



Synapse-specific modulation of synaptic responses by brain states in hippocampal pathways

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2 **pathways**

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4 **Abbreviated title: Hippocampal synaptic responses during the sleep-wake cycle**

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25

Abstract:

26 Changes in synaptic transmission play a major role in memory processes. Modulation of
27 synaptic responses by brain states remains however poorly understood in hippocampal
28 networks, even in basal conditions. We recorded evoked synaptic responses at five
29 hippocampal pathways in freely moving rats. We showed that, at the perforant path to dentate
30 gyrus (PP-DG) synapse, responses increase during wakefulness compared to sleep. At the
31 Schaffer collaterals to CA1 (SC-CA1) synapse, responses increase during non-REM sleep
32 (NREM) compared to the other states. During REM sleep (REM), responses decrease at the
33 PP-DG and SC-CA1 synapses compared to NREM, while they increase at the fornix to
34 nucleus accumbens synapse (Fx-NAc) during REM compared to the other states. These
35 modulations were linked to presynaptic changes in glutamate release. In contrast, responses at
36 the fornix to medial prefrontal cortex synapse (Fx-PFC) and at the fornix to amygdala synapse
37 (Fx-Amy) were weakly modulated by vigilance states. Synaptic responses were also linked to
38 local field potential oscillations and were highly correlated between Fx-PFC and Fx-NAc but
39 not between Fx-Amy and these synapses. These results reveal synapse specific modulations
40 that may regulate information transfer during memory consolidation.

41 **Keywords:** sleep-wake cycle, local field potential (LFP) oscillations, medial prefrontal
42 cortex, nucleus accumbens, amygdala.

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Significance Statement:

45 Surprisingly, the cortical network dynamics remains poorly known at the synaptic level. We
46 tested the hypothesis that brain states would modulate synaptic changes in the same way at
47 different cortical connections. To tackle this issue, we implemented a comparative approach
48 to explore in freely-moving rats the synaptic behavior of five connections upstream and
49 downstream the hippocampus. Our study reveals that synaptic responses are modulated in a
50 highly synapse-specific manner by wakefulness and sleep states as well as by local low and

51 high frequency oscillations at these connections. Moreover, we found large and rapid synaptic
52 changes during wake and sleep state transitions. These effects are likely related to the role of
53 sleep in hippocampal dependent forms of memory.

INTRODUCTION

Mammals continually adapt their behavior to their internal state and surrounding environment. This adaptation is coupled with dynamic brain state changes characterized by rapid shifts in EEG and local field potentials (LFP). The best-defined brain states are those observed during the sleep-wake cycle. Wakefulness is divided into two states in rodents, active wake (AW) and quiet wake (QW) characterized by different motor activities and the presence (AW) or absence (QW) of small amplitude fast oscillations. In contrast, during sleep, brain states are characterized by high amplitude slow oscillations during non-REM sleep (NREM) and low amplitude fast oscillations during rapid eye movement sleep (REM). Both sleep states contribute to consolidate information that has been encoded during wakefulness (Rasch and Born, 2013).

The memory consolidation is also believed to depend on changes in synaptic efficacy in the hippocampal networks. Do vigilance states impact synapses uniformly as recently proposed in the Synaptic Homeostasis Hypothesis (SHY (Tononi and Cirelli, 2014)) or, on the contrary, do they selectively modulate synaptic transmission? SHY states that synaptic responses that increase during wakefulness and decrease during NREM that follows wakefulness. Such global synaptic downscaling during sleep was found in neocortical pathways [(Vyazovskiy et al., 2008), but see (Chauvette et al., 2012) (Cary and Turrigiano, 2021)]. However, it is within the hippocampus (Hpc) that memory mechanisms have been mainly studied. Strangely modulation of synaptic efficacy in hippocampal networks during brain state changes remains poorly described. Studies found that synaptic transmission in the Hpc is differentially gated by vigilance states (Winson and Abzug, 1977). They showed that at the perforant path (PP) to the dentate gyrus (DG) synapse, synaptic responses increase their amplitude during wakefulness compared to sleep. Later, other studies suggested that synaptic transmission at

79 the Schaffer collaterals (SC) to CA1 pathway decreases during REM compared to NREM and
80 with the occurrence of theta oscillation (Leung, 1980). Together, these studies suggested that
81 a given sleep state may exert opposite modulation of synaptic responses in different
82 hippocampal networks, a result that may have important consequences concerning the
83 knowledge we have on the role of brain states in memory processes.

