

Sleep slow oscillations favour local cortical plasticity underlying the consolidation of reinforced procedural learning in human sleep

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Summary

We investigated changes of slow-wave activity and sleep slow oscillations in the night following procedural learning boosted by reinforcement learning, and how these changes correlate with behavioural output. In the Task session, participants had to reach a visual target adapting cursor's movements to compensate an angular deviation introduced experimentally, while in the Control session no deviation was applied. The task was repeated at 13:00 hours, 17:00 hours and 23:00 hours before sleep, and at 08:00 hours after sleep. The deviation angle was set at 15° (13:00 hours and 17:00 hours) and increased to 45° (reinforcement) at 23:00 hours and 08:00 hours. Both for Task and Control nights, high-density electroencephalogram sleep recordings were carried out (23:30–19:30 hours). The Task night as compared with the Control night showed increases of: (a) slow-wave activity (absolute power) over the whole scalp; (b) slow-wave activity (relative power) in left centro-parietal areas; (c) sleep slow oscillations rate in sensorimotor and premotor areas; (d) amplitude of pre-down and up states in premotor regions, left sensorimotor and right parietal regions; (e) sigma crowning the up state in right parietal regions. After Task night, we found an improvement of task performance showing correlations with sleep slow oscillations rate in right premotor, sensorimotor and parietal regions. These findings suggest a key role of sleep slow oscillations in procedural memories consolidation. The diverse components of sleep slow oscillations selectively reflect the network activations related to the reinforced learning of a procedural visuomotor task. Indeed, areas specifically involved in the task stand out as those with a significant association between sleep slow oscillations rate and overnight improvement in task performance.

KEYWORDS

electroencephalogram, implicit learning, memory consolidation, slow oscillations, slow waves, structural learning

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1 | INTRODUCTION

The fundamental role of sleep in the consolidation of acquired memories is nowadays universally acknowledged. Starting from the seminal work of Jenkins and Dallenbach (1924) about the influence of sleep on the retention of verbal memories, at present it is widely accepted that different types of memories, such as declarative, procedural and emotional ones, benefit from sleep. While the associations between specific neural oscillatory patterns occurring during sleep and memory consolidation processes can be thoroughly investigated in animal models using invasive approaches such as intra-cortical electroencephalogram (EEG) recordings, both the higher complexity of human behaviours (i.e. being skilled in performing a task; Peters, Smith, & Smith, 2007), and the use of non-invasive approaches due to rightful ethical issues, make the identification of these associations more challenging.

There is converging evidence that slow-wave activity (SWA; 0.5–4 Hz) accomplishes a prominent role in declarative and procedural memory consolidation occurring during sleep (Rasch & Born, 2013). Different mechanisms produce oscillations in the SWA band (Amzica & Steriade, 1998), but the specific contribution of the diverse components in memory consolidation processes has not been fully elucidated, yet (Crunelli et al., 2018).

Slow-wave activity contains a fundamental contribution from the sleep slow oscillation (SSO), 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). In addition, a contribution to SWA comes from bistable oscillations (delta waves) coordinated by delta clock thalamic neurons in the reticular thalamic nuclei and by intracortical-generated delta waves (Amzica & Steriade, 1998; Crunelli et al., 2018; Steriade, 2003).

Delta activity has been associated to homeostatic regulation and synaptic downscaling (Borbély & Achermann, 1999; Genzel, Kroes, Dresler, & Battaglia, 2014; Tononi & Cirelli, 2014). At variance, no homeostatic behaviour is evident for SSOs (Achermann & Borbély, 1997), which are instead critical for memory consolidation (Genzel et al., 2014; Rasch & Born, 2013). The central role of the SSO in the retention of newly acquired skills has been convincingly elucidated in the active system consolidation hypothesis (Rasch & Born, 2013). The authors assume a pivotal role of slow-wave sleep (SWS) in the retention of declarative memories, as retrieval and encoding have been shown to critically depend on the fine-tuned interaction between cortical SSO, thalamo-cortical sleep spindles and spontaneous hippocampal ripples. In this context, a tight correlation between specific morphological changes of SSOs and the effectiveness of declarative memory consolidation has been observed (Mölle, Eschenko, Gais, Sara, & Born, 2009).

At variance with declarative memories, the identification of the neurobiological mechanisms underlying the consolidation of procedural memories, and specifically of the role of the SSO in these mechanisms, is still an open issue.

Previous studies have shown a use-dependent local increase of SWA power density during sleep following procedural learning paradigms (Hill, Tononi, & Ghilardi, 2008; Huber, Ghilardi, Massimini, &

Tononi, 2004). However, to our best knowledge, no study has ever investigated the modifications of SSO features as a function of previous procedural tasks.

In this context, Huber et al. (2004), who investigated SWA changes related to the visuomotor paradigm of adapting arm movements to a rotated frame of reference (Ghilardi et al., 2000), suggest a prominent role of SSO, as they observed: “an increase in power predominantly in the SWA frequency range, as well as a slight decrease in power in the sigma band. The increase was especially evident within the low delta band (< 2 Hz) and at frequencies corresponding to the slow oscillation (< 1 Hz)”. The increase of SWA during the first cycle of non-rapid eye movement (NREM) sleep was detected in the same areas (right parietal cortex, Brodmann Areas, BA 7 and 40), which are plastically activated by the task, as observed in a previous study (Ghilardi et al., 2000). However, Huber et al. (2004) did not investigate changes of specific SSO characteristics, such as event rate, morphological structure and fast-rhythms grouping (Crunelli & Hughes, 2010; Mölle, Marshall, Gais, & Born, 2002), associated with procedural learning. It is fair to underline that criteria for the detection and characterization of SSOs in humans were established in the years immediately following the study of Huber and colleagues (Massimini, Huber, Ferrarelli, Hill, & Tononi, 2004; Menicucci et al., 2009; Piarulli et al., 2010; Riedner et al., 2007).

