EEG Slow (~1 Hz) Waves Are Associated With Nonstationarity of Thalamo-Cortical Sensory Processing in the Sleeping Human

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Submitted 17 May 2002; accepted in final form 19 November 2002

Massimini, Marcello, Mario Rosanova, and Maurizio Mariotti. EEG slow (~1 Hz) waves are associated with nonstationarity of thalamo-cortical sensory processing in the sleeping human. J Neurophysiol 89: 1205–1213, 2003; 10.1152/jn.00373.2002. Intracellular studies reveal that, during slow wave sleep (SWS), the entire cortical network can swing rhythmically between extremely different microstates, ranging from wakefulness-like network activation to functional disconnection in the space of a few hundred milliseconds. This alternation of states also involves the thalamic neurons and is reflected in the EEG by a slow (<1 Hz) oscillation. These rhythmic changes, occurring in the thalamo-cortical circuits during SWS, may have relevant, phasic effects on the transmission and processing of sensory information. However, brain reactivity to sensory stimuli, during SWS, has traditionally been studied by means of sequential averaging, a procedure that necessarily masks any short-term fluctuation of responsiveness. The aim of this study was to provide a dynamic evaluation of brain reactivity to sensory stimuli in naturally sleeping humans. To this aim, single-trial somatosensory evoked potentials (SEPs) were grouped and averaged as a function of the phase of the ongoing sleep slow (<1 Hz) oscillation. This procedure revealed a dynamic profile of responsiveness, which was conditioned by the phase of the spontaneous sleep EEG. Overall, the amplitude of the evoked potential changed systematically, increasing and approaching wakefulness levels along the negative slope of the EEG oscillation and decreasing below SWS average levels along the positive drift. These marked and fast changes of stimulus-correlated electrical activity involved both short (N20) and long latency (P60 and P100) components of SEPs. In addition, the observed short-term response variability appeared to be centrally generated and specifically related to the evolution of the spontaneous oscillatory pattern. The present findings demonstrate that thalamo-cortical processing of sensory information is not stationary in the very short period (approximately 500 ms) during natural SWS.

INTRODUCTION

Sequential averaging of many trials is the traditional procedure used to extract reliable responses from the background activity of the brain. This method necessarily assumes that inter-trial variability is due to the linear superimposition of ongoing random activity on a deterministic, reproducible response (Aunon et al. 1981; Dawson 1951). This assumption, although corroborated by experimental observations (Arieli et al. 1996), can be violated if the properties of the circuits that generate the response spontaneously change during the period under analysis (Kisley and Gerstein 1999). In this case, the result of sequential averaging has to be considered a poor or misleading estimate of brain reactivity.

This theoretical problem may become critical when addressing the fundamental issue of brain responsiveness during different states of vigilance, especially as slow wave sleep (SWS) emerges. Indeed, intracellular studies in anesthetized and behaving animals (for review see Steriade 2000, 2001) revealed this latter condition as characterized by the occurrence of spontaneous, fast, and pronounced shifts in the general state of the thalamo-cortical networks. During SWS, the membrane potential of all cortical neurons oscillates, with a periodicity of about 1 s, between depolarized (up state) and hyperpolarized (down state) levels (Steriade et al. 1993). The long-lasting hyperpolarizations are due to recurrent phases of global disfacilitation and rhythmically interrupt the periods of wakefulness-like network activity associated with the up state (Contreras et al. 1996; Steriade et al. 2000; Timofeev et al. 2001). This pattern of alternating states is also associated with the continuous fluctuation of the probability of synaptic release at the cortical level: higher at the end of the down state and reduced by about 40–50% toward the end of the up state (Massimini and Amzica 2001). This slow sleep oscillation is an emergent property of the cerebral cortex (Sanchez-Vives and McCormick 2000; Timofeev and Steriade 1996; Timofeev et al. 2000a) and powerfully entrains thalamic neurons (Contreras and Steriade 1995). In addition, this pattern is prevalent during late stages of sleep and is reflected in the human EEG by a low-frequency (<1 Hz) oscillation synchronized in all leads (Achermann and Borbely 1997; Amzica and Steriade 1997).