84 While the PP to DG and SC to CA1 synapses play a critical role in memory, other
85 hippocampal pathways were found to be involved in memory. Among them, connections
86 between the Hpc and the medial prefrontal cortex (PFC) constitute a major hub for memory
87 consolidation (Maingret et al., 2016). The connections between the Hpc and the nucleus
88 accumbens (NAc) have also been involved in forms of memory underlying contextual fear
89 conditioning and appetitive learning (Levita et al., 2002)(LeGates et al., 2018)(Trouche et al.,
90 2019). The connection between the Hpc and the basolateral area of the amygdala (Amy) is
91 also important for encoding a context related to an emotional memory (Zhang et al., 2015).
92 Given the role of the pathways between these areas and the hippocampus in memory and the
93 sleep role in these processes, it is surprising that sleep-dependent modulation of synaptic
94 transmission at these connections have not been studied.

95 To better understand the link between brain state dynamics and synaptic changes, we
96 performed continuous long-term recordings of evoked synaptic responses in five different
97 limbic areas: DG, CA1, PFC, NAc and Amy of freely moving rats. We assessed, within the
98 Hpc, the modulation of synaptic transmission at the PP-DG synapse and at the SC-CA1
99 synapse, and the modulation of synaptic transmission in three hippocampal outputs between
100 the fornix (Fx which consists of axons from the Hpc), and the nucleus accumbens (Fx-NAc
101 synapse), the medial prefrontal cortex (Fx-PFC synapse) and the amygdala (Fx-Amy synapse)
102 (Boeijinga et al., 1993). We wanted to find out whether synaptic responses change
103 simultaneously and in the same fashion in these different hippocampal pathways across

104 different brain states, or not. Altogether our results revealed a synapse-specific modulation of
105 synaptic responses that may contribute to regulate the information transfer to, from and within
106 the Hpc during wakefulness and sleep.

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MATERIALS AND METHODS

Animals

We used data collected from 35 Dark Agouti male rats (Janvier Labs) aged of 10-15 weeks and weighing between 200-250 grams. Animals were maintained in individual cages on a 12hr/12hr light-dark cycle (9am-9pm) at a room temperature of 24°C with food and water *ad libitum*. The animal care and treatment procedures were in accordance with the regulations of the local Lyon 1 University CE2A-UCBL 55) and European Union Council (2010/63/EU) ethics committee for the use of experimental animals. The protocol was approved by the French ethical committee for the use of experimental animals (Permit Number: DR2016-29). Efforts were made to minimize the number of animals, or any pain and discomfort occurred to them during surgical or behavioral procedures.

Surgery

Rats were first anesthetized in an induction chamber under isoflurane (2-2.5%) then placed in a stereotaxic frame where anesthesia was maintained by a 0.75-1% isoflurane gas mix enriched in oxygen. After incision of the scalp, craniotomies were performed at the position of the electrodes and screws. Reference screws were fixed above the cerebellum. All the electrodes were implanted in the right side of the brain, except for EEG electrodes. The position of LFP and stimulating electrodes was illustrated on Figures 1B, 2A&F and 3A&F. One group of rats (n =10) was implanted with a recording array of 8 electrodes in the DG (A: -3.3mm, L: +2.4mm, stereotaxic coordinates are given relative to bregma, in the Antero-Posterior (A), Lateral (L) and Depth (D) dimensions; Figure 1B and Figure 1-1; (Missaire et al., 2021)). The array was lowered about 1mm below the CA1 *stratum pyramidale*, which was

