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Sharply contoured theta waves are the human correlate of ponto-geniculo-occipital waves in the primary visual cortex

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HIGHLIGHTS

- We investigate the presence of ponto-geniculo-occipital (PGO) waves in the human primary visual cortex using stereo-EEG.
- We found sharply contoured theta waves in the visual cortex during phasic versus tonic REM sleep.
- This work suggests that sharply contoured theta waves are the human correlate of PGO waves.

ABSTRACT

Objective: Ponto-geniculo-occipital (PGO) waves occurring along the visual axis are one of the hallmarks of REM sleep in experimental animals. In humans, direct evidence is scarce. There is no systematic study of PGO waves in the primary visual cortex.
Methods: Eleven epilepsy patients undergoing combined intracranial EEG/polysomnography had 71 channels recording physiological EEG activity from various cortical areas; seven channels recorded from the primary visual cortex. An equal number of 4-s phasic and tonic REM segments were selected. Patterns consistent with PGO waves were visually analyzed in both states in the primary visual cortex. Spectral analysis compared activity in the primary visual cortex with the remaining cortical areas.
Results: Visual inspection revealed an increase in sharply contoured theta waves (duration: 150–250 ms) in the primary visual cortex during phasic as compared to tonic REM sleep. Spectral analysis confirmed a 32% increase in mean absolute theta power during phasic versus tonic REM sleep (p corrected = 0.014).
Conclusion: No classical PGO waves, but sharply contoured theta waves were found in the human primary visual cortex during phasic as opposed to tonic REM sleep.
Significance: This research suggests that sharply contoured theta waves are the human correlate of PGO waves described in experimental animal models.

1. Introduction

Ponto-geniculo-occipital (PGO) waves are the hallmark of REM sleep in certain animal species (Siegel, 2011). In the cat, PGO waves have been recorded from the pons (Jouvet et al., 1959), the lateral geniculate nucleus of the thalamus (Mikiten et al., 1961), and the occipital cortex (Mouret et al., 1963), explaining the nomenclature now used. These waves are biphasic sharp field potentials occurring as either singlets during the transition from slow wave sleep to REM sleep (type 1) or in clusters of 3–5 spikes during REM sleep showing a high correspondence to rapid eye movements (type II) (Datta, 1997; Callaway et al., 1987; Nelson et al., 1983). Within the occipital cortex, PGO waves reach their highest amplitude in regions receiving projections from the lateral geniculate nucleus, such as the

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primary visual and visual association cortices (Datta, 1997; Callaway et al., 1987). PGO waves have been attributed a role in dreaming (Hobson and McCarley, 1977; Hobson and Pace-Schott, 2002), brain maturation (Davenne and Adrien, 1984), sensorimotor integration (Callaway et al., 1987; Hobson, 2009), and memory processing (Datta, 2000; Datta et al., 2004).

Studies on PGO waves in humans have been limited mainly to indirect methods of measurement such as functional MRI, PET, MEG and scalp EEG. Functional studies demonstrated activations in the pontine tegmentum, the ventroposterior region of the thalamus, the lateral geniculate nuclei, and the visual cortices, which were thought to be indicative of PGO waves, at the time of rapid eye movements (McCarley et al., 1983; Peigneux et al., 2001; Ioannides et al., 2004; Wehrle et al., 2005; Miyauchi et al., 2009). In addition, scalp EEG studies investigated differences between phasic and tonic REM sleep, demonstrating a decrease in alpha, beta, and theta power during phasic REM sleep, whereas there was an increase in gamma activity over the occipital areas during phasic REM sleep (Waterman et al., 1993; Cantero et al., 1999, 2000; Cantero and Atienza, 2000; Jouny et al., 2000).

In contrast to recordings from scalp EEG in which the signal is attenuated and information from the primary visual cortex is poorly represented, intracranial EEG allows direct recording from the primary visual cortex and comparing EEG signals generated in this region with other cortical areas. Another advantage of intracranial EEG is that artifacts due to rapid eye movements (Waterman et al., 1992) are negligible. Two studies and one case report using intracranial EEG have provided direct insight into the presence of these waves in humans. PGO-like waves were described in the pons (Lim et al., 2007) and subthalamic nucleus (Fernandez-Mendoza et al., 2009) of Parkinson's disease patients, who were implanted for deep brain stimulation. Salzarulo et al. (1975) reported anecdotally, the case of a patient with intractable focal epilepsy in whom PGO activity was suspected in the primary visual cortex. The authors emphasized the difficulty in confirming that they had found PGO waves due to the highly complex background activity of the primary visual cortex in humans compared to that of the cat.

