Sleep Slow Oscillations and Spindles encode ocular dominance plasticity and promote its consolidation in adult humans

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Abstract

Sleep and plasticity are highly interrelated, as sleep slow oscillations and sleep spindles are associated with consolidation of Hebbian-based processes. However, in adult humans, visual cortical plasticity is mainly sustained by homeostatic mechanisms, for which the role of sleep is still largely unknown. Here we demonstrate that non-REM sleep stabilizes homeostatic plasticity of ocular dominance in adult humans. We found that the effect of short-term monocular deprivation (boost of the deprived eye) was preserved at the morning awakening (>6 hours after deprivation). Subjects exhibiting stronger consolidation had increased sleep spindle density in frontopolar electrodes, suggesting distributed consolidation processes. Crucially, the individual susceptibility to visual homeostatic plasticity was encoded by changes in sleep slow oscillation rate and shape and spindle power in occipital sites, consistent with an early visual cortical site of ocular dominance homeostatic plasticity.

Introduction

Neural plasticity is an intrinsic property of the nervous system underlying the brain ability to change in response to environmental pressure. Learning and memory processes plastically and continuously encode new neuronal information during wakefulness, but consolidation mechanisms often extend into sleep[1]. During non-REM (NREM) sleep, replay and pruning processes as well as connectivity rearrangements associated with specific neuronal activity patterns involving GABAergic modulation[2] play a fundamental role in plasticity consolidation.

Two hallmark rhythms characterize the background of on-going oscillations of NREM sleep: slow wave activity (SWA, 0.5-4 Hz) and sigma band (σ, 9-15 Hz). A fundamental contribution to the lower frequency bound of SWA is due to Sleep Slow Oscillations (SSOs), an EEG pattern that corresponds to the alternation between periods of neuronal membrane depolarization and sustained firing (up states) and periods of membrane hyperpolarization and electrical silence (down states) whereas power in the sigma rhythm is provided by the sleep spindles: waxing and waning wave packages that spread throughout the thalamocortical system[3]. Sleep slow oscillations and sleep spindles have been consistently associated with synaptic plasticity, replay and memory consolidation[1,4,5]. SSOs allow homeostatic spike-timing-dependent-plasticity, while replay occurs via cortico-thalamo-cortical interactions that are made effective through thalamus-cortical synchronization in the sigma band: the sleep spindle is the full-fledged expression of this mechanism[6]. Several studies have investigated the role of slow and spindle oscillations in episodic and procedural memory,[7,8] while the contribution of these processes in sensory plasticity is still unclear. Growing evidence indicates that the adult human visual system might retain a higher degree of plasticity than previously thought[9,10]. Some form of Hebbian plasticity is retained in adulthood and mediates visual perceptual learning[11] as well as visuo-motor

learning[12,13]. These two forms of Hebbian plasticity involve changes in neural processing occurring at multiple levels of visual (perceptual learning[14]) and visuo-motor[15] processing, particularly at associative cortical level, and are consolidated both by NREM[12,13] and REM[16] sleep. In contrast, Hebbian plasticity in the primary visual cortex (V1) is very weak or absent in primates after closure of visual critical period.

An established models of sensory plasticity in V1 in vivo is ocular dominance plasticity[17–19] observed after a period of monocular deprivation (MD): the deprived eye loses the ability to drive cortical neurons and ocular dominance shifts in favour of the open eye[19,20]. Ocular dominance plasticity is maximal during development, when it is mediated both by Hebbian and by homeostatic plasticity: homeostatic synaptic scaling[21] underlies the boost of the deprived eye responses observed after the initial depression induced by Hebbian mechanisms[22,23]. In adult humans, recent studies have shown that short-term MD (2-2.5h) unexpectedly shifts ocular dominance in favour of the deprived eye[24–26]. This counterintuitive result is interpreted as a compensatory adjustment of contrast gain, reflecting homeostatic plasticity highly active during all life span. The deprived eye boost is observed also at the neural level, as revealed by EEG[27], MEG[28] and fMRI[29] and, importantly, it is mediated by a decrease of GABAergic inhibition in the primary visual cortex[30]. The effect of short-term MD decays within 90 minutes from eye-patch removal[24,26]. However recent evidence from a clinical study in amblyopic patients, shows that repeated short-term deprivation of the amblyopic eye can promote the long-term (up to one year) recovery of both visual acuity and stereopsis[31], suggesting that the effect of short-term MD can be consolidated over time.

Evidence from animal models shows that NREM sleep is necessary to consolidate Hebbian mechanisms during ocular dominance plasticity within the critical period[32–34], however, it is still

largely unknown whether sleep has similar effects after the closure of the critical period and on homeostatic plasticity induced by MD. This is particularly important given that homeostatic plasticity is retained in the adult human brain[24–26,28,29,35–40].

Here we tackle directly this issue by investigating the effect of sleep on visual homeostatic plasticity in adult humans. Because of common neural mechanisms underlying both homeostatic plasticity and slow wave sleep (e.g. GABAergic inhibition[41,42]), we expected to observe a relation between SSO, sigma oscillations and plasticity in visual areas. Moreover, we anticipated a role of sleep spindles in the consolidation of homeostatic plasticity, reflecting replay mechanisms linked to perceptual memory that could involve both visual[43] and prefrontal cortical areas[44,45].

Results

We assessed visual cortical plasticity by measuring the effect of short-term (2h) of monocular deprivation (MD)on ocular dominance measured by binocular rivalry[46–48] in adult volunteers. In the experimental night, MD was performed in the late evening and was followed by 2h of sleep, during which high-density EEG was recorded (Figure 1A). At this night awakening, ocular dominance was assessed again, and then participants went back to sleep until the morning (4-5 hours of additional sleep). For the control condition, the same participants underwent an identical protocol, but without performing MD.