recognizable by a high rate of spiking activity (D~2.6mm) until the modest spiking activity of the DG was visualized (D~3.5mm). The perforant path (PP) stimulating electrode was then lowered (A: -7.5mm, L: +4mm) while stimulating at 0.33Hz and was fixed at the depth corresponding to the expected evoked response (D~3.7mm; Figure 1-1). This first group of rats was also implanted with one EEG screw above the prefrontal cortex and one EEG screw above the parietal cortex on the left side of the brain. Another group of rats (n=25) was implanted with recording electrodes at three different synapses. First, the CA1 electrode was lowered (A: -4mm, L: 2mm; Figure 2A and Figure 1-1) until visualization of the high spiking activity of the CA1 *stratum pyramidale* (D~2.5mm) and fixed 100-200µm under this layer. We then lowered the Schaffer Collaterals (SC) stimulating electrode (A: -4mm, L: 3.1mm; Figure 1-1) while stimulating at 0.33Hz until visualization of the best evoked response in CA1 (D: 3-3.5mm). Subsequently, we lowered and fixed the recording electrodes in the PFC (A: +2.5 mm, L: 0.5 mm, D: 4 mm; Figure S1F), the NAc (A: +1.2 mm, L: 0.8 mm, D: 7 mm; Figure S1G) and the Amy (A: -3.2, L: 4.8, D: 8.5; Figure S1H). Then, we began the descent of the fornix (Fx) stimulating electrode (A: -1.7 mm, L: 0.7 mm, D: 4.2-4.4 mm) (Figures 2A&F, 3A&F and Figure 1-1) until we obtained stereotyped responses in the PFC, the NAc and the Amy as described in several studies (Mulder et al., 1997), (Mulder et al., 1998). Paired-pulse stimulations were applied with a 50 ms delay to assess paired-pulse depression or facilitation of the PP-DG, SC-CA1, Fx-PFC, and Fx-NAc synapses. For both groups of rats, two EMG electrodes were implanted bilaterally in the neck muscles. All electrodes were connected to an electrode interface board (EIB-27, Neuralynx, U.S.A.) and a protective hat was made with dental cement. At the end of the surgical procedures, a subcutaneous injection of 3 ml of glucose (2.5%) supplemented with carprofen (5mg/kg) was given to the animals.

Recording conditions

One week after surgery, rats were introduced in their recording chambers and plugged for recording. The recording chambers consisted of a 60 x 60 x 60 cm faradized box with removable container for the litter, so that the rats could be changed daily at 10 am without being unplugged. While in the recording chambers, the animals were provided with food and water *ad libitum*. Once the synaptic transmission was stabilized, and after at least two days of habituation, recordings took place during several days.

Recording setup

For the group of rats implanted in the DG, the recording array (700 μm x 300 μm) was made of 8 tungsten wires (45 μm diameter) arranged on two lines of 4 electrodes (Missaire et al., 2021). The stimulating electrode lowered in the PP was made of two stainless steel twisted wires (100 μm in diameter California Fine Wire, U.S.A) de-insulated at the tip. For the second group of rats, the recording electrodes consisted of two twisted tungsten wires (25 μm in diameter California Fine Wire) de-insulated at the tip. Stimulating electrodes were made either with two twisted tungsten wires (45 μm in diameter) or two stainless steel twisted wires (100 μm in diameter California Fine Wire), also de-insulated at the tip. For both groups of rats, EMG electrodes were made by golden plating a small and round solder ball at the de-insulated and hooked tip of a conventional small electric wire. All these electrodes, along with reference screws, were connected to a custom-made 16 channels analog preamplifier using the EIB-27 connector. The signals were then conveyed *via* an electric rotary joint (Plastics One, U.S.A.) to a 16-channel amplifier (AM-Systems, U.S.A.) within which these signals were amplified with a gain of 1000. Signals from the different electrodes were then acquired and digitized at 5 kHz by a custom MATLAB software (The MathWorks, U.S.A.) driving a NI-6343 acquisition board (National Instruments, U.S.A.) before being stored on a computer. For

all rats, continuous LFP recordings were acquired during a full recording period of several days.

