sensory regions and the probability that sensory stimuli will be incorporated into ongoing oneiric experience.

In the current work our primary aim was to map narrow-band changes in topographical EEG patterns in naturalistic early and late REM sleep cycles compared to wakefulness. Our research team is currently following-up this finding of localized increases in low-frequency oscillations during REM sleep by examining the properties of these waves in detail, which will be important to understanding the nature of these waveforms in greater detail as well as any potential mechanistic role they may fulfill. Specifically, our research team (Bernardi et al., in prep) is currently characterizing in detail the properties of local low-frequency oscillations in both the central and occipital regions identified here during REM sleep, including the density, amplitude, duration, spatial extent and negative peaks of individual waves. In line with the remarks above regarding disconnection, in future research it will also be intriguing to investigate whether or how the specific properties of low-frequency oscillations during REM sleep might relate to sensory disconnection.

In summary, our findings show that human REM sleep shows consistent topographical changes in oscillatory power across both early and late sleep cycles compared to wakefulness, consisting of local increases in low-frequency oscillations in central and occipital regions and global decreases in high-frequency oscillations. A speculative hypothesis is that spatially restricted slow oscillations during REM sleep could partially account for the paradoxical nature of REM sleep. Namely, while low-frequency oscillations in primary regions could potentially reduce cortical transmission of bottom-up sensory information, contributing to disconnection (Funk et al., 2016), EEG activation in other cortical regions could facilitate the vivid internal

sensory experiences that frequently occur during this state in the form of dreams (Siclari et al., 2017).

443 **Table 1. Sleep architecture variables for individual participants and group means**

ID	1	2	3	4	5	6	7	8	9	10	11	12	MEAN		STD
TSP (min)	391.9	481.9	376.1	486.5	421.9	512.2	428.4	451.6	490.6	470.1	547.4	553.4	467.7	±	56.3
TST (min)	335.2	413.6	352.7	442.2	374.9	427.0	374.5	419.2	364.5	312.0	486.5	500.5	69.5	±	60.6
WASO (min)	57.0	68.5	23.5	44.5	47.0	85.5	54.0	32.5	126.5	158.5	61.0	53.0	85.4	±	40.3
SE	85.5	85.8	93.8	90.9	88.9	83.4	87.4	92.8	74.3	66.4	88.9	90.4	20.5	±	8.3
N1 (min)	15.0	20.0	22.0	9.0	13.5	21.0	17.0	31.5	11.0	17.5	29.5	31.5	19.9	±	7.7
N1 (%)	4.5	4.8	6.2	2.0	3.6	4.9	4.5	7.5	3.0	5.6	6.1	6.3	4.9	±	1.5
N2 (min)	202.0	235.5	172.0	204.0	191.0	185.0	226.0	255.0	112.5	114.0	225.5	198.5	193.4	±	44.0
N2 (%)	60.3	56.9	48.8	46.1	50.9	43.3	60.4	60.8	30.9	36.5	46.4	39.7	48.4	±	9.9
N3 (min)	58.5	85.0	94.5	105.0	71.0	93.0	69.0	32.5	107.0	74.5	73.5	137.5	83.4	±	26.8
N3 (%)	17.5	20.6	26.8	23.7	18.9	21.8	18.4	7.8	29.4	23.9	15.1	27.5	20.9	±	6.0
REM (min)	57.5	71.0	62.0	122.0	97.5	125.5	60.5	98.0	130.5	103.5	155.5	131.0	101.2	±	32.7
REM first cycle (min)	12.5	15.8	34.1	5.9	22.7	11.4	27.7	7.8	11.7	10.6	13.1	22.8	16.3	±	8.6
REM last cycle (min)	10.5	22.6	7.4	7.3	41.0	36.9	33.2	27.8	6.1	38.6	7.9	28.1	22.3	±	13.7
REM (%)	17.2	17.2	17.6	27.6	26.0	29.4	16.2	23.4	35.8	33.2	32.0	26.2	25.1	±	6.9
REML (min)	160.7	113.0	100.4	75.2	13.0	107.4	161.6	71.1	58.1	68.8	101.0	78.1	92.4	±	41.8
AI	9.3	15.7	9.0	7.9	6.2	6.9	9.3	14.3	6.3	4.0	7.9	8.9	8.8	±	3.3

444

445

446 **Table 2. Global power for the first and last cycle of REM sleep and wakefulness across all frequency bands**

447

	Mean (SD)			*p*-value			
Frequency Band	**REMf**	**REMl**	**Wake**	**REMf > wake**	**REMl > wake**	**REMf > REMl**	**F-value (p)**
Delta [1-4 Hz]	2.75 (1.02)	2.61 (0.91)	2.11 (0.98)	0.04*	0.08	0.41	4.20 (0.03)*
Theta [4-7 Hz]	1.41 (0.55)	1.51 (0.71)	1.61 (1.08)	0.39	0.66	0.35	0.78 (0.39)
Alpha [8-12 Hz]	0.75 (0.07)	0.67 (0.07)	5.12 (1.23)	0.004*	0.004*	0.12	12.91 (0.004)*
Beta [12-20 Hz]	0.27 (0.19)	0.21 (0.10)	0.58 (0.37)	0.01*	0.003*	0.09	9.23 (0.01)*

448 *Note*: * denotes significant differences between conditions.