Consistently with previous reports[24,25], short-term MD shifted ocular dominance in favour of the deprived eye (Figure 1, B1 and B2, black symbols, Friedman test, chi squared (4,72)=21.77, $p<0.0002$, Kendall's W=0.29): the deprivation index (DI) was significantly altered just after eye-patch removal (mean DI ± SE = 0.77 ± 0.04, Wilcoxon signed rank test z(18)=-3.58, $p<0.0003$, p_adj=0.0017, Kendall's W=0.62). Importantly, this form of homeostatic plasticity was maintained after two hours of sleep (mean DI ± SE= 0.87 ± 0.04, Wilcoxon signed rank test

z(18)=-2.74, p<0.006, p_adj= 0.016, Kendall's W=0.47) and during the first 8 minutes after morning awakening (mean DI ± SE = 0.91 ± 0.04, Wilcoxon signed rank test z(18)=-2.17, p<0.03, p_adj = 0.05, Kendall's W=0.14), that is about 6-7 hours after eye-patch removal (Figure 1, B2, black symbols). No consistent changes in ocular dominance were observed in the control night (Figure 1, B1 and B2, grey symbols, Friedman test, chi squared (4,68) =1.91, p=NS). These results are surprising, considering the effect of short-term MD normally decays within one hour after eye-patch removal[24,26] and indicate that sleep consolidated visual homeostatic plasticity. Interestingly, the effect of MD (deprivation index) measured before and after 2h of sleep did not correlate across subjects (Spearman's rho=0.18, p=0.47, data not shown). This suggests that individual sleep pattern interacts with visual homeostatic plasticity and that the instatement and consolidation of plasticity might be mediated by different neural processes, possibly reflected in different features of NREM sleep.

To rule out the effect of total darkness exposure occurring during sleep, we performed an additional control experiment during which participants, after MD, laid down in a completely dark room for 2 hours, without sleeping. In this control experiment (Figure 1**,** B3), we found that the effect of MD (mean DI ± SE = 0.69 ± 0.05, Wilcoxon signed rank test z(18)=-3.5, p<0.0005, Kendall's W=0.8) decayed to baseline within 2 hours of darkness (mean DI ± SE = 1.01 ± 0.07, Wilcoxon signed rank test z(18)=-1, p=NS), similarly to what observed with normal visual stimulation after patch removal.

Having demonstrate a consolidation of the boost of the deprived eye with sleep, two different but intermingled issues arise: 1) how MD affects subsequent sleep, and 2) how sleep contributes to consolidation of visual homeostatic plasticity. As the first 2 hours of night sleep contained none or just a few minutes of REM sleep, both effects have been investigated within NREM sleep.

NREM sleep features were derived from the 2 hours of EEG recording before the night awakening. These include the power scalp distribution of slow wave activity (0.5-4Hz) and sigma (9-15Hz) rhythms, the rate (waves per time unit) and shape of SSO as well as the density (waves per time unit) and power of sleep spindles. We restricted the analysis to an occipital ROI, given early strong evidence of ocular dominance homeostatic plasticity at level of early visual cortex[29] and we considered the changes over the ROI from the control to experimental night of each feature. A control ROI was selected in correspondence of the sensory-motor cortex (See Supp Fig 1).

Specifically, in the occipital ROI, we observed a strong correlation between changes in sleep features and ocular dominance plasticity measured before sleep.

For the SSOs, a strong correlation with plasticity was observed between changes in SSO rate (rho=-0.66, p=0.009, p_{fdr}=0.036, Figure 1, D1) and shape (slope+, rho=-0.64, p=0.012, p_{fdr}=0.037, Figure 1, D2; SSO amplitude, rho = -0.56, p=0.03, p_{fdr}=NS, Supp Figure 2, A) at the level of the occipital ROI: subjects showing a stronger plasticity effect showed 1) increased SSO rate, 2) increased sharpness of transitions from the SSO negative peak, whereas subjects with lower plasticity effect exhibited opposite parameters changes. The opposite changes between subjects with high and low plasticity suggest different local synchronization in the sleeping neurons undergoing the bistability behaviour of SSO. Finally, for the sleep spindles, a correlation with plasticity was observed between their mean power (rho=-0.72, p=0.0033, p_{fdr}=0.025; Figure 1, D3): power of sleep spindles over the occipital sites increased in the experimental night for participants showing higher visual homeostatic plasticity (i.e. a large boost of the deprived eye), while the power was reduced in participants showing a lower response to MD. This result, together with the other sigma power estimates, reinforces the idea behind a modulation of thalamocortical interaction as a homeostatic reaction to MD. Indeed, sigma activity power

expressed during the whole NREM sleep in the occipital ROI correlated with individual ocular dominance shifts (rho=-0.72, p=0.003, p_{fdr}=0.025, Supp Fig 2, B) and overlapping result was observed when considering the sigma rhythm expressed just before SSO events that favour the emergence of full-fledged SSO (rho=-0.70, p=0.0046, p_{fdr}=0.025, Supp Fig 2, C). These strong correlations contrast with the absence of association with the power of slow wave activity during the whole NREM sleep with the plasticity index (Supp Fig 2, D).

The observed significant correlations were specific for occipital ROI (they were not observed in the control ROI position) and were specific to sleep as no correlation between neural rhythms power and visual plasticity was observed in the control experiment (darkness exposure condition, data not shown).

To investigate how sleep contributes to the maintenance of the acquired ocular dominance, we focused on sleep replay mechanisms supporting plasticity consolidation. To this aim, we correlated ocular dominance plasticity measured after night awakening (Figure 1, A, *binocular rivalry after*) with previous 2 hours sleep characteristics in three target ROIs: the occipital, the control sensory-motor and a new prefrontal ROIs.

Concerning the prefrontal ROI, neither power of slow wave activity and sigma bands, nor SSO rate and shape were associated with visual plasticity consolidation (Supp Fig. 3). Only the sleep spindles density in the prefrontal ROI strongly correlated (rho=-0.81, p=0.0004, p_{fdr}=0.01) with the effect of MD as maintained after sleep (Figure 1, D4): participants retaining the stronger effect after 2h of sleep showed substantial increase of spindle density. No correlation was observed in the other ROIs.