Electrical stimulation

During recording, stimulations consisted of 200 μ s monophasic current pulses delivered by an isolated pulse stimulator (model 2100 AM-Systems). The interval between two stimulations on the same electrode was at least 30 seconds, and for the second group of rats implanted for recording at three synapses the delay between the two stimulation sites Fx and SC was at least 15 seconds. During the habituation period, evoked responses were tested by gradually incrementing the current intensities of the electrical stimulations until we obtained clear and typical post-synaptic potentials on at least one pathway. For PP stimulation, the intensity ranged from 140 to 640 μ A (mean: 231 μ A). For SC, the stimulation intensity ranged from 120 to 300 μ A (mean: 202 μ A). For Fx, the stimulation intensity ranged from 80 to 600 μ A (mean: 291 μ A). Stimulus intensities were selected at around 50-75% of the intensity necessary to evoke the maximum amplitude of fEPSP. To control a potential disturbing effect of electrical stimulation on vigilance states, we compared for each rat the amount of vigilance states during several days of stimulation with a period of the same duration without stimulation. We found that electrical stimulation had no effect on vigilance state amounts (Figure 4-1).

Short-term plasticity evoked by paired-pulse stimulation

Paired-pulse stimulation of synaptic responses at short intervals evoked paired pulse depression (PPD) or facilitation (PPF) of responses at many brain synapses. PPD and PPF represent a form of short-term plasticity. Modulation of the paired-pulse ratio (PPR) of evoked synaptic responses has been shown to depend on presynaptic mechanisms of

neurotransmitter release (Stevens and Wang, 1995) (Salin et al., 1996). Paired-pulse stimulation of evoked responses was carried out using a 50 ms inter-stimulus interval during 6 hours. While paired-pulse depression was observed at PP-DG synapse (Figure 1H), paired-pulse facilitation was found at SC-CA1, Fx-NAc, and Fx-PFC synapses (Figure S3C). For quantification of the paired-pulse stimulation, we divided the slope of the second stimulation by the first one. We thus obtained a percentage of paired-pulse depression or facilitation (paired-pulse ratio) for each synapse of each animal in the different vigilance states (Figure 1H and Figure 1-3).

Histological verification

At the end of all recordings, electrode locations were marked by passing currents (1s or 3s, 500 μ A) under anesthesia (isoflurane 2%). The brain was then extracted, cryoprotected in a sucrose solution (30 %) and frozen. Transverse sections (40 μ m) were performed using a cryostat and a neutral red staining was carried out on brain slices. The electrode placements were thus verified and reported on schemes taken from the atlas of Paxinos and Watson(Anon, 2021). The microphotographs of the histological sections showed the typical locations of the stimulation and recording sites that correspond to the areas targeted by stereotactic coordinates (Figure 1-1).

Vigilance state classification

Offline inspection of EMG, EEG (only for the group of rats implanted at the PP-DG synapse) and/or LFP spectral analysis were used to identify the vigilance states of the animals by bouts of five seconds. We classified them into 5 categories: two waking states (quiet wakefulness and active wakefulness – QW and AW) and three sleeping states (NREM, intermediate sleep or IS and REM). IS was not included in either NREM or REM because it

corresponds to a very different brain state (Gervasoni et al., 2004). AW was recognizable by a theta rhythm in CA1, DG and EEG signals, and an important muscular activity on EMG. QW was characterized by a weak muscular activity and delta-like activity in the PFC, NAc and EEG recordings. NREM was characterized by the occurrence of slow waves in PFC, NAc and EEG signals and a very weak muscle activity. REM was determined by a prominent theta rhythm in CA1, DG and EEG recordings and muscle atonia on EMG (Figure 4-1). IS, located between NREM and REM, was characterized by a combination of slow waves and theta rhythm in PFC and EEG recordings, along with muscle tone declining toward atonia. Because of the very short duration of IS (Figure 4-1), and thus the very small number of synaptic responses collected during that state, we choose not to analyze it. Recording periods that did not fulfill the criteria for vigilance states (due to movement artifacts or drowsiness between wakefulness and NREM) were discarded.