Given the importance of PGO waves for fundamental neurodevelopmental and neurocognitive functions, such as brain maturation (Davenne and Adrien, 1984), sensorimotor integration (Callaway et al., 1987; Hobson, 2009), and memory processing (Datta, 2000; Datta et al., 2004), as well as the limited direct evidence of the human correlate of PGO waves (Salzarulo et al., 1975; Lim et al., 2007; Fernandez-Mendoza et al., 2009), we aimed to investigate systematically the presence of PGO-like activity in the primary visual cortex through intracranial EEG recordings in a series of epileptic patients who underwent presurgical epilepsy evaluation. Patients with refractory focal epilepsies are the only human subjects in whom extensive intracranial cortical EEG studies are undertaken. For this reason, they represent, as a group, a privileged access not only to pathological but also to normal brain neurophysiology. We visually inspected any presumed PGO patterns found in the primary visual cortex and subsequently quantified our findings via spectral analysis. In the one existing case report in the human primary visual cortex, PGO activity was suggested to be mainly in the theta frequency band (Salzarulo et al., 1975). We hypothesized that there would be a greater presence of theta band activity during phasic versus tonic REM sleep in the primary visual cortex compared to all other combined cortical areas, therefore advocating that this activity should be considered PGO activity.

2. Methods

2.1. Patient selection

The subjects were prospectively recruited from consecutive patients with refractory focal epilepsy who underwent continuous scalp and intracranial EEG recordings (7–21 days) including one full night of polysomnography (PSG) at the Montreal Neurological Institute and Hospital (MNI) between October 2013 and February 2015. Selection criteria required patients to have: (i) presence of intracranial EEG channels with only physiological activity located in either the primary visual cortex or any other cortical area (for definition of EEG channels with non-epileptic physiological EEG activity see Section 2.3. below); (ii) absence of generalized seizures for 12 h before or during the recording, or symptomatic partial seizures 6 h before or during the recording (Frauscher et al., 2015a,b; and (iii) a minimum of 15 rapid eye movement bursts throughout their pooled REM time.

Five of 10 identified patients had channels recording only physiological activity from the mesial occipital lobe in the close vicinity to the calcarine fissure (primary visual cortex). In order to increase the number of channels recording non-epileptic physiological activity from the primary visual cortex, we added one patient from our institution who fulfilled all the criteria except the presence of scalp EEG (sleep was scored using intracranial EEG, electrooculography and electromyography of the mentalis muscle). Clinical and demographic data are provided in Supplementary Table S1, MNI positions of the channels are given in Supplementary Table S2. This study was approved by the Research Ethics Board of the MNI. All patients signed a written informed consent.

2.2. Depth electrode implantation and intracranial EEG recording

All patients had multi-contact intracerebral depth electrodes implanted stereotactically through an oblique or orthogonal approach (range, 7–16) using an image-guided system. The most lateral contacts of the electrodes were in the neocortex, whereas the mesial contacts targeted the mesial-most part of the explored lobe. All analyses were done using bipolar montages from one contact to the neighboring contact.

The precise location of electrode contacts were determined by pre-implantation MRI co-registered with peri-implantation CT using Statistical Parametric Mapping 8 software for eight patients or peri-implantation MRI for three patients. Electrode implantation and positioning was tailored according to the clinical hypothesis for each patient (see Supplementary Table S1). Fig. 1 provides the localization of the seven evaluated electrode channels in or close to the primary visual cortex (one of the 6 patients had two channels in the primary visual cortex, one supra- and one infra-calcarine). Fig. 2 illustrates schematically the localization of all investigated electrode channels inside and outside the primary visual cortex (there was a total of 71 channels gathered from 11 patients).

Sleep staging was performed with scalp EEG recordings obtained through subdermal thin wire electrodes (Ives, 2005) placed during electrode implantation at F3, F4, Fz, C3, C4, Cz and P3, P4, Pz. During sleep recording, additional electrooculography and electromyography electrodes of the mentalis muscle were used. To avoid the acute effects of electrode implantation on the cortex and effects of anaesthetic drugs, sleep recordings were performed at least 72 hours after the insertion procedure.

The EEGs were recorded using the Harmonie EEG system (Stellate, Montreal, Québec, Canada). For all patients, EEG signals used a low-pass filter of 500 Hz and were sampled at 2000 Hz.