This result suggests that, while visual plasticity induces changes in sleep features at the level of the occipital cortex, its consolidation involves prefrontal areas and sleep spindles.

Discussion

We investigated the interplay between visual homeostatic plasticity and sleep in healthy adult humans after a short MD period. We report for the first time that different features of NREM sleep affect and are affected by homeostatic ocular dominance plasticity in adult humans: the plastic potential of the visual cortex is reflected by the expression of SSO and sigma activity in occipital areas and sleep consolidates the effect of short-term MD via increased spindles density in prefrontal area.

Role of sleep in visual plasticity consolidation

We found that sleep promotes consolidation of visual homeostatic plasticity induced by 2 hours of MD for up to 6 hours, whereas normally 90 minutes of wakefulness are enough to extinguish this effect. Importantly, this effect was specifically induced by sleep: two hours of dark exposure after MD did not prevent the decay of the effect. Results from animal models have shown that NREM sleep consolidates ocular dominance plasticity during the critical period[32,34,49]. This sleep-dependent consolidation relies on Hebbian mechanisms and it is mediated by synaptic potentiation through increased NMDAR and PKA activity[32] and decreased GABAergic inhibition[34]. Here we show for the first time that NREM sleep can promote the consolidation of ocular dominance plasticity also past the critical period in humans and we provide a first evidence that sleep endorses visual homeostatic plasticity.

The hypothesis that during NREM sleep synaptic weights down-scale in compensation for neural activity during wakefulness[50], albeit integrating a huge body of experimental findings, meets obstacles in explaining experiments indicating potentiation of cortical synapses in several models[51] . The nowadays picture is therefore complex, without any unitary theory.

We report that NREM sleep consolidates the homeostatic boost of the deprived eye induced by deprivation. However, homeostatic plasticity process triggered by MD is associated with up-scaling of the deprived eye synaptic weights, but also with down-scaling of the non-deprived eye[27–29,39] and thus NREM sleep appears to intervene in a rebalancing process involving overall cortical activity.

The density of sleep spindles was associated with the MD effect maintained after sleep in a distinct cluster of electrodes distributed over the mesial frontal and prefrontal cortex. Sleep spindles have been described as replay events of new information acquired during wakefulness and in the course of consolidation during NREM sleep, which might mark phasic activations of a circuit involving the hippocampus[52]: indeed the consolidation of several forms of plasticity has been associated with sleep spindle density[53,54] and some forms of visual plasticity (e.g. perceptual learning) are reflected in changed activity and connectivity within the hippocampus[55], which has dense anatomical connections with the primary visual cortex[56]. The involvement of frontal areas might reflect the updating of visuo-spatial schemas induced by monocular vision, with new associations accompanied by increase in ventromedial prefrontal-hippocampal coupling during wakefulness[44,57], and the expression of sleep spindles invading the prefrontal cortex during NREM sleep for hippocampal replays[58].

Altogether, this result shows for the first time that activity in non-visual areas plays a role in modulating the decay of short-term visual plasticity in adult humans and that this activity might be crucial to promote the consolidation of the plastic changes induced by MD and previously observed in amblyopic patients[31], where the boosting effect can become permanent when short-term MD is repeated in consecutive days with sleep occurring in between sessions.

Sleep and the plastic potential of visual cortex

We found that the expression of SSO in visual areas reflects the interindividual variability in visual homeostatic plasticity: from the control to the experimental night, their rate increased and their shape changed in occipital sites proportionally to the shift in ocular dominance induced by MD, as measured immediately before sleep.

Less SSOs observed in low plasticity subjects also means less downstate periods. During the downstate a large majority of neurons are silent for fractions of second and restorative processes occurring at the level of individual brain cells occur[59]. Thus, less SSOs could indicate an average lower need of such processes due to the previous sensory deprivation. In this line, also sleep after blindfolding healthy volunteers exhibits a dramatic decrease of SSOs[60]. At the other end, more SSOs in subjects with high visual plasticity could indicate the homeostatic activation of this mechanism endorsing the ocular dominance shift. SSO shape changed accordingly after MD: subjects with high visual plasticity show greater SSOs with steeper downstate exit slope (slope+) compared to their basal characteristics. Larger SSOs indicate larger groups of cortical neurons synchronously involved in these bistable events, while a steeper positive slope has been associated with a stronger coupling with thalamic structures.

Altered activity in the slow wave frequency band (the band including SSOs) was also observed in sleep subsequent sensorimotor deprivation[61], however SSO events were not studied directly in this experimental model. The type of plasticity induced by sensorimotor deprivation differs from the effect of short-term MD, consistently with Hebbian mechanisms mediating sensory-motor plasticity and homeostatic mechanisms mediating short-term ocular dominance plasticity. Short-term MD induces opposite changes in VEPs, increasing VEPs amplitude of the deprived eye and decreasing that of the non-deprived eye[61], while sensorimotor deprivation reduces SEPs/MEPs related to the immobilized arm leaving unaltered SEPs/MEPs related to the free arm (Huber et al.,

2005). These differences might explain the different pattern of sleep changes observed after sensorimotor deprivation and after MD: while Huber et al (2006)[61] reported a significant decrease in slow wave activity power, we did not observe a main effect of our experimental manipulation, reflecting balanced overall activity changes of the deprived and non-deprived eye between the pre- and post- deprivation state. However, we reported a strong correlation between SSO rate/shape parameters and the MD effect, suggesting that SSO encodes homeostatic plasticity in the adult visual cortex.