According to these data, during SWS, the whole thalamo-cortical system seems to swing rapidly between substantially different configurations, ranging from functional disconnection to network activation. These fast, global changes must be taken into account to obtain a realistic profile of brain activity during sleep. However, to our knowledge, the issue of realtime thalamo-cortical responsiveness during natural SWS has never been addressed.

We wondered whether, and in what way, the electrical activity correlated to a sensory stimulation may vary as a function of the fluctuating state of the thalamo-cortical circuits during natural SWS. We chose to address this question directly in the sleeping human brain. In particular, our approach is based on the use of the low-frequency component of the

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We demonstrate that sleep slow waves are associated with short-term nonstationarity of sensory processing in the thalamo-cortical networks of humans. Our results are discussed in the light of intracellular and behavioral correlates of SWS.

METHODS

All night sessions of stimulation and recordings were carried out on six healthy volunteers (2 females and 4 males). Informed consent was given, and the subjects were requested to undergo only mild sleep deprivation prior to the recording session. No pharmacological substance was used to induce sleep. Median nerve SEPs were evoked by electric stimulation at the right wrist using constant current square-pulse trains that were evolved over the brachial plexus. The cortical evoked potential was recorded from the scalp in bipolar derivation (C3–C4, P3, and P4) with reference to the contralateral ear to monitor the spontaneous EEG signals together with electro-oculograms and submental EMG. The afferent peripheral volley was detected at the Erb point, which was considered representative of the slow oscillation, a single oscillatory cycle had to have a period (negative-to-negative peak) between 0.8 and 1.2 s and had to be synchronized in all leads. The cortical evoked potential was recorded on the scalp in bipolar derivation (C3’–Fpz) to minimize the contributions of far field potentials by common mode rejection (Mauguie`re, 1988). Filters were set between 0.1 and 100 Hz for spontaneous monopolar EEGs and between 30 (or 10) and 3,000 Hz for evoked potentials. Sampling frequency was 1 and 10 KHz, respectively. Signals were continuously digitized, monitored, and stored on hard disk during the recording session. To check the stability of stimulation and recordings throughout the night, sequential averages of the evoked potentials were displayed on-line and refreshed once every 1,000 trials. Data regarding periods of stimulation during wakeness, before and after sleep, were also collected. A typical recording session lasted from 6 to 7 h. Acquisition and on-line analysis was performed using LabView (National Instruments, Austin, TX).

Off-line analysis of the dataset was performed using Igor-Pro (Wavemetrics, Lake Oswego, OR). As a first step, artifact rejection was carried out by visual inspection of the digitized signals. Next, we scrolled the spontaneous EEG signals in search of periods characterized by a regular and slow (approximately 1 Hz) oscillatory pattern. Our aim was to identify the slow oscillation with a minimal confound with the other sleep rhythms evolving in the upper range of the delta band. In humans, the slow oscillation prevails during sleep stages 3 and 4 and appears to arise from the rhythmic recurrence of K-complexes (Amzica and Steriade 1997, 1998b). In our protocol, to be considered as representative of the slow oscillation, a single oscillatory cycle had to have a period (negative-to-negative peak) between 0.8 and 1.2 s and had to be synchronized in all leads. We extracted the above criteria from the parameters describing the sporadic K-complexes that we recorded from the same subjects during earlier sleep stages. Indeed, the K-complex represents a clearly identifiable fore-runner of the slow oscillation (Amzica and Steriade 1997, 1998b). In Fig. 1A, the time-course of sporadic K-complexes is compared with