On this basis, we enrolled healthy volunteers for performing a visuomotor task experiment consisting of reaching targets on a monitor while adapting arm movements to a rotated frame of reference. Differently from previous studies (Ghilardi et al., 2000; Huber et al., 2004), the experimental design was ad hoc modified to induce a reinforcement learning effect, aimed at boosting the procedural one: learning how to perform a specific procedural task is faster when it is anticipated by experiences sharing similar features: in the visuomotor domain, subjects are faster to counter a novel rotation frame if preceded by a set of tasks with variable, even different, rotation angles (Bond & Taylor, 2017). Reinforcement learning is in fact related to the abstraction of new rules, and it has been demonstrated to activate the rostro-caudal axis of the frontal cortex and the dorsal premotor cortex (Badre, Kayser, & D’Esposito, 2010).

Herein we investigated SWA (absolute and relative) power and SSO features to verify whether they share a common role, or they rather exert different functions in brain plasticity. To this aim, we mapped changes of cortical distributions of SWA and SSO features: (a) putatively linked to reinforcement and procedural learning-related plastic changes; and (b) we evaluated associations between behavioural output (i.e. overnight changes in task execution performance) and SWA/SSO features.

2 | MATERIALS AND METHODS

2.1 | Participants and experimental protocol

Ten right-handed healthy volunteers (mean age 23 years, range 20–28 years; five males, five females), participated in the study.

The eligibility of each volunteer was evaluated by semi-structured interviews conducted by a senior physician and psychiatrist (AG) on the basis of the following inclusion criteria: no history of psychiatric/neurological disorders (including sleep disorders based on the Pittsburgh Sleep Quality Index), being drug free for at least 6 months, no (or corrected) visual deficits. All eligible volunteers signed an informed written consent. The study was approved by the Local Ethical Committee and complied with the tenets of the Declaration of Helsinki (2013). Enrolled volunteers were instructed to restrain from alcohol intake, coffee intake and physical work in the days of the experimental sessions.

2.2 | Experimental procedures

Each volunteer spent 3 nights at the sleep laboratory at a time distance of 1 week from another: (a) an adaptation night during which the volunteer slept wearing the EEG cap without signals recording; (b) a Control night (CN; no rotation task); (c) a Task night (TN; rotation task). During the adaptation night, sleep EEG was continuously monitored by a sleep expert (AI, ZA and MD) in order to detect difficulties in achieving and maintaining sleep. None of the volunteers showed difficulties in sleeping in the laboratory setting. For each volunteer, the order of CN and TN sessions was randomized following a restricted randomization procedure (Lachin, Matts, & Wei, 1988): five subjects were submitted first to CN and then to TN, and the other five to TN and then to CN.

During both CN and TN, sleep EEG was recorded using a Net Amps 300 system (Electrical Geodesic) with a 128-electrodes HydroCel Geodesic Sensor Net. Electrode impedances were kept below 50 k Ω and signals were acquired with a sampling rate of 500 Hz, using Electrical Geodesic Net Station software, Version 4.4.2.

Before each CN and TN, the volunteer was asked to perform three sessions (S1 at 13:00 hours, S2 at 18:00 hours, and S3 at 23:00 hours) of a visuomotor task (each lasting about 10 min). After the last session (S3), the volunteer was allowed to sleep undisturbed

until 07:30 hours. A re-test visuomotor task session (S4) was conducted 30 min after awakening (Figure 1). The 30-min period was introduced both to counter the effects of sleep inertia (Tassi & Muzet, 2000) and to allow a gradual adaptation to daylight.

During the visuomotor task, each participant had to sit in front of a PC monitor (60 cm from the screen to the eyes) and handle a joystick with the dominant hand. A custom-made PC program was implemented for performing the task: eight radial empty circles (diameter 2 cm) placed at 15 cm from the monitor centre were presented on the screen (the angular displacement between adjacent circles was of 45°); a black-filled circle (diameter 2 cm) was presented at the centre of the monitor. The task consisted in moving a pointer from the central black-filled circle to reach the peripheral circle that changed from empty to grey-filled (visual target) using the joystick. A hit was obtained whenever the participant reached the target within 800 ms from its colour change, and moved back the cursor to the central black circle before the presentation of the next target. Whenever the hit was successful, a feedback was provided to the participant by changing the target colour to black-filled until the presentation of the next target (at that time, the previous target was restored to empty-filled).

Each session was divided into five blocks of trials; during each block, 90 targets were randomly presented with a time lag of 1.5 s between consecutive targets. At the end of each block, the volunteer could rest and decide when to start the next block by pressing the spacebar.

The visuomotor task we developed is similar to that used by Ghilardi et al., (2000) and Huber et al., (2004). At variance with those studies, a joystick was used, and the task was repeated multiple (three) times before sleep. Two different versions of the task were performed before the experimental nights. The task associated to the CN consisted in reaching the target without any rotation of the frame of reference, while the task associated to the TN consisted in reaching the target while adapting the cursor's movements to a rotated frame of reference (same as rotating the monitor around its perpendicular axis but obtained via software). Each volunteer had thus to adapt his/her arm movement to compensate

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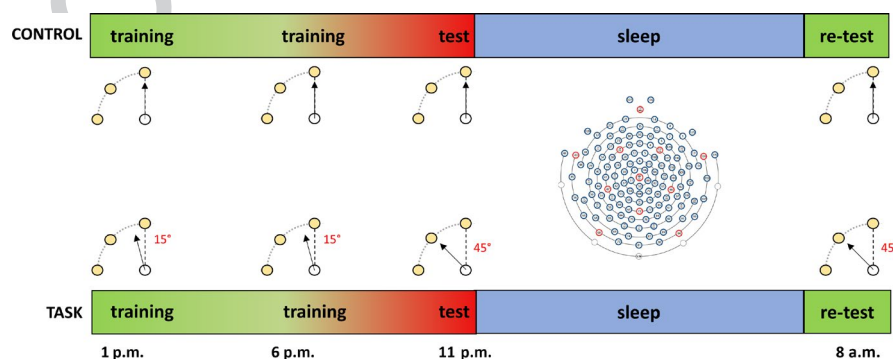


FIGURE 1 Experimental protocol. Timeline of the experimental procedures from session 1 (S1) to session 4 (S4). For the Control session, no deviation angles during blocks of visuomotor task execution were imposed; for the Task session, different deviation angles during blocks of visuomotor task execution were imposed: 15° for S1 and S2, and 45° for S3 and S4. Note that only three out of the eight circles are shown in the procedural task scheme

the angular deviation caused by the rotated frame. The angular deviation was set at 15° in S1 and S2, and at 45° in S3. The angular deviation of S4 (task performed the morning after sleep) was set at 45° as in S3.