The expression of oscillating activity in the sigma band also changed as a function of the individual plastic potential of the visual cortex. Most of the sigma activity during NREM sleep relies on the pacemaker cells within the reticular thalamic nucleus forcing patterned activity in thalamocortical and cortical cells. The paradigmatic expression of this activity is the sleep spindle during which ideal conditions for fine scale plasticity occur: thalamic inputs during spindles yield to dendritic depolarization but keeping the cell from firing and triggering calcium entry into dendrites[62]. Recordings in vivo from lateral geniculate nucleus and visual cortex have shown that SSOs and sigma activity are strongly coordinated within thalamocortical circuits[63], and evidence are accumulating for reticular thalamic plasticity sustaining spindle-based neocortical–hippocampal communication[64]. Therefore, during NREM sleep, any factor modulating the activity of one of the two structures affects both and this lays the foundation for coordinated cortico-thalamic plastic changes[4,65–68].

Overall, these results suggest that SSOs and sigma activity reflect the degree of homeostatic plasticity induced by short-term MD. Both homeostatic plasticity[41,69] and SSO[42,70] are linked to GABAergic inhibition, the observed effect could therefore in principle be mediated by a change in excitation/inhibition balance in the visual system. Importantly, in humans, GABA

concentration measured after 2 hours of MD in V1 decreased proportionally to the observed ocular dominance shift[30], and slow wave activity expression increases in response to GABA agonists administration[71]. Interestingly, a recent study[72] reported that complementary changes in the excitation/inhibition balance measured in the visual cortex of adult humans during NREM and REM sleep are correlated with visual plasticity induced by perceptual learning, further pointing to a leading role of GABAergic inhibition in mediating these two phaenomena.

Conclusions

Sleep oscillatory activity can reflect the plastic potential of the occipital cortex: people highly susceptible to a visual manipulation (short-term monocular deprivation) affecting primary visual cortex activity show increased SSO and sigma activity in occipital sites. Sleep can also extend for many hours an otherwise transient unbalance of visual cortical activity, and sleep spindles in frontal regions appear to support the process as subjects exhibiting stronger consolidation had increased frontopolar sleep spindle density, as it occurs for many memory consolidation processes.

Materials and methods

Participants

Nineteen healthy volunteers (mean age ± SD 24.8 ± 3.7 years, range 21-33 years; 8 males), participated in the study. The eligibility of each volunteer was verified by semi-structured interviews conducted by a senior physician and psychiatrist (AG) based on the following inclusion criteria: no history of psychiatric/neurological disorders (including sleep disorders),

being drug free for at least one month. All subjects had normal or corrected-to-normal visual acuity. Enrolled volunteers received the following instructions to be accomplished in each day of the experimental procedures: to avoid any alcohol intake, coffee intake in the evening before sleep sessions and physical work out just before all the experimental sessions (both the sleep and the morning sessions). All subjects performed the three experimental conditions, except for one subject, who did not perform the control night condition because of personal problems. Four participants were excluded from the EEG analysis because of poor signal quality in the EEG signal occurred during the sleep recording. Sample size was determined based on previous studies on sleep and plasticity (e.g. visual[72–74] and visuo-motor learning[12,75,76]) using a within-subject design, indicating that robust results can be observed with a sample size of 10-15 participants.

Ethics statement

All eligible volunteers signed an informed written consent. The study was approved by the Local Ethical Committee (Comitato Etico Pediatrico Regionale—Azienda Ospedaliero-Universitaria Meyer—Firenze), under the protocol "Plasticità del sistema visivo" (3/2011) and complied the tenets of the Declaration of Helsinki. Participants were reimbursed for the time at a rate of 100€ per night and 50€ for the morning session experiment.

Monocular deprivation

Monocular deprivation (MD) was performed by applying a custom-made eye-patch on the dominant eye. Eye dominance was defined according to the binocular rivalry measurement performed in the baseline. The eye-patch was made of a translucent plastic material that allows light to reach the retina (attenuation 15%) but completely prevents pattern vision. MD lasted 2h, during which participants stayed in the laboratory control room under experimenters' supervision and did activities such as reading and working on the computer. In the last half hour all subjects underwent the EEG montage so that at the patch removal, after the acquired eye dominance measurement, they could go to sleep without any delay.

Binocular Rivalry

Visual stimuli were generated by the ViSaGe stimulus generator (CRS, Cambridge Research Systems), housed in a PC (Dell) controlled by Matlab programs. Visual stimuli were two Gaussian-vignetted sinusoidal gratings (Gabor Patches), oriented either 45° clockwise or counterclockwise (size: 2s = 2°, spatial frequency: 2 cpd, contrast: 50%) displayed on a linearized 20inch Clinton Monoray (Richardson Electronics Ltd., LaFox, IL) monochrome monitor, driven at a resolution of 1024x600 pixels, with a refresh rate of 120 Hz. To facilitate dichoptic fusion stimuli were presented on a uniform grey background (luminance: 37.4 cd/m2, C.I.E: 0.442 0.537) in central vision with a central black fixation point and a common squared frame. Subjects received the visual stimuli sitting at a distance of 57 cm from the display through CRS Ferro-Magnetic shutter goggles that occluded alternately one of the two eyes each frame.

Each binocular rivalry experimental block lasted 3 minutes. For each block, after an acoustic signal (beep), the binocular rivalry stimuli appeared. Subjects reported their perception

(clockwise, counterclockwise or mixed) by continuously pressing with the right hand one of three keys (left, right and down arrows) of the computer keyboard. At each experimental block, the orientation associated to each eye was randomly varied so that neither subject nor experimenter knew which stimulus was associated with which eye until the end of the session, when it was verified visually.

High density EEG recordings

EEG was recorded using a Net Amps 300 system (Electrical Geodesic Inc., Eugene, OR, USA) with a 128-electrodes HydroCel Geodesic Sensor Net. During the two hours of recordings, electrode impedances were kept below 50 KΩ and signals were acquired with a sampling rate of 500 Hz, using the Electrical Geodesic Net Station software, Version 4.4.2. EEG recordings were analysed using tailored codes written in Matlab (MathWorks, Natick, MA, USA) and EEGLAB toolbox functions[77].