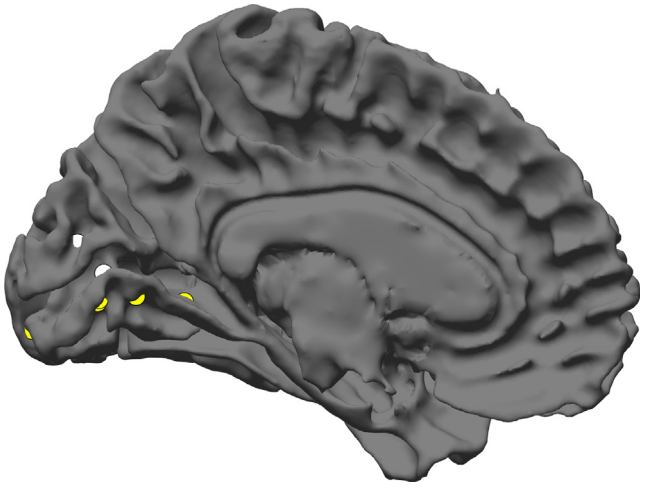

Fig. 1. Location of electrode channels recording non-epileptic physiological activity in or close to the primary visual cortex. The surface corresponds to the white/gray matter boundary of the left hemisphere of the symmetric ICBM 152 nonlinear atlas, version 2009c (Fonov et al., 2009). The dots in yellow correspond to channels in the left hemisphere, and the dots in white to channels in the right hemisphere represented here on the left one. Five S-EEG electrode channels are in the superior aspect of the lingual gyrus, and two channels in the inferior aspect of the cuneus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3. Selection of intracranial channels recording non-epileptic physiological activity

In order to analyze only physiological EEG activity, we selected and defined healthy channels as those that were not within the seizure-onset zone, with only very rare or no epileptic discharges, and without any slow wave anomalies or artifacts. Electrode channels revealed by MRI to be placed within lesions were also excluded, irrespective of the type of activity seen on the EEG recording. Two board certified electrophysiologists held a common scoring session in which healthy channels were selected for each patient. Additionally, we made sure that the patients selected with channels in the primary visual cortex had routine wake recordings showing an alpha rhythm, lambda waves, a clear reaction to eye opening and eye closure and a good response to photic stimulation. This further supports that the channels chosen for analysis were representative of the healthy primary visual cortex.

2.4. Visual scoring of sleep & assessment of PGO waves during phasic and tonic REM segments

Sleep was scored manually using scalp EEG (10 patients) or intracranial EEG (1 patient) in 30-second epochs by a board certified sleep expert (Berry et al., 2012). We chose to compare segments of phasic REM sleep to segments of tonic REM sleep because of the strict relationship found between REMs and PGO waves in the animal (Callaway et al., 1987; Nelson et al., 1983). Two authors selected bursts of rapid eye movements eight seconds in duration of which the middle 4 s were used for analysis; these were representative of phasic REM segments. All bursts were defined as those clearly standing out from the background, and the minimum number of segments required for each patient was 15. Marking of phasic REM segments stopped after 20 segments. We aimed at choosing an equal amount of phasic REM segments from each REM cycle of the night: For instance, if a patient had four REM cycles, we chose five phasic REM segments from each of the four REM cycles in order to reach the target number of 20. For analysis, each phasic REM segment that was marked had a control REM segment without rapid eye movements (tonic REM segment) that was marked using the same segment duration. The tonic REM segments were selected, if possible, in the same REM cycle as the phasic REM segment. The recordings of six patients showing seven healthy channels in the primary visual cortex were chosen for the visual scoring of any obvious pattern differences between phasic and tonic REM segments.

2.5. Spectral analysis of phasic and tonic REM segments

Channels recording non-epileptic physiological activity were run through a spectral analysis with a Fast Fourier Transform with epochs of 1.024 s using the software of the Harmonie EEG system. If several adjacent bipolar channels of an individual electrode recorded non-epileptic physiological activity from the same cortical area, we selected only the most mesial or most lateral bipolar channel for the analysis in order to minimize the correlation between measurements.

As we aimed at performing comparisons across subjects, we computed the absolute and relative power values of all bands for further statistical analyses. The frequency bands defined were Delta (0.3–4 Hz), Theta (4–8 Hz), Alpha (8–12 Hz), Beta (12–30 Hz), and Gamma (30–80 Hz).