In line with previous studies (Ghilardi et al., 2000; Ghilardi, Moissello, Silvestri, Ghez, & Krakauer, 2009), the individual performance at the task was evaluated using the directional error (DE) as a marker of spatial accuracy of the movements. The DE is defined as the unsigned angle between the line from the monitor centre to the target, and the line from the centre to the reversal point of the trajectory (point of the trajectory most distant from the monitor centre). For each session, the mean DE was estimated as the average over the session's blocks.

2.2.1 | Sleep electroencephalogram preprocessing and staging

Electroencephalogram signals were off-line band-pass filtered between 0.3 and 45 Hz, and referenced to the average of the mastoids' potentials (Berry et al., 2017). Channels located on the neck, forehead and cheeks that mostly contribute to movement-related noise were discarded, retaining thus 90 channels out of 128.

Signals were visually inspected and sleep-scored according to the AASM criteria (Berry et al., 2017). Noisy channels were substituted with signals obtained via spline interpolation (Junghöfer, Elbert, Tucker, & Rockstroh, 2000), and epochs contaminated by artefacts (e.g. movements, muscle contractions) were discarded.

Electroencephalogram pre-processing and analyses were performed using tailored codes written in Matlab (MathWorks); scalp maps were obtained using modified EEGLAB Toolbox functions (Delorme & Makeig, 2004).

Both for CN and TN, we evaluated sleep macrostructure by extracting a set of time-domain parameters: sleep latency (time length of the transition from lights-off to the first N2 sleep episode, min); wake after sleep onset (WASO) event count; WASO duration (min); total N2, N3 and rapid eye movement (REM) stages duration (min); and REM latency (time from sleep onset to the first REM sleep episode, min).

2.2.2 | Non-rapid eye movement sleep spectral characterization

Noisy signals were substituted with signals obtained using spline interpolation (Junghöfer et al., 2000). EEG signals were then re-referenced to the average over the electrodes in line with the work of Huber et al. (2004).

Non-REM sleep (sleep stages N2 and N3) EEG power was estimated for five frequency bands of interest: SWA (0.5–4 Hz); theta (θ : 4–8 Hz); sigma (σ : 12–16 Hz); beta (β : 17–30 Hz); and gamma (γ : 30–45 Hz).

Power densities were estimated applying a Hamming-windowed FFT on 10-s consecutive EEG epochs and log-transformed. In the following analysis, we considered both absolute and relative powers. For each epoch, 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 epochs.

The relative power was obtained for each band and electrode as the ratio between the absolute power in the band and the average band power over the electrodes and NREM epochs (Huber et al., 2004).

2.2.3 | Sleep slow oscillation detection and characterization

Sleep slow oscillation events within NREM sleep periods (sleep stages N2 and N3) were detected and characterized using a previously published and validated Likeness Method (for schematic illustrations of the SSO detection algorithm, see Menicucci et al., 2009 and Piarulli et al., 2010). EEG signals, after a proper pre-processing (see Section 2.3.1) were filtered in the 0.5–4 Hz band (Chebyshev II filter). According to the Likeness Method, we first classified as a classical SSO each wave consisting of: (a) two zero-crossings separated by 0.3–1.0 s, the first one having a negative slope; (b) a negative peak between the two zero-crossings with a voltage < 80 μ V; (c) a negative-to-positive peak amplitude of at least 140 μ V. Then, concurrent SSO waves (within a 400 ms interval) were grouped into events and sorted according to time locations of their negative peaks.

As a further step, events were enriched by clustering full-fledged SSOs with concurrent similar waves (selected based on their phase synchronization with classical SSO), even if sub-threshold with respect to standard criteria (Massimini et al., 2004).

For each subject, session (CN–TN) and electrode, SSOs were characterized by the following parameters: SSO rate (number of waves per minute); pre-down state peak amplitude; negative peak (down state) amplitude; and positive peak (up state) amplitude (Menicucci et al., 2009).

The pre-down state peak was identified as the local maximum in the time interval starting from 250 ms before the SSO negative zero-crossing to the zero-crossing itself. The pre-down state amplitude was estimated from a baseline level defined as the mean value of the signal in the window from 750 ms before to 250 ms before the negative zero-crossing. Note that the time window for the pre-down state peak detection was chosen in line with previously published studies (Menicucci et al., 2013, 2015). At variance with previous studies investigating the pre-down state peak (Menicucci et al., 2013, 2015), we here estimated this component for all the SSO events and not just for the temporally isolated ones (SSO events separated from the previous and following ones by at least 4 s). Results obtained from the whole SSO dataset qualitatively overlapped those obtained from the subset of temporally

isolated SSOs (the latter were more noisy owing to the lower number of retained SSO events), thus we carried on the analysis on the complete dataset (data not shown).

Fast-rhythms grouping during the up state of the SSO was estimated as the power density difference between the up and down states in σ (12–16 Hz), β (17–30 Hz) and γ (30–45 Hz) bands. Band power densities were estimated both for the down and up states using a Hamming windowed FFT (window length of 500 ms), respectively, centred on the SSO negative and positive peaks (Mölle et al., 2002).

2.3 | Statistical analyses

Herein, both between nights comparisons (TN–CN) and correlations were subject based, that is, the average of each feature was estimated for each condition and, when appropriate (SWA and SSO parameters), for each electrode.

T-statistics permutation tests based on 1,000 randomizations (paired samples; Ludbrook & Dudley, 1998) were used for assessing CN and TN overnight differences in visuomotor task performance (by comparing the DE values obtained during S4 with those of S3), and for assessing differences between sleep macrostructure recorded during TN and CN (by comparing each sleep macrostructural parameter).