Experimental procedures

Experimental procedure comprises three sessions, and for each volunteer, sessions were completed within a month and at least one week apart. The experiment took place in a dark and quiet room, with a comfortable bed equipped for EEG recordings and the apparatus for measuring binocular rivalry placed next to the bed. Each volunteer spent two nights (from 9:30 PM to 8AM) and a morning (from 9 AM to 14 AM) at the laboratory: i) a Monocular Deprivation Night (MDN), in which participants underwent 2h of MD before sleep; ii) a Control Night (CN), in

which no MD was performed before sleep, but participants waited two hours in the laboratory performing the same activities and undergoing eye dominance measures at the same times as in MDN; iii) a Monocular Deprivation Morning (MDM), during which subjects, after the MD, lied in the same bed of night sessions, resting in the dark for two hours, avoiding sleeping, in order to study the acquired eye dominance extinction without visual stimuli. The order of the night session was randomized and balanced within the experimental group and during both nights, sleep was interrupted after two hours for performing an ocular dominance measure via binocular rivalry experiment (it took about 10 min), after which volunteers could sleep undisturbed until 7.30 AM (from 4 to 5 hours).

For assessing ocular dominance during night sessions, binocular rivalry was measured at four different times: before MD (or waiting for the CN, night *baseline*, 2x3min blocks), after 2h of MD and before sleep (or waiting for the CN, *before sleep*, 2x3min blocks), after the first 2h of sleep (*after sleep*, 2x3min blocks) and after the second awakening (*morning awakening*, 5x3min blocks measured 0, 5, 10, 15 and 30 min after eye-patch removal). Similarly, during the MDM session, binocular rivalry was measured at three times: before MD (morning *baseline*, 2x3min blocks), after 2h of MD and before dark exposure (*before dark*, 2x3min blocks), after the 2h dark exposure (*after dark*, 2x3min blocks).

During the night sessions, EEG was acquired from the in-bed time until subjects were woken up for performing the binocular rivalry measures after two hours of sleep, whereas during the MDM session, EEG was acquired in the two hours of dark exposure. According to EEG recordings, in the night sessions participants fell asleep easily and fast (sleep latency 9±2 min – mean±se), showed a normal organization of sleep structure (37±3% spent in N2 stage, and 50±3% spent in N3 stage, on average), exhibited none (8 out of 15 subjects in the MDN and 4 out of 15 subjects

in the CN) or few minutes of REM sleep (9±2 min) and none of them had wakefulness episodes after sleep onset.

In the MDM session none of the subjects were allowed to feel asleep as EEG was monitored in real-time and, in case of drowsiness signs (EEG slowing to theta), a bell tolled in the resting room.

A diagram of the experimental paradigm for the MDN is reported in Figure 1A.

Monocular deprivation and control nights EEG processing

To prepare EEG signals for the planned analysis, they underwent some preprocessing. EEG pre-processing and analyses were performed using tailored codes written in Matlab (MathWorks, Natick, MA, USA); scalp maps were obtained using EEGLAB Toolbox functions[77].

For night sessions, scalp EEG signals were re-referenced to the average mastoid potential[78] and underwent an automated threshold-crossing detection algorithm[79] for identifying epochs affected by movements. After confirmatory visual inspection, most part of these epochs were discarded. Moreover, decline in channel signal quality (often due to instability or loss of contact with the scalp during recordings) was studied on the basis of signal statistics and detected bad channels were excluded for the segment of decline (EEGLAB Toolbox[77]). At the end of these pre-processing steps, all recordings showed more than 90% of artifact-free epochs.

The artifact-free EEG segments were scored according to the AASM criteria[80] and NREM segments analysed for estimating power band content and identifying sleep patterns such as SSOs and sleep spindles.

For power band content of NREM sleep, two frequency bands of interest were considered: slow wave activity (0.5–4 Hz), and sigma (9–15 Hz). Power densities were estimated applying a Hamming-windowed FFT on 10 sec consecutive EEG segments and log-transformed (dB). For each segment, electrode and band, the absolute power was estimated by averaging over its frequency bins. The absolute power of each band and electrode was then obtained averaging among segments.

Monocular deprivation morning EEG processing

For the MDM session, EEG signals were high pass filtered at 0.1 Hz (Chebyshev II filter) and notch filtered at 50 Hz and its first harmonic (100 Hz). Channels located on the forehead and cheeks which mostly contribute to movement-related noise were discarded retaining thus 107 channels out of 128[79]. Epochs with signals exceeding 100μV were automatically discarded; retained signals were visually inspected for the removal of artefacts and noisy channels. Rejected signals were substituted with signals obtained via spline-interpolation[81] and furtherly submitted to the Independent Component Analysis for separating and removing components expressing eye movements, heart beats, line and channel noise - component selection supported also by the AI system of ICLabel[82]. After artefact removal procedures, EEG signals were re-referenced to the average of the mastoid potentials[79,83].

The artifact-free EEG segments analysed for estimating power band content in five frequency bands of interest were considered: theta (4–8 Hz), alpha (8–12 Hz), low beta (20–30 Hz), high beta (20–30 Hz) and gamma (30-45 Hz). Power densities were estimated applying a Hamming-windowed FFT on 4 sec consecutive EEG segments and log-transformed (dB). For each segment,

electrode and band, the absolute power was estimated by averaging over its frequency bins. The absolute power of each band and electrode was then obtained averaging among segments.

Sleep Slow Oscillation detection and characterization

SSO events within NREM sleep periods were detected and characterized using a previously published and validated algorithm[79,84]. For each subject, night session and electrode channel, SSOs were characterized by the following parameters: detection density (number of waves per minute), peak to peak (down to up state) amplitude, negative and positive slopes to and from the negative peak[85]. Moreover, the sigma-activity (9-15Hz) expressed in the 1s window preceding each SSO was estimated as a known thalamocortical entrainment marker functioning as precursor of SSOs emergence[86].