449

Table 3. Source delta power [1-4 Hz] first and last cycle REM contrasted with wakefulness

Region	*p*-value cluster	Peak MNI			*Z*-value
		X	Y	Z	
First cycle REM > wake					
R postcentral gyrus, R precentral gyrus, R SMG, R PCC	*p*<0.0001	45	-23	39	4.36
L postcentral gyrus, L precentral gyrus, L PCC	*p*<0.0001	-9	-25	44	3.77
R parietal operculum	*p*=0.02	45	-21	18	3.67
Last cycle REM > wake					
R postcentral gyrus, R precentral gyrus, R SMG, R PCC	*p*<0.0001	38	-20	46	3.79
L postcentral gyrus, L precentral gyrus, L SMG, L PCC, L SMC	*p*<0.0001	-12	-20	40	3.58
L parietal operculum	*p*=0.01	50	-21	19	3.53

Note: All clusters significant at $p < 0.05$, FDR cluster corrected (height threshold, $p < 0.01$). SMG=supramarginal gyrus; PCC=posterior cingulate cortex; SMC=supplementary motor cortex.

457 **Figure Legends**

458

459 **Figure 1. (a)** Global PSD for the first and last cycle of REM sleep and quiet wakefulness. Group
460 average global power spectra (average of all 185 EEG sensors) separated by state (wake (black
461 line), the first cycle of REM sleep (orange line) and the last cycle of REM sleep (red line)).
462 Asterisks indicate significant differences between conditions (p<0.05; repeated measures
463 ANOVA) for delta (1-4 Hz), theta (4-7 Hz), alpha (8-12 Hz) and beta (12-20 Hz) frequency
464 bands. **(b)** Representative EEG data across scalp regions for eyes-closed (EC) wakefulness and
465 REM sleep (central region: Fcz, CpZ; occipital region: OZ; other regions: frontotemporal (FT9),
466 parietal (P3, Po7). **(c)** Topography of REM sleep delta power. Left panel: Topographical
467 differences in delta power [1-4 Hz] in the first and last cycle of REM sleep contrasted with wake.
468 Right panel: Topographical differences in delta power [1-4 Hz] in phasic and tonic REM sleep
469 contrasted with wake. Bottom row: t-values for all electrodes (2-tailed, paired t-test); black dots
470 indicate significant differences between states (p<0.05) after correcting for multiple comparisons
471 with statistical non-parametric mapping (SNPM) cluster size test.

472

473 **Figure 2.** EEG topography of REM sleep contrasted with quiet wakefulness in theta, alpha and
474 beta frequency bands. Topographical differences in oscillatory power between the first cycle of
475 REM sleep contrasted with wake (left panel), the last cycle of REM sleep contrasted with wake
476 (central panel), and the first cycle of REM sleep contrasted with the last cycle of REM sleep
477 (right panel) for theta (4-7 Hz), alpha (8-12 Hz) and beta (12-20 Hz) frequency bands. t-values
478 are plotted for all electrodes (2-tailed, paired t-test); white dots indicate significant differences

between states (p<0.05) after correcting for multiple comparisons with statistical non-parametric mapping (SNPM).

Figure 3. (a) Source topography of increased delta power [1-4 H] in the first (top row) and last (bottom row) cycle of REM sleep contrasted with wake. *T*-values are plotted for all vertices (2-tailed, paired *t*-test) exhibiting significant differences between states (p<0.05) after correcting for multiple comparisons using topological false discovery rate (FDR) cluster correction (height threshold: p<0.01). **(b)** Compared to wake, increased delta power was observed in primary sensory (S1), primary motor (M1) and primary visual (V1) cortices, but was not significantly increased in inferior parietal lobule (IPL), anterior cingulate cortex (ACC) or orbitofrontal cortex (OFC) associative regions. The bottom and top of the boxes show the 25th and 75th percentiles (the lower and upper quartiles), respectively; the inner band shows the median; and the whiskers show the upper and lower quartiles ±1.5 × the interquartile range (IQR). Asterisks indicate significant differences between states (* = p<0.05; ** = p<0.01; *** = p<0.001; one-tailed paired *t*-test).

Figure 4. (a) Replication study. Scalp topography of differences in oscillatory power between REM sleep contrasted with wakefulness in a replication sample (N=33) for delta (1-4 Hz), theta (4-7 Hz), alpha (8-12 Hz) and beta (12-20 Hz) frequency bands. Black dots indicate significantly increased power in REM sleep compared to wakefulness; white dots indicate significant decreases in REM sleep compared to wakefulness (SNPM cluster corrected p<0.05). **(b)** Comparison of REM and NREM delta power. Scalp topography of delta power shown separately for NREM sleep, REM sleep and NREM > REM sleep as well as *t*-values for NREM > REM

sleep delta power. The minimum and maximum values for each topographic map are plotted with the corresponding numeric range for the color scale shown in the upper left. Black dots indicate significantly increased power in REM sleep compared to wakefulness (SNPM cluster corrected $p<0.05$).

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