For each SWS parameter (absolute and relative power densities in the five bands of interest and SSO features), electrode-wise differences between TN and CN were estimated by paired *t*-tests; *t*-values significance was then assessed using a single threshold permutation test for the maximum *t*-statistic based on 1,000 randomizations (Nichols & Holmes, 2001; see Appendix S1, SI-statistics).

Associations between sleep (SWA and SSO parameters) and behavioural output were investigated by Pearson's correlation analyses: electrode-wise correlations with DE measures were conducted for each DE measure–SWS parameter couple.

Three sets of correlation analyses were thus conducted:

1. correlations with the absolute DE values in the evening (S3) before sleep, accounting for the putative effect of motor ability on the following NREM sleep;
2. correlations with DE changes over the wake period (S3 minus S1), accounting for the putative effect of motor ability improvement during the day on the following NREM sleep;
3. correlations with DE overnight changes (S4 minus S3), accounting for the putative relation between NREM sleep and behavioural overnight improvement.

For each DE measure–SWS parameter couple, the significance of Pearson's correlation values was assessed applying a single threshold permutation test for the maximum *r*-statistics based on 1,000 randomizations (see SI-statistics). Note that SWS parameters (absolute and relative powers and SSO features) were estimated for all the electrodes.

The single threshold permutation tests were chosen to deal with the multiple testing issue that arises when considering simultaneous testing on dense electrode arrays, as: (a) it does not require any assumption on data normality; and (b) is a simple yet robust approach to control for type I statistical errors (i.e. rejection of a true null hypothesis). All statistical analyses were conducted using tailored codes written in Matlab code (MathWorks), and tests were considered significant at a value of $p < .05$ after correction for multiple comparisons.

3 | RESULTS

3.1 | Behavioural output

A significant overnight improvement in visuomotor task performance was apparent for TN (lower DE in S4 as compared with S3, $p < .05$; Figure 2); no significant performance change was observed for CN.

3.2 | Non-rapid eye movement sleep spectral analysis

Sleep macrostructural parameters did not differ between CN and TN (SI-Table S1).

When considering absolute powers, comparisons between TN and CN showed: (a) a widespread significant increase of SWA during TN as compared with CN (Figure 3a; and SI-Table S2); (b) no significant change for any other band (theta, sigma, beta and gamma; SI-Table S2).

When considering relative powers, comparisons between TN and CN showed: (a) a local significant increase of SWA during TN as compared with CN in left centro-parietal electrodes (Figure 3b; SI-Table S2); (b) no significant change for any other band (theta, sigma, beta and gamma; SI-Table S2).

No significant correlation was found between EEG band powers (both absolute and relative) and either absolute DE at S3 (ability to perform the task in the evening), DE improvement over the wake period (S3–S1) or overnight changes of DE (S4–S3), coherently for TN and CN (SI-Tables S3, S4 and S5).

3.3 | Sleep slow oscillation features

When considering SSO, comparisons between TN and CN highlighted the following.

1. A significant increase of SSO rate from CN to TN in bilateral fronto-central regions (Figure 4).
2. A significantly higher amplitude of the pre-down state peak (early positive peak) during TN in frontal regions left central, and parietal regions (Figure 5a).