Synaptic responses

Figures 1,2&3 show a schematic of the position of recording and stimulating electrodes used to study the five synapses of interest linked to the hippocampal circuit. Animals were only included in the dataset after histological verifications of the electrode sites (Figure 1-1).

At the PP-DG synapse, animals displayed a clear positive (excitatory) peak with a delay of 3.5-5.5 ms after the stimulus artefact in at least one of the 8 electrodes of the recording array. The positive polarity of the fEPSPs recorded at this synapse (Figure 1C&D) corresponds to the depolarizing responses of the intracellular synaptic potentials generated at this synapse (Colino and Malenka, 1993). For the slope analysis of these fEPSP evoked potentials, data were averaged on all electrodes displaying a clear positive peak with a linear slope. In

278 average, during 24h, we analyzed the following number of fEPSPs: during AW = 627 ± 48 ,
279 during QW = 479 ± 26 , during NREM = 792 ± 35 , during REM = 252 ± 16 , n = 10 rats).

280 At the SC-CA1 synapse, evoked responses presented one clear excitatory negative
281 peak with a delay of 5-10 ms after electrical stimulation. The negative polarity of the fEPSP
282 recorded at this synapse (Figure 2B&C) corresponds to the depolarizing responses of the
283 intracellular synaptic potentials generated at the SC-CA1 synapse (Andersen et al., 1980). In
284 average, during 24h, we analyzed the following number of fEPSPs by rats: AW = 635 ± 75 ,
285 QW = 648 ± 51 , NREM = 850 ± 31 , REM = 277 ± 23 , n = 11 rats).

286 Stimulation of the fornix evoked a monosynaptic response in the three efferent
287 structures (PFC, NAc and Amy). For the PFC, the majority of recording sites were located in
288 the pre-limbic area (Figure S1F&K); for the NAc, the recording sites were located in the shell
289 (Figure 1-1); and for the Amy, the recording sites were located in the basolateral area (Figure
290 1-1). The fornix connections are constituted by axons of the ventral hippocampus and also the
291 dorsal CA1 hippocampus (Trouche et al., 2019). Evoked LFP responses at the Fx-NAc, Fx-
292 PFC and Fx-Amy synapses were analyzed when these responses presented the three following
293 criteria: an early negative deflection of around 5ms after stimulation called N5, and two
294 positive peaks at around 9 ms and 23 ms after stimulation referred as P10 and P25 (Figures
295 2G&H, 3B&C and 3G&H). The positive polarity of the fEPSP at Fx-NAc synapse (the
296 monosynaptic P10 component, Figure 3C) corresponds to the depolarizing responses of the
297 intracellular synaptic potentials generated at the Fx-NAc synapse (Mulder et al., 1997)
298 (Boeijinga et al., 1993) (Mulder et al., 1998). The Fx-NAc synapse we recorded here mainly
299 corresponds to the connections of the pyramidal cells of the ventral hippocampus to the
300 dopamine D1 receptor-expressing medium spiny neurons in the medial NAc shell, although a
301 contribution of pyramidal cell axons from the dorsal hippocampus to fast-spiking interneurons
302 in the NAc is also present (Trouche et al., 2019). At the Fx-NAc synapse, data from 11

animals were conserved and responses were analyzed during a 24h period. A total of 4882 responses were thus collected during AW, 4374 during QW, 7210 during NREM and 2089 during REM (means by rats: AW = 444 ± 73 , QW = 398 ± 64 , NREM = 655 ± 94 , REM = 190 ± 32). For the Fx-PFC synapse, the dataset was constituted of 9 animals (mean \pm SEM by rats: AW = 539 ± 80 , QW = 469 ± 38 , NREM = 823 ± 45 , REM = 242 ± 11). Evoked LFP responses at the Fx-Amy synapse were analyzed when these responses presented the three following criteria: an early negative deflection of around 5ms after stimulation called N5, and two positive peaks at around 9 ms and 23 ms after stimulation referred as P10 and P25 (Figure 3G&H). For the quantification of the evoked response at this synapse we computed the positive slope of the component P10. The shape of evoked responses we obtained at this synapse was very similar to the one observed in anesthetized rats (Mulder et al., 1998). The evoked responses recorded at synapses downstream the Hpc (Fx-NAc, Fx-PFC and Fx-Amy synapses) mainly reflect synaptic responses (Boeijinga et al., 1993). However, as with other evoked synaptic responses recorded in LFP, we cannot eliminate a contribution from population spike and active conductance mixed with the synaptic response. To minimize such a contribution, we preferred the measurement of the slope to the measurement of the peak amplitude of the response. Slope measurement is also less subject to amplitude variations due to baseline LFP oscillations.