![FIG. 1. Pattern identification and phase-averaging procedure. The method is applied only to few oscillatory cycles by way of example. A: time-course of the sporadic K-complexes (left) and one of the oscillatory cycles (right) selected for analysis during deep SWS (stages 3 and 4) is shown. According to intracellular and human EEG studies, we identified the slow oscillation as a pattern arising from the rhythmic recurrence of K-complex–like graphoelements. The spontaneous EEG (top), recorded during late stages of SWS, displays slow (<1 Hz) regular fluctuations (B). The minimum voltage marking the transition from the negative to the positive slope is taken as a reference (EEG-Ref) to group the single trials as a function of the phase of the EEG. The stimuli (triangles), falling ±50 ms from EEG-Ref, are selected and grouped as Stim-Refs, on a cycle-by-cycle basis. The single responses, corresponding to the Stim-Refs are averaged together to generate the Ph-AVG0. The Ph-AVGs preceding and following Ph-AVG0 are generated by grouping, for each cycle, the stimuli preceding and following Stim-Ref. Since the slow sleep oscillation is a rhythmic and regular pattern, each phase-average reflects the stimulus-correlated activity produced around a given phase of the cycle. The mean, spontaneous EEG cycle, to which the Ph-AVGs are phase-locked, is superimposed (thick line) on the single cycles. All potentials with positivity upward.](image)
the one of the oscillatory cycles selected for analysis during sleep stage 4 in the same subject. Once the spontaneous pattern was identified, time-stamps were manually inserted, on a cycle-by-cycle basis, in correspondence with the minimum voltage marking the transition from the negative to the positive slope of the selected oscillatory cycles. We chose this point (EEG-Ref) of the spontaneous EEG oscillation as a reference to align the evoked responses, because of its sharpness and because of its intra- and inter-subject reproducibility. Following this procedure, we detected 1,300–2,200 slow oscillatory cycles in each subject during a full night of recording.

Based on the identification of the reference points (EEG-Refs) on the spontaneous signal, we proceeded to select and group the single responses in relation to the phase of the oscillatory cycle. We called this procedure phase-averaging. To do this, the temporal relation between the occurrence of the stimulation and EEG-Ref was evaluated on a cycle-by-cycle basis. Specifically, for each cycle we selected the stimulus (Stim-Ref) that occurred within ±50 ms from EEG-Ref and consequently around the negative-to-positive slope transition of the EEG (Fig. 1). Depending on the quantity of artifacts on the evoked signal and depending on the time spent in deep sleep stages by the different subjects, we were able to collect a minimum of 615 and a maximum of 1,230 Stim-Refs in each subject. Stim-Refs were used to group the single responses to be averaged as phase-average0 (Ph-AVG0). Phase-average1 (Ph-AVG-1) and phase-average1 (Ph-AVG1) were calculated, respectively, taking as a reference the stimuli preceding and following Stim-Ref in each cycle. In the same way, for each subject, we calculated between four and five phase-averages both before and after Ph-AVG0 (Fig. 1). The final product of our analysis is a sequence of 9–11 averages, each resulting from the contribution of 615–1,230 single responses and each describing 180 ms of stimulus-correlated electrical activity. The sequence, being built around the reference point EEG-Ref, is conditioned by the evolution of the cycle and provides a dynamic picture of responsiveness by exploring the processing of the same sensory input during the different phases of the EEG slow oscillation. The latter is only used as an index of the state of the thalamo-cortical system and, since it has much lower frequency content (0.7–4 Hz), does not directly contribute to the shape of the evoked potential (band-pass 30–3,000 Hz).

The signal-to-noise ratio characterizing Ph-AVGs was lower than that normally achieved by traditional sequential averaging, due to the selection of a relatively small number (615–1,230) of single trials. Even so, the typical components of the somatosensory evoked potential were clearly detectable and easily measurable. To demonstrate that the changes in amplitude characterizing the Ph-AVGs during the different phases of the oscillatory cycle were related to actual changes in the state of the networks rather than due to the superimposition of random residual variability, a statistical test was performed. In each subject, the peak-to-peak amplitudes of the main components of the response (N20, P60, and P100) were calculated on the single trials giving rise to each Ph-AVG. Next, as exemplified in Fig. 2 (where N20 is evaluated), a two-tailed, paired Student’s t-test between the amplitudes of the single responses collected around the negative phase of the EEG oscillation versus the ones falling around the positive phase was performed. A \( P < 0.01 \) was considered an index of phase-dependent significant changes in responsiveness.