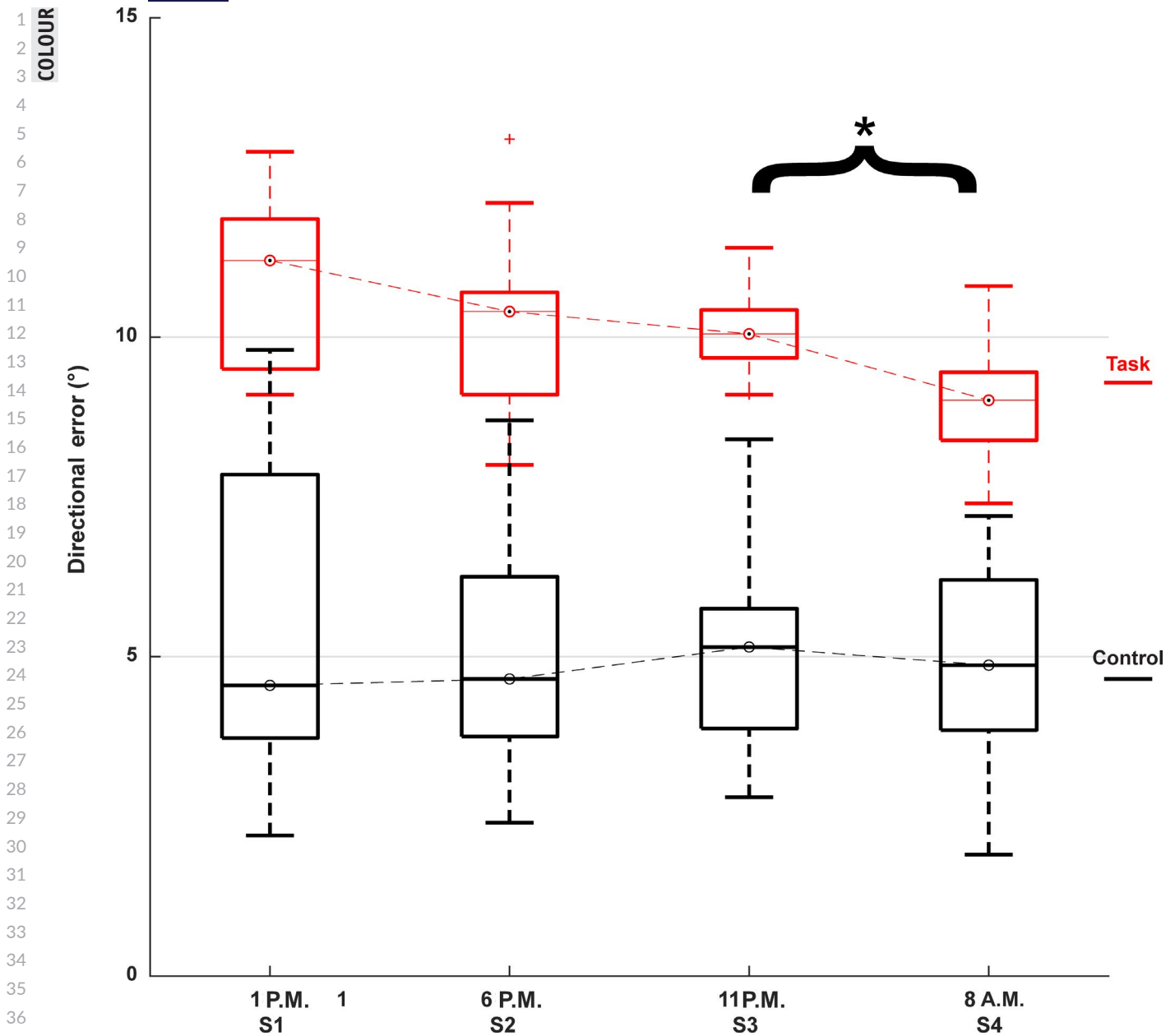


FIGURE 2 Visuomotor task performance. Trends of performance (directional error, DE) are shown for the Task session (red) and the Control session (black). S1, S2, ..., S4 stand for session 1, session 2, ..., session 4. A significant improvement (significant decrease of DE— $p < .05$ according to permutation-based t -test—indicated with asterisk and brace in the figure) was apparent in the Task session when comparing session 4 with session 3 (post- versus pre-sleep comparison). “+” symbol identifies outliers (a sample is an outliers if it is greater than $q3 + 1.5 \times (q3 - q1)$ or less than $q1 - 1.5 \times (q3 - q1)$, where $q1$ and $q3$ are, respectively, the 25th and 75th percentiles of the data distribution)

3. No significant difference in the down state (negative peak) amplitude (Figure 5b).
4. A significantly higher amplitude of the up state (late positive peak) during TN in prefrontal and frontal regions, and in right parietal regions (Figure 5c).
5. A significantly higher sigma activity crowning the up state for TN in right parietal regions (Figure 5d).
6. No significant difference either for beta or gamma activity crowning the up state (SI-Table S2).

The t -values significance thresholds for TN-CN comparisons are presented in SI-Table S2.

3.4 | Sleep slow oscillation and behavioural output

No significant correlation was found between SSO features and either DE at S3 or DE improvement over the wake period (S3–S1; SI-Tables S4 and S5).

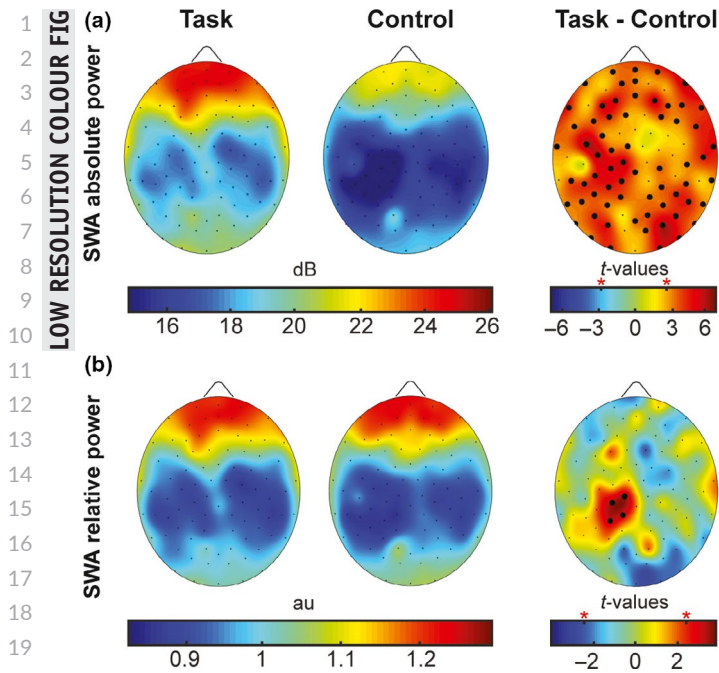


FIGURE 3 Differences in slow-wave activity (SWA) power between Task night (TN) and Control night (CN). Average SWA maps of TN and CN are presented on the left (columns 1–2): absolute power in (a), and relative power in (b). Band power comparisons between TN and CN showed: (i) significantly higher SWA (0.5–4 Hz) absolute power over the whole scalp during TN (a); and (ii) significantly higher SWA relative power in left centroparietal electrodes (b). The t -values maps related to comparisons are presented on the right (column 3): electrodes showing significant between-condition differences are represented by black dots. Red asterisks on colour-bars identify thresholds for significance at $p < .05$ corrected for multiple comparisons

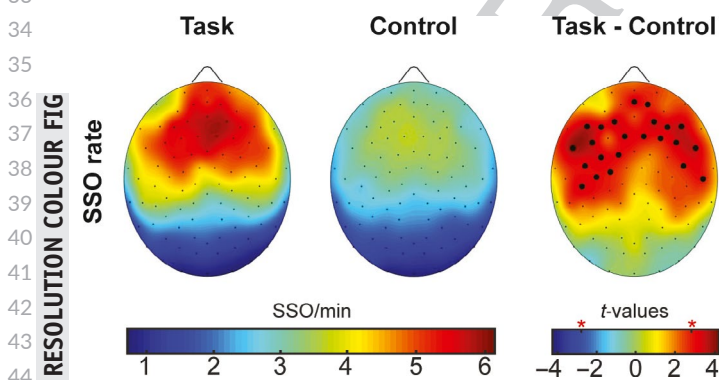


FIGURE 4 Sleep slow oscillation (SSO) rate and procedural learning. A significantly higher SSO rate was observed on fronto-central electrodes during Task night (TN) as compared with Control night (CN). Average maps of SSO rate are presented on the left. The t -values map related to the comparison is presented in the right panel: electrodes showing significant between-condition differences are represented by black dots. Red asterisks on the colour-bar identify thresholds for significance at $p < .05$ corrected for multiple comparisons

A significant correlation between the improvement of visuomotor task performance in the morning after TN (i.e. overnight changes of DE) and SSO rate during TN was found in right frontal regions, central regions (midline and right hemisphere) and in right parietal regions (Figure 6; SI-Table S3). At variance, no significant correlation was found between any SSO feature and overnight changes of DE also when considering CN session (SI-Table S3).