Slope measurement of evoked responses

fEPSPs of 24h continuous recording were extracted and analyzed offline for slope measurements. The stability of the shape and the amplitude of the evoked responses recorded over 24h was verified by superimposing averaged fEPSP obtained during 3-hour recordings (i.e. 8 superimposed averaged traces). Animals with unstable recordings (i.e. sudden change of shape or progressive and wide changes in fEPSP slope) have been removed from the

database. Time cursors for fEPSP slope analysis were positioned manually. The slope was computed at the initial part of fEPSP for PP-DG, SC-CA1 and the slope (between 20% and 80%) of the response for Fx-NAc, Fx-PFC and Fx-Amy synapses. The slope of the fEPSPs was then normalized by dividing their value by the average of the slopes of fEPSPs recorded over 24 hours.

To assess synaptic variability (Figure S2), the coefficient of variation (CV) of each distribution of synaptic slopes was computed during the different vigilance states. The CV is the square root of the variance of the distribution divided by its mean (Martin, 1966) (Otmakhov et al., 1993). CV is used as an index in quantal analysis and it is assumed to be independent on quantal size. In case of synaptic efficacy changes, an increase or decrease in CV suggest a presynaptic modulation. In contrast, if synaptic response is modulated at a purely postsynaptic site, it will not alter the CV.

Modulation of synaptic responses during transitions between vigilance states

In order to study the time course of synaptic changes during transitions between vigilance states, we averaged the two last fEPSPs (slope) evoked during the episode of a given state (corresponding to a period of 30s, the interval between two stimulations), and the two first fEPSPs evoked during the following state. We thus obtained four time points for each transition between vigilance states, and the differences of the fEPSP slope between these points were tested by a Friedman ANOVA test. The differences between these different segments were then further assessed by a post-hoc Dunn's multiple comparison test. Epochs with wakefulness transitions to drowsiness and with NREM transition to IS were removed from the transition analysis.

Modulation of synaptic responses within vigilance state episodes

To assess the dynamic modulation of evoked responses within the different episodes of wakefulness, NREM and REM, we selected ‘long duration’ episodes (i.e. episodes lasting at least 100 s). We subdivided these datasets into first, middle and last third of the episodes.

Analyses of pre-stimulus LFP recordings

Besides the shift in brain states during vigilance states, studies have found that locally generated oscillations also modulate communication between cortical areas (Fernández-Ruiz et al., 2021). The importance of LFP oscillations is underlined by the Communication Through Coherence hypothesis (Fries, 2005) proposing that ongoing oscillations provide a flexible way to synchronize neuronal firing in distant areas during cognitive processes that involve them. However, the changes in synaptic responses by oscillations have not yet been explored during the different vigilance states. To test the Communication Through Coherence hypothesis that poses that “postsynaptic rhythm modulates synaptic input gain”, the link between pre-stimulus LFP oscillations and synaptic response was assessed. Ongoing LFPs were first recorded in the DG, CA1, PFC, NAc and Amy simultaneously with the synaptic responses. The correlation between the pre-stimulus LFP oscillations at different band waves (slow waves: 0.5-2 Hz, delta: 2-4 Hz, theta: 5-8 Hz, sigma: 9-14 Hz, low gamma: 38-45 Hz; high gamma: 55-95 Hz) and the slope of evoked fEPSPs was then analyzed for each synapse of interest. We thus band pass filtered the LFP signals obtained in the bands of interest (forward and reverse filtering using `filtfilt()` function). Measurement of the power of the filtered LFP was then carried out over a pre-stimulus period of 2 s for slow waves, 1s for delta oscillations, 500 ms for theta and sigma oscillations and 250 ms for low and high gamma oscillations (custom-written MATLAB scripts (MathWorks)). The calculation of the instantaneous phase of theta oscillations was obtained by the argument of the complex analytical signal of the Hilbert transform and the frequency was obtained by the calculus of

the derivative of the instantaneous phase divided by 2π . The amplitude of the oscillations was calculated by the modulus of the analytical signal of the Hilbert transform.