2.6. Data analysis

To test our primary hypothesis that there is increased theta activity in the primary visual cortex during phasic REM compared to tonic REM sleep (likely reflecting PGO activity), we compared the difference in the absolute power between the primary visual cortex (7 channels) and all other cortical regions combined (71 channels of the same 6 patients) during this period. To make this comparison, the ratio in absolute power between phasic and tonic REM sleep in the theta frequency range was calculated, and a two sample T-test was performed to check if the mean difference

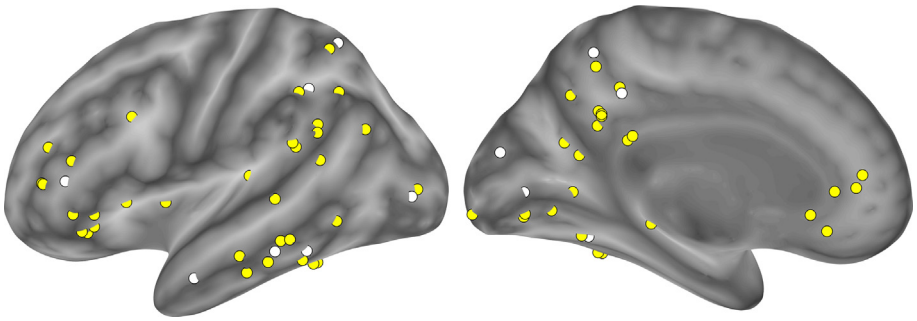

Fig. 2. Illustration of the S-EEG channels in the lateral (left) and mesial (right) view of the inflated white/gray matter surface of the symmetric ICBM 152 nonlinear atlas, version 2009c (Fonov et al., 2009). The dots in yellow correspond to channels in the left hemisphere, and the dots in white to channels in the right hemisphere represented here on the left one. The representation here is necessarily schematic given that the electrodes are intracerebral. Supplementary Table S2 provides the actual MNI coordinates of the channels. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