4 | DISCUSSION

We investigated changes of SWS following multiple repetitions during the day of a procedural learning task. We adopted the procedural task developed by Ghilardi et al. (2000): a visuomotor task of adapting arm movements to a rotated frame of reference. The procedural task was administered using a reinforcement learning paradigm (Bond & Taylor, 2017): differently from previous works reporting the effects of a single session of the task before sleep, herein the task was repeated three times (13:00 hours, 17:00 hours and 23:00 hours) before sleep, increasing the deviation angle in the last session (15°, 15°, 45°; Figure 1). The deviation angle of the last pre-sleep session was maintained in the re-test session performed the morning after sleep.

Before proceeding with the discussion, we would like to acknowledge a limitation of this study: if on the one hand, the use of reinforcement has helped to boost procedural learning effects; on the other hand, the experimental design does not allow to disentangle pure procedural from reinforcement learning effects.

The introduction of a second control condition (procedural learning without reinforcement) would have been appropriate in principle but not feasible in the same group as it would have led to unavoidable pitfalls: the simple procedural “control” condition would influence or be influenced by the following/previous reinforced experimental condition (the first learning session always affects the second learning session, whatever the order within a reasonable time interval between nights). Further studies attempting to disentangle reinforcement from procedural learning effects should use two different groups (one submitted to the reinforced procedural task and the other to the simple procedural task).

The “reinforced” procedural task was associated with stable task performance throughout the day (from S1 to S3, as apparent in Figure 2; however, of note, S3 was characterized by a higher deviation angle as compared with the previous sessions), and a significant improvement across sleep in line with findings from Huber et al., 2004 (S3–S4; Figure 2).

Herein, we performed two complementary analyses of SWA: one studied the absolute SWA power, the other replicated the approach of Huber et al. (2004) using relative powers.

We observed an increase of SWA absolute power over the whole cortical mantle in the TN, including thus premotor and motor regions and posterior ones specifically involved in visuomotor integration. However, as SWA increase extends well beyond these task-specific areas, we hypothesize a concurrent (if not

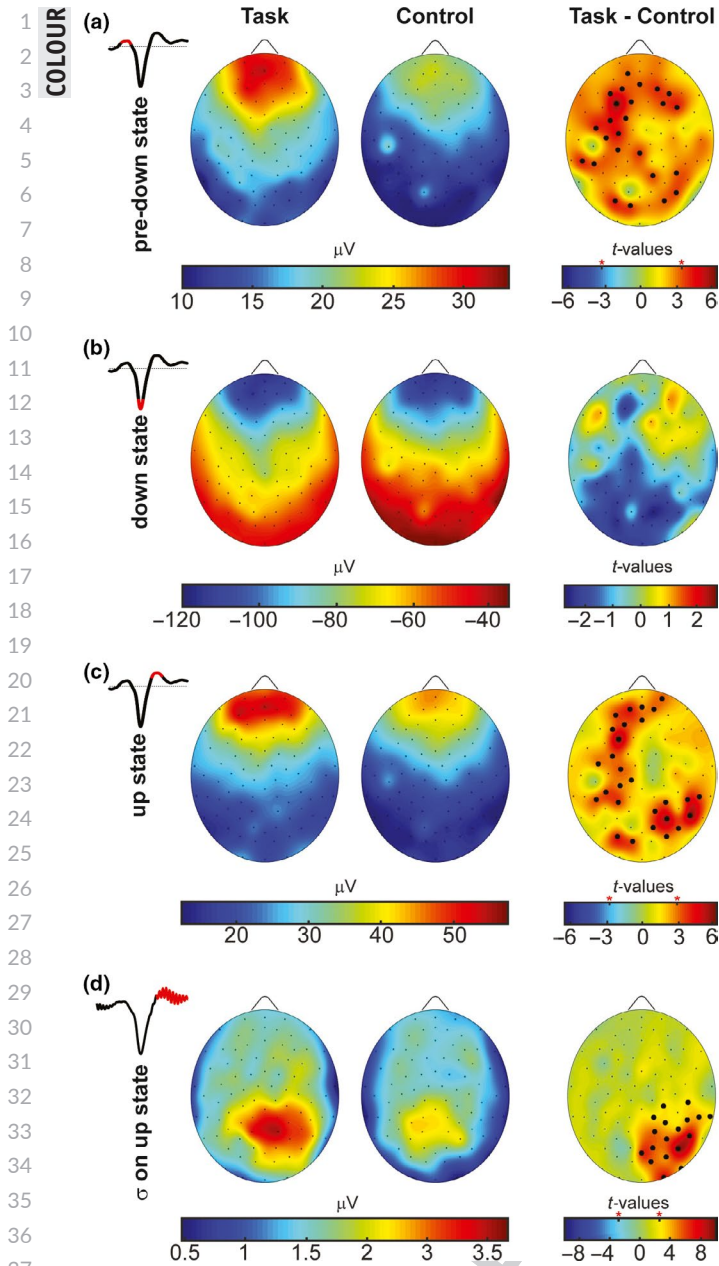


FIGURE 5 Sleep slow oscillation (SSO) shape analysis. (a–c) The amplitude distribution of the SSO components over the scalp detected during Task night (TN on the left) and Control night (CN in the middle), and the between-session comparison map (t-values). (a) The pre-down state amplitude during TN resulted significantly higher as compared with CN in large scalp areas ranging from prefrontal and frontal electrodes to left central and parietal ones. (b) The negative peak amplitude (down state) did not show any significant differences between the two nights. (c) The late positive peak amplitude (up state) was significantly higher in frontal, left central and right parietal electrodes. (d) Sigma power density crowning the up state. Note that sigma crowning is estimated as the mean sigma power during the up state minus the mean sigma power during the down state. Sigma crowning was significantly higher in parietal regions of the right hemisphere during TN as compared with CN. For all t-values maps, electrodes showing significantly higher values in TN as compared with CN are identified by black dots. Asterisks on the colour-bars denote the t-threshold corresponding to $p < .05$ corrected for multiple comparisons

(Ghilardi et al., 2000), others an activation in the left hemisphere (Mutha et al., 2011), and still others reported bilateral activations (Graydon, Friston, Thomas, Brooks, & Menon, 2005; Grefkes, Ritzl, Zilles, & Fink, 2004).