To further evaluate the dependence of cortical responsiveness on the phase of the spontaneous sleep EEG, the Ph-AVGs were compared with randomly generated averages (random-AVGs). The latter were produced by shuffling the total pool of single-responses (approximately 10,000), giving rise to the entire sequence of Ph-AVGs. Thus the random-AVGs had the same total mean of the Ph-AVGs but no phase-locking to the oscillatory cycle. To identify the additional phase of variability that was specifically related to the oscillatory cycle, we calculated and compared, sample-by-sample, the SD from the total mean obtained both for Ph-AVGs and random-AVGs (Fig. 3).

Finally, to exclude any peripheral origin of the variability observed at the scalp derivation, the above procedures were applied to the evoked signal recorded over the brachial plexus.

**RESULTS**

**Spontaneous oscillatory pattern and state-dependent changes**

Our analysis was restricted to sleep stages 3 and 4, during which periods characterized by a stable slow (approximately 1 Hz) oscillatory pattern can be identified (Achermann and Borbely 1997; Amzica and Steriade 1997). In all subjects, the EEG pattern was dominated during these stages by slow waves synchronous in all leads. The typical oscillatory cycle was composed of a negative deflection followed by a smoother, positive wave (spectral content of the single cycle: 0.7–4 Hz). The cycles occurred in sequences, giving rise to a slow (0.7–1.2 Hz) oscillatory pattern (see Fig. 1, top trace). During a typical overnight recording session, the mean number of detected cycles was around 2,000. Maximum amplitude of the fluctuations was always recorded at the vertex (C3, C4).

The mean total somatosensory response associated with the slow sleep oscillation (SWS-AVG) was computed by sequentially averaging the single trials collected during periods characterized by a continuous and stable oscillatory pattern. The SWS-AVG had common basic components in all subjects (\( n = 6 \)): a sharp negative deflection at about 20 ms (N20) followed by two positive peaks (P22 and P35) and two prominent positive waves with maximum voltage around 60 and 100 ms (P60 and P100; see SWS-AVG in Figs. 4B and 5B). In all cases, the averaged response computed during periods of wakefulness (W-AVG) displayed slightly larger amplitudes (Figs. 4B and 5B). In particular, N20, a reflection of the primary cortical activation, increased peak-to-peak (P15-N20) in all subjects (\( P < 0.01 \) in 4 subjects). Moreover, in line with previous results (Nakano et al. 1995), the latency of this same component decreased, from SWS to wakefulness, by 0.5–1.2 ms in all subjects. An additional state-dependent change in response was found in two subjects: during wakefulness the two positive components, P35 and P60, were replaced by a single positive wave peaking at 45 ms (P45; Fig. 5B).

**Phase-dependent variability**

From 9 to 11 Ph-AVGs were generated for each subject when the individual responses, which occurred during the oscillatory cycles, were grouped in clusters according to their time relations to the spontaneous EEG oscillation phase. In Figs. 3A, 4A, and 5A, the final product of the phase-averaging procedure is shown for three different subjects. Even a cursory visual inspection of the series of Ph-AVGs revealed evident changes in the shape of the responses underlying the different phases of the oscillatory cycle. These changes in shape appeared to be due to significant modifications in amplitude involving the various components of the somatosensory evoked potential. Consistently, in all subjects (\( n = 6 \)), the general amplitude of the response increased around the negative peak of the EEG oscillation. To statistically evaluate this trend, a Student’s t-test between populations of single responses falling on opposite phases of the cycle (negative vs. positive EEG peak) was performed. Significant (\( P < 0.01 \)) fluctuations in amplitude were detected for N20 (P15-N20) and...
for P60 (N45-P60) in five subjects and for P100 (N70-P100) in three subjects.

To further characterize the share of response variability specifically related to the evolution of the oscillatory cycle, we shuffled the total pool of single-responses to produce random clusters of single trials from which random-AVGs were calculated. In all cases, the dispersion of Ph-AVGs, expressed as the SD from the total mean, was significantly larger than that computed for random-AVGs (Fig. 3B). We called this additional amount of dispersion “phase-dependent variability.” Interestingly, as shown in Fig. 3B, phase-dependent variability was selectively located at latencies corresponding to the typical components (N20, N45, P60, and P100) of cortical somatosensory evoked potentials.