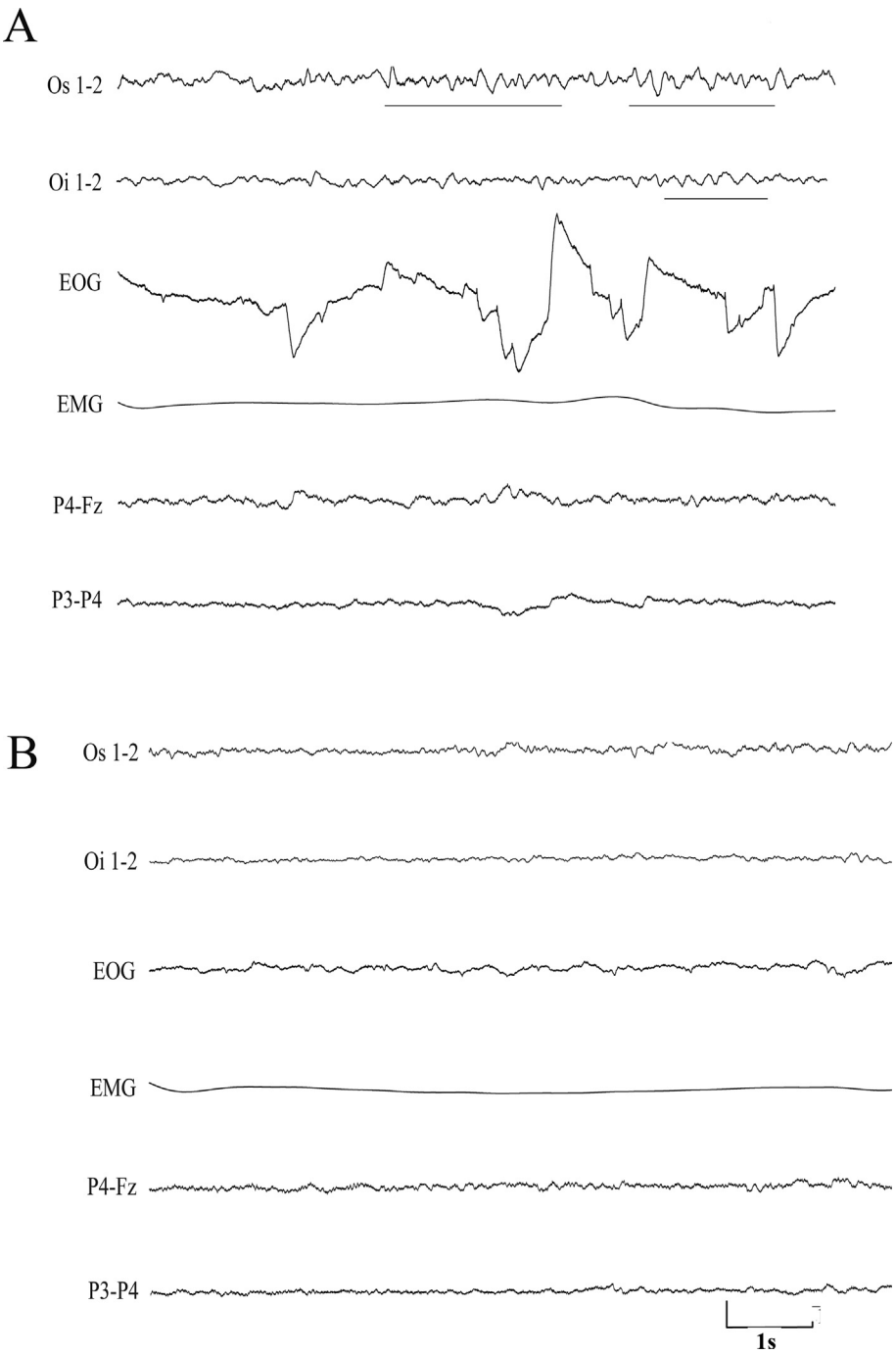

Fig. 3. A. EEG sample of the type of activity seen during most phasic REM periods. Theta transients presumably representing the correlate of human PGO waves are underlined; this activity occurs in the context of REM bursts. B. EEG sample representing what was commonly seen during tonic REM periods (Os & Oi set at 50 μV; EOG set at 15 μV; EMG set at 10 μV; P3-P4 and P4-Fz set at 7.50 μV). Electrode Os was inserted through the superior occipital lobe targeting the pericalcarine aspect of the cuneus; electrode Oi was inserted through the inferior occipital lobe targeting the pericalcarine aspect of the lingual gyrus.

in theta power in the primary visual cortex was different when compared to all other cortical regions.

In order to explore all the frequency bands and brain regions, including the channels from the other patients as well (total of 11 patients), we did a permutation-based hypothesis test to determine if the difference in the mean value of the relative energy content of the bands between the phasic and tonic periods was larger in some region than in the ensemble. We selected eight cortical regions with more than three channels (Fig. 2): lateral frontal (14 channels), mesial frontal (7 channels), lateral parietal (12 channels), mesial parietal (12 channels), lateral temporal (12 channels), basal temporal (3 channels), lateral occipital (4 channels), and mesial occipital (7 channels). P-values were corrected with the Bonferroni correction to account for 40 multiple comparisons (eight regions × five frequency bands).

3. Results

3.1. Visual detection of PGO waves

Six patients with 7 channels in or close to the primary visual cortex (Fig. 1) showed transients within the theta frequency band,

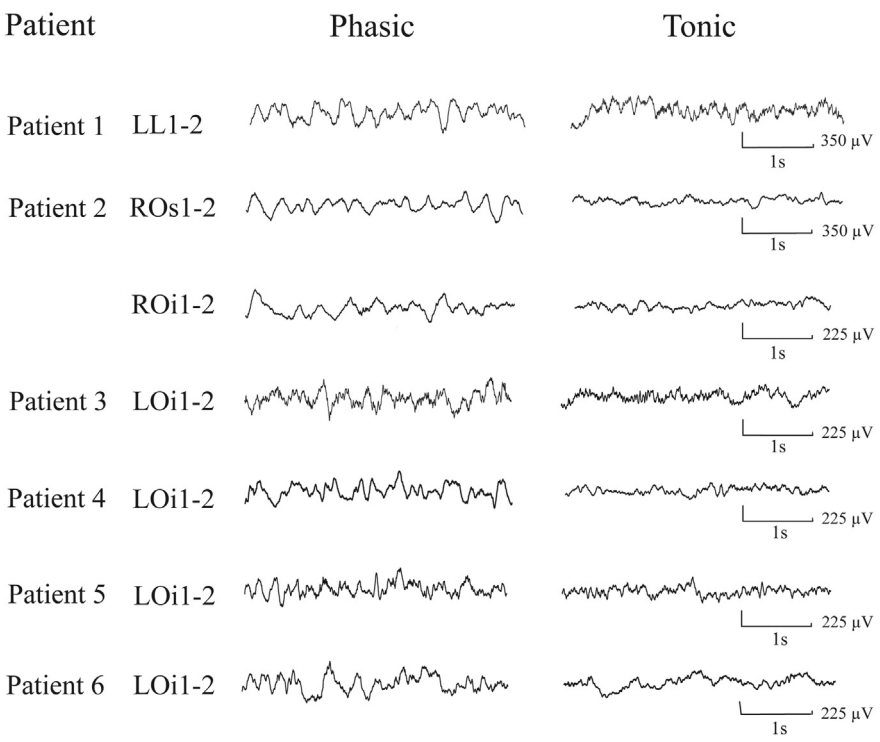

Fig. 4. Typical EEG activity contrasting phasic versus tonic REM sleep in the primary visual cortex of the six patients identified for this project. During phasic REM sleep, we observe theta transients with durations between 150 and 250 ms not seen during tonic REM sleep. No classical PGO waves were however identified. Electrode LL was inserted through the left inferior occipital lobe targeting the pericalcarine aspect of the lingual gyrus; electrode ROs was inserted through the right superior occipital lobe targeting the pericalcarine aspect of the cuneus; electrode ROi was inserted through the right inferior occipital lobe targeting the pericalcarine aspect of the lingual gyrus; electrode LOi was inserted through the left inferior occipital lobe targeting the pericalcarine aspect of the lingual gyrus.

more during phasic REM (Fig. 3A) than tonic REM sleep (Fig. 3B). This theta activity was sharply contoured and had a duration of 150–250 ms (Fig. 4).