A striking difference emerges between the analyses on absolute powers and those on relative ones: the two analyses appear to be complementary and reveal two different aspects of SWA: on the one hand a general task-dependent absolute SWA increase, and on the other a very local increase in centro-parietal areas possibly related to visuomotor adaptation. These results suggest that sleep homeostasis has both a global component (as apparent from SWA absolute power) and a local component triggered by the

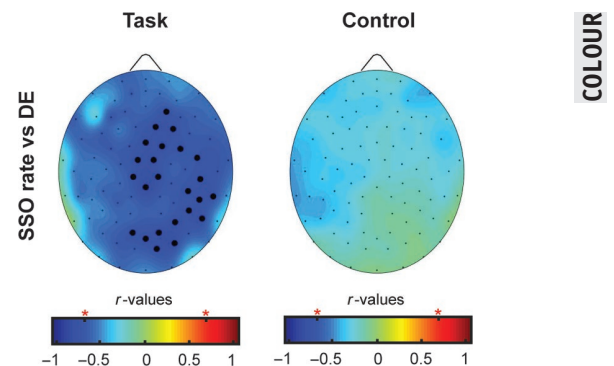


FIGURE 6 Correlation between directional error (DE) and sleep slow oscillation (SSO) rate performed for each experimental session (Control night [CN] and Task night [TN]). No significant correlation was found for CN (right plot), while a significant negative correlation on fronto-central and parietal electrodes with a right hemispheric prevalence was observed for TN. The negative correlation indicates that subjects with a higher overnight improvement in task performance (decreased DE) showed a greater increase of SSO rate. Electrodes showing significant correlations are identified by black dots. Red asterisk on the colour-bar indicates r-values corresponding to $p < .05$ corrected for multiple comparisons

prominent) role of enhanced wakefulness intensity induced by the skill-demanding paradigm of the Task session. Indeed, SWA plays a general homeostatic role for rebalancing neuronal activity as a function of the intensity and duration of waking as consistently described in the delta homeostatic model (Feinberg & March, 1995), in the two processes model (Borbély, Daan, Wirz-Justice, & Deboer, 2016), and in the synaptic homeostasis hypothesis (Tononi & Cirelli, 2006).

At variance, when considering relative SWA power, we found a local increase of SWA in a centro-parietal cluster of electrodes situated in the left hemisphere. There is converging evidence of a fundamental role of the superior parietal cortex in the adaptation to novel visuomotor conditions (Mutha, Sainburg, & Haaland, 2011); however, the debate remains open on its possible lateralization. Studies have reported a right lateralization

1 learning task (SWA relative power), as already indicated by Huber
2 et al. (2004).

3 Beyond assessing SWA spectral power, a measure that provides
4 an integrated yet rough estimate of slow-oscillation number and
5 amplitude (Siclari, Bernardi, Cataldi, & Tononi, 2018) together with
6 delta waves (Crunelli et al., 2018), we investigated how specific char-
7 acteristics of SSOs relate to the overnight performance increase in
8 the procedural task.

9 The analysis of SSOs had thus the objective of providing specific
10 and sensitive markers of learning-dependent plasticity, ruling out
11 the influence of delta wave activity that is instead associated with
12 homeostatic regulation processes (Genzel et al., 2014; Tononi &
13 Cirelli, 2014).

14 The dichotomy between SSO and delta waves has been described
15 by several studies both in the animal model and in humans (Dang-Vu
16 et al., 2008; Genzel et al., 2014; Kim, Gulati, & Ganguly, 2019; Mölle
17 et al., 2002): Dang-Vu et al. (2008) found that SSOs are selectively
18 associated to BOLD activations in the brainstem, cerebellum and
19 parahippocampal gyrus, while delta waves to frontal BOLD activa-
20 tions (Dang-Vu et al., 2008). In addition, the SSO underpins both un-
21 consciousness (Gemignani et al., 2015) and it is critical for memory
22 consolidation (Genzel et al., 2014; Rasch & Born, 2013; Timofeev &
23 Chauvette, 2017), while delta activity has been associated to ho-
24 meostatic regulation and synaptic downscaling (Genzel et al., 2014;
25 Tononi & Cirelli, 2014). Indeed, delta activity decreases across sleep
26 cycles, and it is enhanced in the sleep following sleep deprivation:
27 the substitution of sleep spindles with smooth delta waves in the
28 sleep following deprivation is a proof of the common thalamic or-
29 igin of these rhythms (Achermann & Borbély, 1997; Bersagliere &
30 Achermann, 2010; Borbély & Achermann, 1999; Campbell, Higgins,
31 Darchia, & Feinberg, 2006).

32 Although a role in thalamic plasticity has been recently sug-
33 gested also for delta activity (Crunelli et al., 2018), the complemen-
34 tary mechanisms—unconsciousness and plasticity—gathered in the
35 SSO make this wave a convincing electrophysiological candidate for
36 a leading role in plastic regulatory processes underlying the con-
37 solidation of different types of memories (be they declarative or
38 not-declarative; Miyamoto, Hirai, & Murayama, 2017).