In addition, LFP power spectra were computed for every 5 s epoch within the 0-100 Hz frequency range using a Fourier transform analysis. These spectral analyses were performed using the Chronux toolbox (Chronux data analysis platform from <http://chronux.org>). To normalize data, power spectral densities were averaged for each frequency range on a 24 h period and each vigilance state. Data were then normalized to the total power (sum of power spectral densities on the 0-100 Hz range on a 24 h period with all vigilance states).

Statistical analysis

All statistical analyses were performed using R (R Core Team 2021). Figures were created using “ggplot2” R package. For the Friedman tests, the effect size was estimated by computing Kendall W effect size using the “rstatix” package. The effect size (to compare means) is considered large when it is greater than 0.8, medium when it is greater than 0.5 and small when it is less than this value. Given the multiple sources of variability (animal, position of electrodes) and the heteroscedasticity of the variables quantifying oscillations (oscillation power), the statistical analyses of the Figure 4 were carried out using linear mixed-effect models (LMM). Mixed-effect models incorporate both fixed-effect parameters and random effects. Lmer of “lme4” package provides tools to analyze mixed effects of linear models (Bates et al., 2015). In contrast with classical regression assumes observations are independent of each other, LMM can account for repeated measurements by estimating random effects in addition to fixed effects for the entire dataset. We analyzed the influence of four possible fixed effects on the slope of evoked responses: (i) four vigilance states as factor; (ii) power of frequency bands as numeric; (iii) six frequency bands (slow waves: 0.5-2 Hz,

403 delta: 2-4 Hz, theta: 5-8 Hz, sigma: 9-14 Hz, low gamma: 38-45 Hz; high gamma: 55-95 Hz)
 404 as factor (see paragraph above); (iv) time of recording (on 24h). Type II analysis of variance
 405 Wald chi-square tests were used to assess the significance of each fixed effect to the model.
 406 For classical linear correlation, the coefficient of determination R^2 , allows to estimate the
 407 predictive capacity of the model. The total variance in y (y = synaptic slopes) is explained by
 408 all the predictors in the model. However, this coefficient favors the most complex models. In
 409 order to select the best model, an information criterion approach is preferred, since Akaike
 410 information criterion (AIC) and Bayesian information criterion (BIC) indicators penalize for
 411 the number of predictors. Thus, AIC and BIC tests were performed to test model fit before
 412 and after sequential addition of random effects. After carrying out these tests, subjects were
 413 considered as random effects (for intercept and slope) in all statistical analyses. The fixed
 414 effects represent the mean effect across all animals after removal variability (i.e. model: lmer
 415 (Dependent Variable (synaptic slopes) ~ 1 + Independent Fixed Effects + (1|animals), data)).
 416 To optimize our model, we checked the normality of the model residual. To assess the
 417 relationship between the oscillation power and synaptic slopes we computed the beta
 418 estimates (β) of the regression curves. β , the slopes of predictors, assess the relative
 419 contribution of each predictor (oscillation power at a given frequency band) to the overall
 420 prediction of the dependent variable (synaptic response quantified by synaptic slopes). The
 421 higher the betas are in absolute value, the stronger the link between synaptic responses and
 422 oscillations. Beta zero (β_0), the intercept of the regression curves, corresponds to the average
 423 synaptic slope during the different vigilance states. To compare between the different datasets
 424 shown in Figure 4, we also computed marginal (R^2_m , the proportion of variance explained by
 425 fixed effect factors) and conditional coefficients of determination (R^2_c , the proportion of
 426 variance explained by fixed and random effect factors)(Nakagawa and Schielzeth, 2013). For
 427 clarity reasons, only the marginal coefficient of determination (R^2_m) is mentioned in the