3.2. Spectral analysis in the primary visual cortex versus all other cortical regions

Spectral analysis was performed in the six patients with seven intracranial depth EEG channels located in the primary visual cortex and compared to 33 intracranial depth EEG channels located in the other cortical regions, collectively. In Fig. 5, we compared the ratio of absolute energy in the theta band during phasic and tonic REM sleep in the primary visual cortex versus the remaining channels. In line with our primary hypothesis, we found a 32% increase in theta power between phasic and tonic REM sleep in the primary visual cortex. This increase was statistically significant when compared to all other cortical regions, which showed no change (0.3%) in theta power between phasic and tonic REM sleep (two-sample *t*-test, $p = 0.014$).

We obtained the probability of each channel being in the primary visual cortex V1 from a probability atlas of the visual cortex in MNI space (Wang et al., 2015). We did not find a significant correlation between the change in theta band energy and the probability of belonging to the primary visual cortex (rho = −0.58, $p = 0.17$). In fact, two of the channels in which no change was observed in the theta band energy were the ones with highest probability of belonging to V1.

Moreover, we did not find a significant correlation between duration of REM sleep and change in theta band energy (correlation coefficient = −0.4, $p = 0.4$).

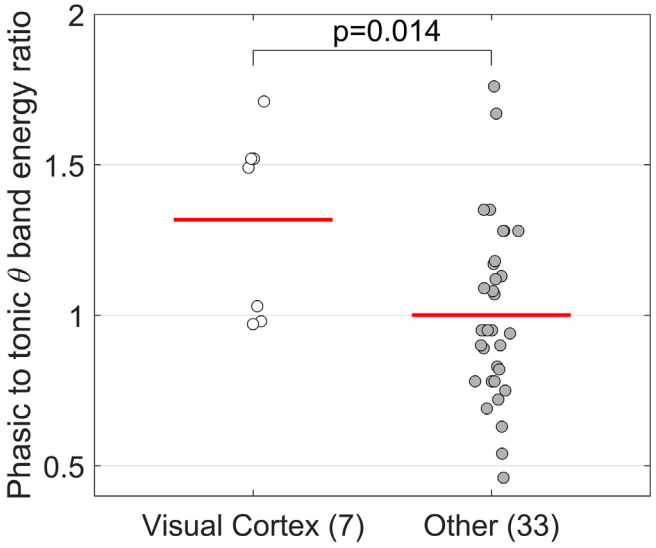

Fig. 5. Mean ratio of theta band energy between phasic and tonic REM sleep in the primary visual cortex (7 channels) compared to all other cortical areas (33 channels) of the same patients. There was an increase of 32% in the theta band energy during phasic compared to tonic REM sleep in the primary visual cortex. The increase was significantly higher than for all other investigated areas, which showed no change ($p = 0.014$).

3.3. Spectral analysis of five different spectral bands across all investigated eight cortical regions

For this analysis, we included 71 channels recording physiological brain activity from all investigated 11 patients. There was a

55.9% increase of relative theta band energy in the primary visual cortex during phasic compared to tonic REM sleep (p corrected = 0.042). Moreover, there was a 16.9% decrease of delta band energy in the visual cortex during phasic compared to tonic REM sleep (p corrected = 0.002). Differences of relative power in the alpha, beta, and gamma bands between phasic and tonic REM sleep were not significant in the primary visual cortex in comparison to all other regions (all P-values uncorrected and corrected > 0.05). Fig. 6 illustrates the findings of relative spectral differences in tonic and phasic periods in the eight investigated cortical regions for the theta and delta frequency bands for all patients. Supplementary Fig. S1 provides the findings of relative spectral differences in tonic and phasic REM sleep in the eight investigated cortical regions for the alpha, beta, and gamma frequency bands. Supplementary Fig. S2 provides the ratio of relative energy during phasic and tonic periods for different frequency bands and brain regions.