Sleep Spindle detection and characterization

The sleep spindle recognition was carried out according to the approach proposed and validated by Ferrarelli et al. (2007)[87], with some minor adaptations; the actual procedure is summarized below.

EEG data for all NREM sleep periods were band-pass filtered between 9 and 15 Hz (–20 dB at 8 and 16 Hz) and for each channel, the upper and lower envelopes of the filtered signal were derived. The spindle detection was based on the signal derived as the point-by-point distance between the upper and the lower envelopes (signal amplitude). Because signal amplitude varies between channels, for each NREM period and channel a value was estimated as the mean signal

amplitude increased by twice its standard deviation. Thus, for each channel a threshold was defined as the weighted average over the values calculated for each period, with the weights corresponding to the period lengths. Sleep spindles were thus identified as the fluctuations in the amplitude signal exceeding four times the threshold. Based on the detected spindles, for each EEG channel, the measures characterizing each sleep recording were the density (spindle events per time unit) and the spindle power. The spindle power was derived as the average over the spindle events of the sigma band (9-15 Hz) power of each detected wave.

Binocular Rivalry

The perceptual reports recorded through the computer keyboard were analysed using Matlab, the mean phase duration and the total time of perceptual dominance of the visual stimuli presented to each eye and mixed percepts were computed for each participant and each experimental block. The three-minute blocks acquired after the morning awakening were binned as follows: 0-8 min, 10-18 min, 30 min.

The effect of MD was quantified by computing a deprivation index (DI)[30] summarising in one number the change in the ratio between deprived and non-deprived eye mean phase duration following MF relative to baseline measurements according to the following equation:

Deprivation Index (DI) =

$$(baseMPD_{dep-eye}/depMPD_{dep-eye}) * (depMPD_{Ndep-eye}/baseMPPD_{Ndep-eye})$$

Eq1

In Eq. 1, MPD represents Mean Phase Duration computed in seconds, base stands for baseline measurements, dep for measurements acquired after MD. A deprivation index value equal to 0 represents no change in the ratio between dominant and non-dominant eye mean phase duration, while a value >1 represents a decrease in dominant-eye predominance and a value <1 an increase in dominant eye predominance during binocular rivalry.

Statistical analyses

The variation of deprivation indices measured during the two-night experiments was tested using repeated measures Friedman Test with 1 factor (TIME) with 5 levels (*before, after, morning1, morning2, morning3*). Observed statistical power for the Friedman Test was estimated with the Kendall's W. One-sample two-tailed Wilcoxon signed rank tests were used for post-hoc tests, against the H0 median=1. The Benjamini & Hochberg (1995)[88] correction for multiple comparisons was applied for post-hoc tests.

The variation of sleep characteristics according to the MD intervention and the dependence on the one hand on the acquired eye dominance (as measured by the deprivation index before sleep) and on the other on the residual dominance evaluated after two hours of sleep (as measured by the deprivation index after sleep) was evaluated considering the regions of interest (ROI) selected on the basis of the specific assumptions made beforehand: occipital ROI, frontopolar ROI and sensorimotor control ROI. Lists of the electrodes in the HydroCel Geodesic Sensor Net belonging to each ROI are provided in the Suppl. Fig. 1.

For the effect of MD intervention, the Wilcoxon signed rank test was applied on all the EEG sleep features. To this aim each sleep feature was averaged over the electrodes belonging to occipital and sensorimotor control ROIs and thus compared between nights (a total of 16 tests were carried out). For the dependence on the individual deprivation indices, the non-parametric Spearman correlation was determined for each EEG sleep feature averaged over the ROIs. A total of 16 tests were carried out for studying the association with the acquired ocular dominance (occipital and sensorimotor control ROIs), and another 24 for the association with the residual dominance after sleep (occipital, frontopolar and sensorimotor control ROIs).

For each group of multiple tests, the Benjamini & Hochberg (1995)[88] procedure for controlling the false discovery rate (FDR) of the family of hypothesis tests concerning all sleep features estimated in the three ROIs was applied. The false discovery rate was set equal to 0.05.