In contrast with the results concerning cortical components, when we performed the same analysis on the afferent peripheral volley, we could not detect any statistically significant difference. Accordingly, in this case, the dispersion of Ph-AVGs around the total mean was small and comparable to that of the corresponding random-AVGs (data not shown).

**Time-course of phase-dependent variability**

The phase-dependent variability had a reproducible time-course across subjects. In all cases the amplitude of N20 underwent modifications that were temporally correlated with the dynamics of the EEG slow oscillation. The peak-to-peak amplitude of N20 started to increase after the onset of the EEG negative slope and rose progressively until it approached, and in some cases (n = 2) overshot, wakefulness levels around the onset of the positive EEG trend (Fig. 4C). Once past this point, N20 decreased, reaching 60–80% of its maximum around the plateau of the positive EEG wave (Figs. 2B, 4C, and 5C). The phase-dependent fluctuation of N20 was statistically consistent in five of six subjects. By contrast, a clear modulation of the latency of N20 during the oscillatory cycle was found in only one subject. In this case, the latency was increased by 0.7 ms around the negative-to-positive slope transient of the EEG, where the larger responses were found.

A similar dynamics characterized the amplitude-modulation of later positive components (P60 and P100). The amplitude of...
P60 fluctuated ($P < 0.01$ in 5 subjects) between a maximum around the onset of the positive EEG deflection and a minimum around the plateau of the positive EEG wave (Figs. 3A, 4A, and 5, A and C). P100, a slower evoked component, was not well represented in all subjects because of the high-pass analog filtering conditioning the evoked signal. However, when clearly detectable, P100 underwent a powerful phase-dependent modulation; it gradually reached its maximal amplitude close to the negative-positive EEG transient and virtually faded before the beginning of the negative drift (Figs. 3A, 4A, and 5, A and C).

Overall, the global amplitude of the evoked potential oscillated significantly and coherently with the spontaneous EEG slow fluctuation, increasing and approaching wakefulness levels along the negative slope of the EEG and decaying below SWS levels during the positive slope. In particular, in correspondence with the positive phase of the EEG oscillation, very little stimulus-correlated activity was still detectable (at least, in the explored frequency band: 30–3,000 Hz) at latencies longer than 60 ms. As shown in Figs. 4B and 5B, in terms of amplitude, the response could vary more in the short temporal window (approximately 540 ms) in between Ph-AVG-3 and Ph-AVG0, than in the transition from SWS to wakefulness. Therefore the phase-dependent, short-term, response variability appeared to be of the same order, if not larger, when compared with the state-dependent one (see also Figs. 4C and 5C).

**Discussion**

The major finding of our study is that thalamo-cortical sensory processing, during deep SWS, is not stationary in the very short period (approximately 500 ms), being significantly conditioned by the evolution of a spontaneous cortical oscillation (Figs. 2A, 3A, and 4A). Indeed, depending on its actual timing with respect to the EEG cycle, the amplitude of the evoked potential fluctuated significantly around the mean sleep value calculated by standard sequential averaging.

To extract phase-dependent variability, we adopted a model based on the hypothesis that the slow ($<1$ Hz) oscillation of the sleep EEG may reflect relevant changes in the functional (biophysical/computational) state of the thalamo-cortical networks. This prediction is based on a wealth of intracellular data systematically collected over the last 10 years, both in anesthetized and behaving cats (reviewed in Steriade 2001). The final output of our procedure is the Ph-AVG, a signal that contains 180 ms of stimulus-correlated electrical activity produced around a given phase of the spontaneous EEG oscillation.

During the evolution of the cycle, the response varied significantly depending on the phase of the oscillation as confirmed by the statistical evaluation performed on the different pools of single responses (Fig. 2). This phase-dependent variability was preferentially located at given latencies (around 20, 40, 60, and 100 ms) as indicated by the profile of dispersion of the Ph-AVGs around the total mean and was lost when random-AVGs were calculated (Fig. 3B). Moreover, the modulation of responsiveness associated with the sleep EEG oscillation appeared to be introduced at the central level, since the Ph-AVGs computed on the signal recorded at the brachial plexus overlapped precisely.