4. Discussion

PGO waves have been attributed a fundamental role for neurodevelopment and neurocognitive processes (for a review see Gott et al., 2017). In contrast to the literature in animals, the knowledge of the human correlate of PGO waves is mainly gathered from noninvasive neurophysiological and functional imaging studies which provide an indirect estimate of neuronal activity (McCarley et al., 1983; Cantero et al., 1999, 2000a; Cantero and Atienza, 2000; Jouny et al., 2000; Peigneux et al., 2001; Ioannides et al., 2004; Wehrle et al., 2005; Miyauchi et al., 2009; Waterman et al., 1993). This limitation can be overcome by intracranial electroencephalography used in presurgical epilepsy evaluation. This study directly investigated the presence of PGO activity in the human primary visual cortex in a series of epilepsy patients undergoing invasive EEG investigation. We found sharply contoured theta transients as presumed human correlate of classical PGO waves observed in the primary visual cortex of some animal species.

4.1. Increase in theta power during phasic versus tonic REM sleep

We found a 32% increase in absolute theta power in the primary visual cortex during phasic as compared to tonic REM sleep, which is a change not observed in all other investigated cortical regions. We suggest that these theta waves might be the human correlate of PGO waves because they were more frequent during phasic compared to tonic REM sleep. Indeed, previous studies in animal models as well as in the human showed a relationship between REMs and PGO waves (McCarley et al., 1983; Peigneux et al., 2001; Ioannides et al., 2004; Miyauchi et al., 2009; Wehrle et al., 2005). Our findings, however, are in contrast to previous studies using scalp EEG, showing a decrease rather than an increase in theta power during phasic compared to tonic REM sleep. This is likely explained by the different recording methods: intracranial EEG allows a direct access to midline brain regions and the primary visual cortex, whereas the signal of scalp EEG is generated mostly in the neocortex close to where it is measured and reflects minimally the signal of deep sources (see e.g. Watanabe et al., 2017). Therefore the presence of a decrease of theta power during phasic as opposed to tonic REM sleep in previous scalp EEG studies (Waterman et al., 1992; Jouny et al., 2000) does not contradict a focal increase in theta in the primary visual cortex.

4.2. Decrease of delta power during phasic versus tonic REM sleep

There is a 16.9% reduction in delta power during phasic compared to tonic REM sleep in the primary visual cortex. This decrease in delta activity has not been described in the primary