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Conflict of interest

The authors declare no conflict of interest

Figure

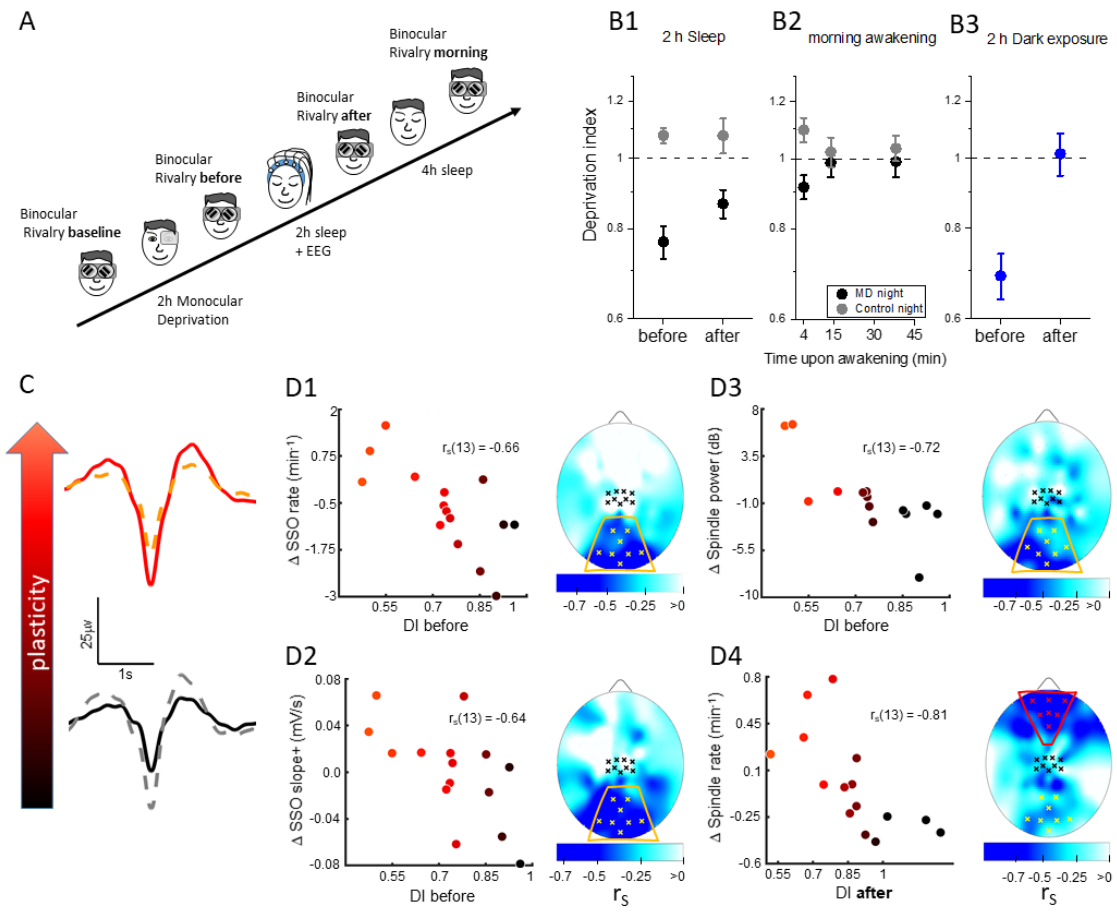

Figure 1. A) Diagram of the experimental paradigm for the MD night condition. Ocular dominance was measured by means of binocular rivalry before and after 2h of monocular deprivation (MD). Afterwards, participants went to sleep while their EEG activity was recorded with a 128 electrodes system. Binocular rivalry was measured after 2 hours of sleep and in the morning, after 4 additional hours of sleep. **B1**) The MD effect (deprivation index) measured before and after 2 hours of sleep in the MD (black symbols) and control (grey symbols) night. (**B2**) same as B1 but for the morning awakening, occurring after 4 additional hours of sleep. (**B3**) the deprivation index measured before and after 2h of dark exposure without sleep performed in the monocular deprivation morning session. Error bars represent 1±SEM. (**C**) grand average of

sleep slow oscillations (SSOs) derived for the MD and control night sleep from the electrodes belonging to the occipital ROI (yellow dots mark electrodes belonging to the ROI in D panels). Solid lines refer to the MD night template, dashed lighter lines to the control night templates. The upper red/orange templates refer to the subject with the highest plasticity (lowest deprivation index), the lower black/grey templates refer to the subject with the lowest plasticity (highest deprivation index). (deprivation index). **(D1)** The changes from the control night to the MD night of the rate of SSOs was considered for correlation with the deprivation index measured before sleep (DI before). Scatterplot shows the significant correlation estimated in the occipital ROI (yellow dots mark electrodes belonging to the ROI). Color of dots spans from black to red as a function of individual plasticity. No significant correlation appeared when considering the control ROI defined in the sensory-motor cortex (black dots). The scalp map shows the spatial distribution of correlation; (**D2**) same as D1 but for the steepness of slope+ of SSOs; (**D3**) same as D1 but for the mean sleep spindle power measured during NREM sleep; (**D4**) the changes from the control night to the MD night of the sleep spindle density was considered for correlation with the deprivation index measured after sleep (DI after). Scatterplot shows the significant correlation estimated in the prefrontal ROI (red dots mark electrodes belonging to the ROI). No significant correlation appeared when considering both the control ROI defined in the sensory-motor cortex (black dots) and the occipital ROI (yellow dots) The scalp map shows the spatial distribution of correlation.

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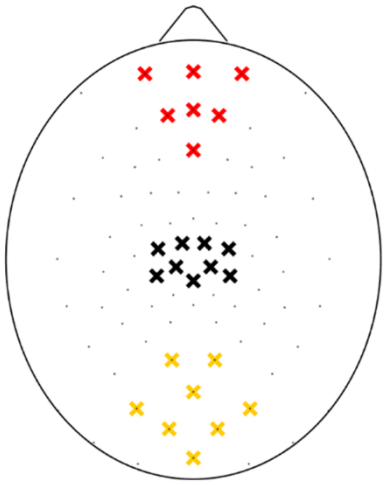
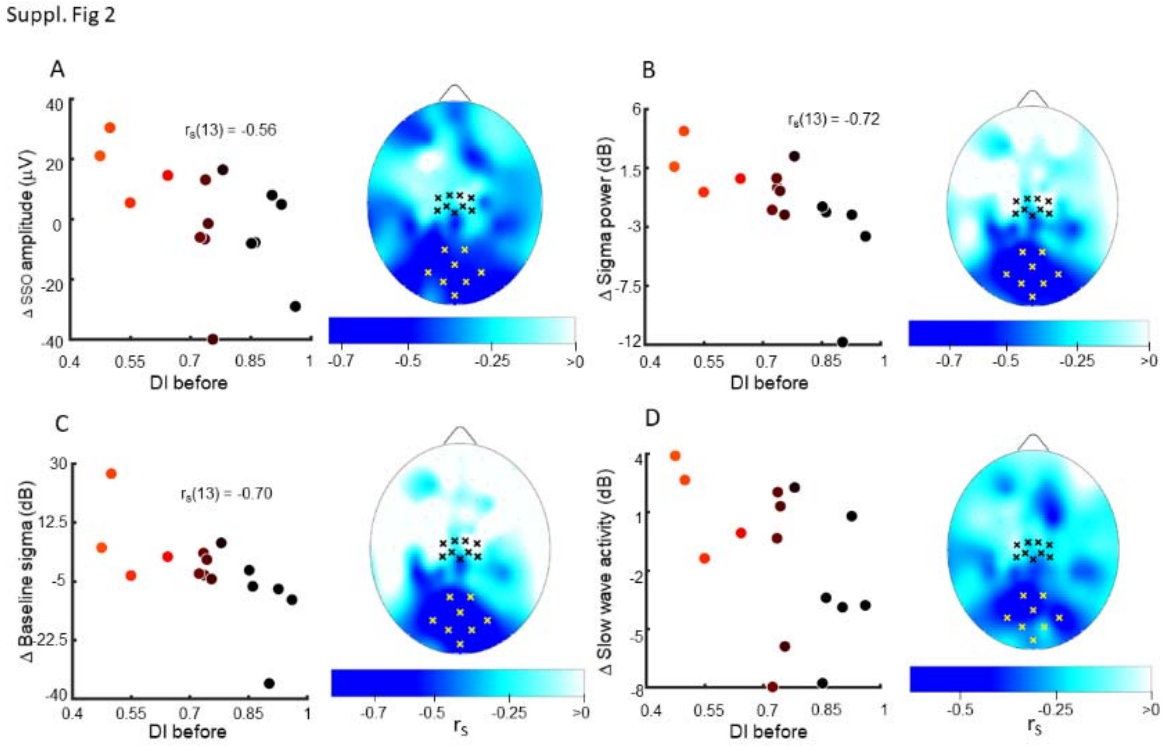
Supplementary Material