In all subjects, we observed a progressive increase of the evoked potential amplitude during the negative trend of the EEG slow fluctuation. The largest responses were observed around the transient from the negative to the positive slope of
the EEG. Past this point, the amplitude of stimulus-correlated activity started to decrease and, around the end of the positive slope, showed a marked depression, particularly of later components (P60 and P100). The interpretation of these results in the light of the precise cellular and network events underlying the slow oscillation cannot be straightforward. Several studies, both using EEG recordings (Achermann and Borbely 1997; Amzica and Steriade 1997) and magnetoencephalography (Simon et al. 2000), have confirmed the presence of a slow oscillation in the human sleep EEG. Indeed, also in the sleeping human, the slow oscillation coherently reflects synchronous fluctuations of the membrane potential of cortical neuron. However, the exact phase relation between the scalp-recorded human sleep EEG and the underlying intracellular dynamics are not known and can only be extrapolated from the results of animal experiments. According to field potential recordings performed with high-impedance electrodes in the ketamine-xylazine anesthetized cat (Amzica and Steriade 1998), the long-lasting hyperpolarization of cortical neurons is associated with a surface-negative deflection, while the beginning of the depolarizing phase is marked by the onset of a surface-positive one. In the discussion that follows we will assume that a similar rule also applies to human EEG scalp recordings.

When calculated by means of standard sequential averaging, N20, a scalp-recorded reflection of the first evoked depolarizing event in the primary somatosensory cortex (Allison et al. 1991), increased in latency (0.5–1.3 ms) and slightly decreased in amplitude (by 5–25%) during SWS compared with wakefulness. This result is in accordance with previous studies about state-dependent changes of SEPs in humans (Addy et al. 1989; Emerson et al. 1988; Goff et al. 1966; Noguchi et al. 1995). However, a new and different picture emerged when N20 was computed with relation to the phase of the EEG cycle. Here the amplitude of N20 fluctuated, approaching wakefulness levels in correspondence with the onset of the positive EEG trend and decreasing below SWS mean values, around the positive plateau. This rapid fluctuation of the amplitude of a primary somatosensory response might be related to rhythmic spontaneous changes occurring both at the thalamic and the cortical level.

Indeed, a first possible role could be played by a fluctuation in the level of thalamic gating. This possibility is suggested by...
intracellular data (Timofeev et al. 1996) recorded in the ventro-lateral thalamus of anesthetized cats in which the brachium conjunctivum was stimulated. This study clearly demonstrated the role played both by recurrent thalamic hyperpolarizations and the cyclical shunting of the membrane of relay neurons in periodically preventing prethalamic inputs from being transferred to the cortex during the slow oscillation. While we have detected a clear modulation of the response by the slow oscillation, we have never observed, at any point of the cycle, a complete failure of thalamo-cortical transmission. This discrepancy with the intracellular study could be explained by the fact that 1) our responses were collected during the natural slow oscillation, a pattern more variable and less marked than the one obtained during ketamine-xylazine anesthesia; and 2) we stimulated a peripheral nerve, thus recruiting different fibers with various time-constants, possibly allowing for temporal summation of excitatory postsynaptic potentials (EPSPs) up to firing threshold in yet hyperpolarized thalamic relay neurons.

On the other hand, the major source of phase-dependent variability could be at the cortical level. Indeed, important changes in postsynaptic cortical responsiveness are expected to occur during the oscillatory cycle; taking into account the time-course of the fluctuations involving both the input resistance of cortical neurons (Contreras at al. 1996) and the probability of synaptic release (Massimini and Amzica 2001), a progressive increase of the cortical postsynaptic response is expected to occur toward the transition between the down state and the up state, thus presumably, around the negative-to-positive EEG slope transition. We actually measured the largest responses around this point. In addition to the above-mentioned mechanisms, a possible role of glial cells in the cyclical modulation of cortical excitability during SWS has been recently suggested (Amzica and Massimini 2002; Amzica et al. 2002) and cannot be ruled out.