39 The thorough investigation of SSO features was also based on
40 a fundamental statement of Huber et al. (2004): "... Consistent with
41 a homeostatic response, there was an increase in power predom-
42 inantly in the SWA frequency range, as well as a slight decrease
43 in power in the sigma band. The increase was especially evident
44 within the low delta band (< 2 Hz) and at frequencies correspond-
45 ing to the slow oscillation (< 1 Hz)...". In line with this finding and
46 following the hypothesis of a pivotal role of the SSO in promoting
47 plastic cortical changes (Landsness et al., 2009), we characterized
48 changes of features of SSOs associated with the consolidation of
49 a procedural learning in the context of a reinforcement paradigm.
50 We observed:

51
52 1. a higher SSO rate in bilateral fronto-central regions (including
53 sensorimotor and premotor areas);

2. a higher amplitude of the two positive deflections enclosing the
down state (pre-down state and up state) in frontal areas (in-
cluding premotor regions), in left sensorimotor and right parietal
regions;
3. a higher amount of sigma activity crowning the up state in parietal
regions of the right hemisphere;
4. a significant correlation between the improvement of visuomotor
task performance and SSO rate in right premotor regions, central
and right sensorimotor areas, and in right parietal regions.

The increased SSO rate during TN over fronto-central and right
posterior territories could reflect plastic effects on cortical circuit-
ries involved in the task: (a) premotor and sensorimotor areas pro-
moting the acquisition and consolidation of new motor schemes
(Ghilardi et al., 2000); (b) task-specific associative parietal areas (BA
7–40; Ghilardi et al., 2000; Huber et al., 2004); (c) frontal territories
related to the effects of reinforcement learning (Badre et al., 2010)
and motor programming (Picard & Strick, 2001; Rakusa, Busan,
Battaglini, & Zidar, 2017).

We further explored associations between task-induced cortical
plasticity and SSO by studying its morphological changes. The
two positive phases of the SSO, namely the pre-down state and the
up state, appeared to be selectively affected by learning: interest-
ingly, both positive phases showed a significant amplitude increase
in frontal areas, left central and right parietal regions, the former
involving wider scalp territories.

We have previously hypothesized (Menicucci et al., 2013) that
the pre-down state can be considered as a marker of local cortical
excitability.

Because spontaneous SSOs share the same molecular and neu-
rophysiological mechanisms of K-complexes (Crunelli, Cope, &
Hughes, 2006; Steriade, 2006), the pre-down state as the P200, which
represents its counterpart in K-complexes (Laurino et al., 2014; Laurino,
Piarulli, Menicucci, & Gemignani, 2019), could well act as an ignition for
the opening of activity-dependent K^+ -channels (Sanchez-Vives et al.,
2010), promoting thus the initiation of a down state. According with
this interpretation, the higher amplitude of the pre-down state in TN
as compared with CN, observed in frontal areas, in left premotor, left
sensorimotor and in right parietal areas could reflect a task-specific in-
crease of the local cortical excitability in the areas selectively activated
by the procedural learning task and by reinforcement learning.

The up state amplitude, on the other side, reflects the size of
the underlying synchronized neuronal population characterized
by membrane potential fluctuations towards depolarization levels,
which in turn are mainly promoted by thalamo-cortical interplays
(Timofeev & Chauvette, 2011).

During the up state, Ca^{2+} entry in dendrites of cortical neurons
promotes synaptic and cellular plasticity and reactivates cortical and
subcortical memories, thus favouring their consolidation (Destexhe,
Hughes, Rudolph, & Crunelli, 2007; Rasch & Born, 2013; Sejnowski
& Destexhe, 2000).

From an electrophysiological standpoint, Ca^{2+} entry depolar-
izes neurons' membrane potentials, inducing a synchronized neural

spiking that is detectable by surface EEG as a high-frequency EEG activity crowning the up state, mainly in the sigma band, the frequency range of thalamic spindle activity (Lüthi, 2014). In line with these findings, we observed a significant increase of sigma activity crowning the SSO up state in right parietal regions, including associative areas crucial for visuomotor integration (Ghilardi et al., 2000).

At a behavioural level, Huber et al. (2004) highlighted a positive effect of SWS on memory consolidation, as apparent by correlations between local increases of SWA and specific indices of task improvement. We found a tight association between the overnight improvement in task performance (reduction of the DE) and SSO rate in right frontal regions including premotor areas, in central and right sensorimotor areas and in regions belonging to the right parietal lobe (Figure 6). We hypothesize that the enhanced visuomotor ability is sustained by reinforcement learning, as indicated by the significant correlations with SSO rate in right frontal regions (Badre et al., 2010), and procedural learning, as apparent from the correlations over right premotor areas, central sensorimotor regions and right parietal areas (Ghilardi et al., 2000).

We believe that at this point some considerations are due: scalp areas showing significant correlations between SSO rate and overnight task performance are different from those showing a significant SSO rate increase in the comparison between TN and CN. This apparent discrepancy is solved when looking at the different aims of the within-condition correlation analyses with DE and the between-condition comparisons of SWS parameters:

- within-condition correlation analyses give insights on which SWS features are associated with the degree of overnight performance improvement (i.e. the higher the SSO rate, the higher the overnight improvement);
- between-condition comparisons unveil the effects of the reinforced procedural task (implicit learning) performed during wakefulness on the following sleep (as compared with a control condition), independently from the degree of overnight performance improvement.

These findings taken together strongly suggest a specific involvement of SSOs in procedural memory consolidation: changes in the topology of SSO features such as SSO rate, pre-down state and up state peak amplitude as well as sigma crowning selectively reflect the complex pattern of network activation related to the reinforced learning of a procedural visuomotor task. Indeed, the diverse components of SSO seem to support different yet partially overlapping circuitries that taken together contribute to the retention of the newly acquired skills. More, the areas specifically involved in procedural and reinforcement learning emerge from the correlation analysis as those showing a significant association between SSO rate and overnight improvement in the task performance.

In conclusion, we confirm that SWA homeostasis has a local task-related component, and we show that SSO features are

selective and sensitive markers of the complex pattern of cortical, cortico-thalamo-cortical and thalamo-cortical activations underlying the retention of newly acquired skills related to a procedural task.

CONFLICT OF INTERESTS

No conflicts of interest declared.

AUTHOR CONTRIBUTIONS

AG, DM and JA conceived the experiment; JA, AZ and DM performed the EEG recordings; AP, DM and ML conducted the analyses; AG, AP and DM wrote the manuscript. All authors read and approved the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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