Suppl. Fig 1

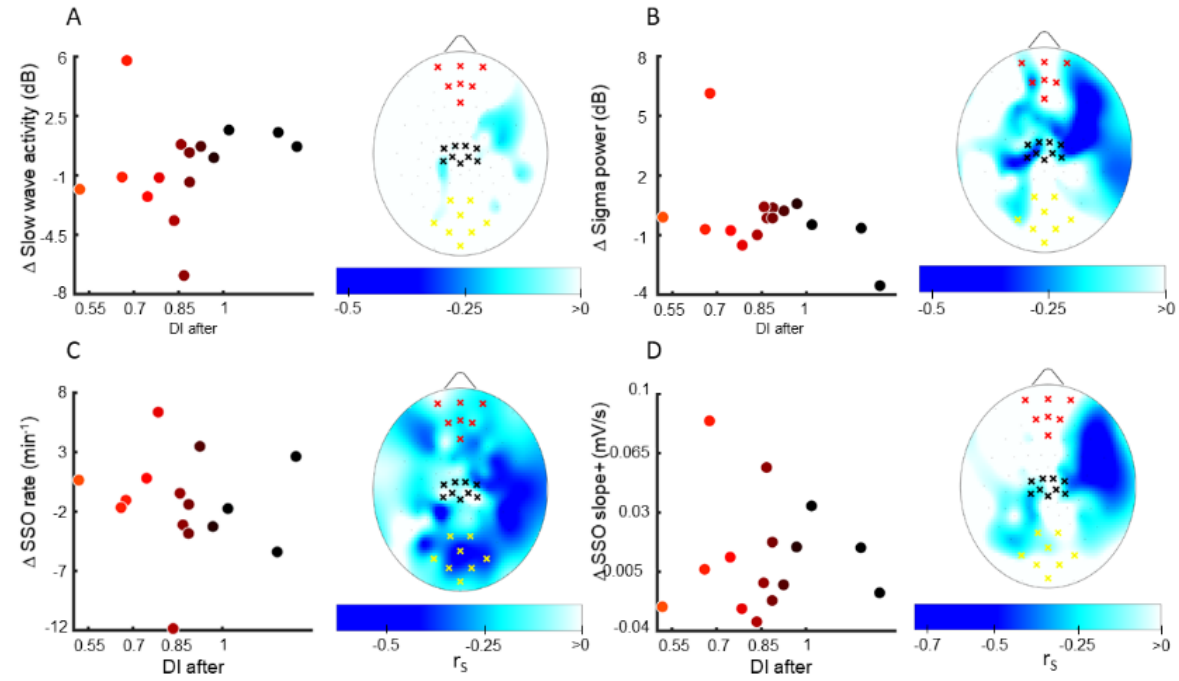


Suppl. Figure 1. Electrodes in the HydroCel Geodesic Sensor Net belonging to each ROI. Yellow crosses mark electrodes belonging to the occipital ROI, red crosses mark electrodes belonging to the prefrontal ROI and black crosses mark electrodes belonging to the sensory-motor control ROI.



Suppl. Figure 2. A) The changes from the control night to the MD night of the mean sleep slow oscillations (SSO) amplitude measured during NREM sleep was considered for correlation with the deprivation index measured **before** sleep (DI before). Scatterplot shows the putative relationship between SSOs amplitude averaged over the occipital ROI (yellow crosses mark electrodes belonging to the ROI). Colour of dots spans from black to red as a function of individual plasticity. No significant correlation appeared when considering the control ROI defined in the sensory-motor cortex (black crosses). The scalp map shows the spatial distribution of correlation; (B) same as A but for the sigma activity power; (C) same as A but for the baseline sigma rhythm expressed before SSO events; (D) same as A but for the power of slow wave activity. Of note, for (D) no significant correlation appeared when considering both ROIs.

Suppl. Fig 3



Suppl. Figure 3. A) The changes from the control night to the MD night of slow wave activity power was considered for correlation with the deprivation index measured **after** sleep (DI after). The scalp map shows the spatial distribution of correlation: no significant correlation appeared when considering any electrodes in the defined ROIs (black crosses: sensory-motor control ROI, yellow crosses: occipital ROI, red crosses: prefrontal ROI). Scatterplot shows the putative relationship between slow wave activity power averaged over the prefrontal ROI and DI after. Colour of dots spans from black to red as a function of individual plasticity. (B) same as A but for the sigma activity power; (C) same as A but for the occurrence of sleep slow oscillations (SSO); (D) same as A but for the steepness of slope+ of SSOs.