Later components of the response, which reflect further cortical processing (Allison et al. 1989; Desmedt et al. 1983), were also strongly conditioned by the phase of the spontaneous EEG oscillation. P60 displayed a variation in amplitude of about 50% and rose and decayed in phase with the EEG negative-positive fluctuation. The next positive component of the evoked potential, P100, had a similar time-course but a more dramatic evolution, virtually disappearing in correspondence with the positive EEG plateau. As indicated by intracellular studies in the cerebral cortex of cats, during the evolution of the depolarizing phase, the probability of transmitter release

**FIG. 5.** Long latency components of the evoked potentials are also affected by the phase of the cycle. In A, the spontaneous EEG dynamics (top) are displayed together with the corresponding sequence of Ph-AVGs (bottom). In this subject, the cortical evoked potential was recorded with wider band-pass (10–3,000 Hz), allowing for a better representation of lower frequency components (P60 and P100). Marked changes of stimulus-correlated activity occur along the evolution of the EEG cycle. In particular, P100 almost disappears in correspondence with the plateau of the positive wave. In B, Ph-AVG-3 and Ph-AVG0 are expanded and compared with the average profiles obtained during wakefulness and SWS. In terms of amplitude, Ph-AVG0 is comparable to the average wakefulness response (W-AVG). On the other hand, Ph-AVG-3 reveals a marked suppression of correlated activity, below the total average level of SWS. In C, the time course of the amplitude fluctuation of different components is displayed (mean ± SE) and compared with the total average levels calculated during wakefulness and SWS. In terms of amplitude of the single components, the cycle dependent modulation of the response appears to be larger than the state-dependent one. All potentials with positivity upward.
progressively decreases (Massimini and Amzica 2001) and synaptic interactions among cortical neurons gradually run
down, leaving leak currents to prevail (Contreras et al. 1996;
Timofeev et al. 2000b). This spontaneous drift, bringing the
cortical network toward a state of disfacilitation and functional
disconnection may explain the marked obliteration of long-
latency, stimulus-correlated potentials observed around the end
of the positive EEG slope.

In summary, we tested the reactivity of the human thalamo-
cortical system by means of simple, sensory stimulation during
SWS. In line with previous results, during this state, the aver-
age response was delayed and the amplitude slightly reduced
with respect to wakefulness. Surprisingly, when responsiveness
was evaluated in relation to the actual microstates run
through by the slowly oscillating thalamo-cortical networks,
low-amplitude, wakefulness-like evoked potentials were
found to rapidly alternate with low-amplitude ones. This fluc-
tuation in thalamo-cortical reactivity may reflect the main
feature of the slow sleep oscillation: the spontaneous and
rhythmic recurrence of phases of global disfacilitation within
periods of increased network excitability. Of course, the large
amplitude responses, observed around the negative-to-positive
slope change of the EEG, do not necessarily reflect a wakeful-
ness-like elaboration of sensory information. Nevertheless,
the presence of short temporal windows, during which the
thalamo-cortical system seems to be more open to external
stimuli, is consistent with the well-known notion that even the
deply sleeping brain can detect and process meaningful events
(Langford et al. 1974; Oswald et al. 1960; Portas et al. 2000).
On the other hand, our results show that the slow oscillation,
an internally generated dynamics that is expressed by all cortical
areas during deep sleep, continuously alters the pattern of
thalamo-cortical responsiveness to a constant sensory input. In
a series of classic works, carried out on the somatosensory,
thalamo-cortical system of humans, Libet has demonstrated
that a minimum duration (more than 500 ms) of stable evoked
neural activity is required for the transition from sensory de-
tection to conscious sensory experience (Libet 1999; Libet
et al. 1967, 1991). We hypothesize that a lack of stationarity,
affecting thalamo-cortical processing in the space of a few hundred milliseconds, may contribute to impair conscious sen-
sory integration during SWS.

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