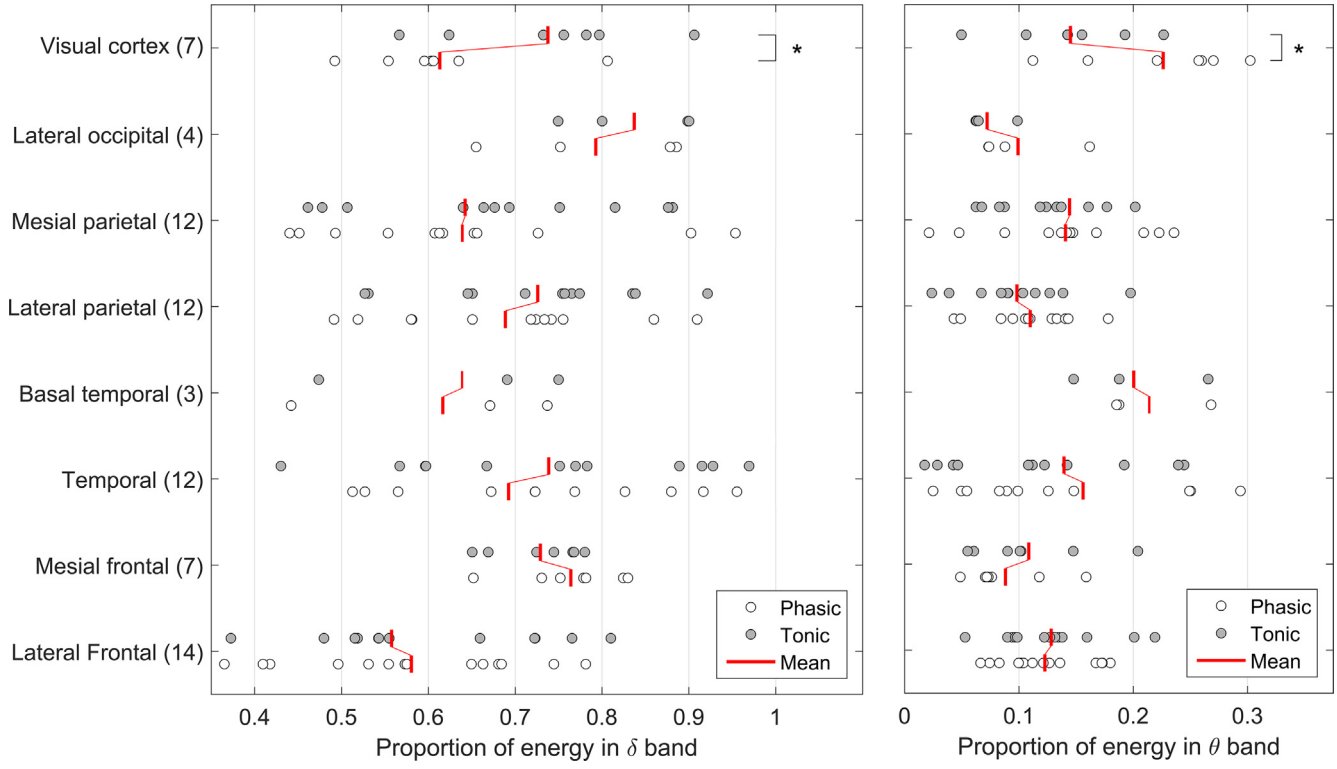

Fig. 6. The mean values of relative power in the delta and theta frequency bands between phasic and tonic REM sleep in the eight cortical regions studied. Significant differences were found for a relative 16.9% *decrease* in delta band energy in the primary visual cortex (p = 0.002) and a relative 55.9% *increase* of theta band energy in the primary visual cortex (p = 0.042) during phasic compared to tonic REM sleep.

visual cortex, and its functional significance is unclear. We previously described a decrease in power in frequencies <30 Hz during phasic compared to tonic REM sleep across different regions investigated. This decrease was interpreted as the expression of an increased EEG desynchronization at the time of REMs (Frauscher et al., 2016), which might be due to an increased cholinergic drive present during phasic REM sleep (Shouse et al., 1989). Previous scalp studies in humans showed conflicting results, likely explained by the different methods applied and also by the effect of eye movement contamination on scalp recording during phasic REM sleep (Jouny et al., 2000).

4.3. Contribution of the findings of the present study to the existing literature

Surface EEG and MEG have relatively poor spatial resolution and are not very sensitive to deep generators, particularly for spontaneous activity such as PGO waves. Direct intracranial EEG recordings can overcome these limitations, but this approach is invasive and the number of subjects is limited. Our study extends previous direct recordings in the pons and subthalamic nucleus (Fernandez-Mendoza et al., 2009) by investigating directly the primary visual cortex and showing an enhanced theta power during phasic as opposed to tonic REM sleep. We speculate that these waves might present the human correlate of PGO waves. Interestingly, the duration of the theta waves identified in our study in the primary visual cortex is similar to that type II waves described in the human from the subthalamic nucleus (Fernandez-Mendoza et al., 2009).

4.4. Strengths and potential limitations

We directly assessed neuronal activity through intracranial EEG. One of the major advantages of intracranial EEG is the high spatial resolution. In contrast to recording conditions on the scalp, depth electrodes are in direct contact with or in close vicinity to the physiological and epileptic generators that not only include the crowns of gyri, but also along sulci, white matter, and from structures seated deeply in the brain allowing a three dimensional picture of brain neurophysiology. Moreover, we assessed data through both qualitative and quantitative analysis making our findings less rater-dependent and more generalizable.

Placement of electrodes in the occipital lobe is considerably rarer than in other lobes, as posterior cortex epilepsy is less frequent than temporal or frontal lobe epilepsy. This explains the fact that even at a large tertiary epilepsy surgery center such as the MNI, only six patients with normal physiological EEG activity in proximity to the visual cortex were identified over a 2.5-year period. Moreover, all electrode contacts in the mesial occipital cortex were localized close to or in the primary visual cortex; hence we cannot draw conclusions on the presence of PGO-like waves in the other areas of the mesial occipital lobe. Finally, although we carefully selected healthy channels, influence of antiepileptic medications as well as epileptic activity in general cannot be completely excluded.

5. Conclusion

No classical PGO waves, but sharply contoured theta waves are found in the human primary visual cortex during phasic REM sleep. This finding suggests that sharply contoured theta waves might be the human correlate of PGO waves. Investigation of the influence of non-invasive auditory, tactile, or visual stimulation on rate and amplitude of these theta transients is an important next step in corroborating the present findings.

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Disclosure of Conflicts of interests

The authors have no potential conflict of interest with the present study. Outside of the submitted work, B.F. received speaker/advisory board fees sponsored by UCB and Novartis. J.G. and N.v.E. have received fees for consultancy from Precisis Inc. S.J., D.K.N., and F.D. have nothing to declare.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clinph.2018.04.605.

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