Results section. For Pearson correlation and partial correlation measurements, the package “correlation” was used. Partial correlations are a measure of the correlation between two variables that remains after controlling for all the other relationships. Fisher z-transformation was used to normalize the Pearson correlation coefficients. This explains why in Figure 7 the correlation coefficient values can be greater than 1. To detect non-linearity between theta phase and synaptic responses (Figure 5), surrogates are obtained by randomizing the data using R. In this Figure, the fitting curves and the coefficients of determination of the correlations were carried out using OriginPro software. One asterisk means that the coefficient is significant at the 5% level, 2 is at the 1% significance level, and 3 is at the 0.1% significance level.

RESULTS

Synaptic responses at the PP-DG, SC-CA1, Fx-NAc, Fx-PFC and Fx-Amy pathways were monitored during long-term recording in freely moving rats in order to fully depict the modulation of evoked responses during brain state changes. We first described the behavior of each synapse throughout the sleep-wake cycle.

Vigilance state dependent modulation of evoked responses at the Perforant Path to Dentate Gyrus synapse.

453 As shown in a representative sample of one-hour recording (Figure 1C), the slope of
454 the fEPSP at PP-DG synapse was dynamically modulated during vigilance states. Increases in
455 synaptic response were thus observed during AW episodes (indicated by full line arrows),
456 whereas drops in synaptic amplitude were found during REM episodes (indicated by dashed
457 line arrows). When averaged on a 24h period of continuous recording, the PP-DG fEPSP
458 waveforms taken from the same animal clearly showed different amplitudes of the synaptic
459 responses during wakefulness and sleep (Figure 1D). The analysis from the entire group of 10
460 rats indicated a variation of fEPSP slopes at the PP-DG synapse in the following direction:
461 $AW > QW > NREM > REM$ (Figure 1E; Friedman test, $\chi^2(3) = 30$, $p = 1.38e-06$; post-hoc
462 Dunn's test $p=0.01$ between AW and QW, QW and NREM and NREM and REM; $p = 0.002$
463 between AW and NREM and QW and REM; $p = 0.001$ between AW and REM; Kendall's
464 effect size $=0.89$). The synaptic slopes' variability as assessed by the coefficient of variation
465 was higher during REM than during AW (Figure 1-2).

466 Given the vigilance state-dependent changes at the PP-DG synapse, we then
467 determined the time course of these synaptic changes during transitions between two different
468 consecutive vigilance states. For each transition between wake and sleep states, we observed a
469 significant modulation of synaptic responses (Figures 1F & 1-3). Large and rapid increase in
470 the synaptic responses of 22 % was thus observed during transitions from REM to AW
471 between two consecutive synaptic responses (i.e. 30s inter-stimulus interval, Friedman test
472 $\chi^2(3) = 19.7$, $p = 1.98e^{-04}$). Moreover, synaptic responses were rapidly modulated within 30 s
473 between AW and QW (Friedman test $\chi^2(3) = 20.6$, $p = 1.25e^{-04}$). Fast changes in synaptic
474 responses were also found for other state transitions (from NREM to REM: a 12% decrease,
475 Friedman test $\chi^2(3) = 23.9$, $p = 2.65e^{-05}$). We next examined changes in synaptic responses
476 within each vigilance state episodes (Figure 1G). To do so, we computed the evolution of the
477 synaptic responses across the course of the different episodes of AW, QW, NREM, and REM

478 by dividing each episode by thirds (see star Methods). fEPSPs were not modulated during
479 AW ($p = 0.078$), QW ($p = 0.521$) or NREM ($p = 0.436$) episodes. In marked contrast, the
480 synaptic slopes deeply decreased during the course of REM episodes (Friedman test, $\chi^2(2) =$
481 13.9, $p = 0.0008$), from the beginning to the middle ($p = 0.021$) and from the middle to the
482 last part of the episode ($p = 0.002$) suggesting that synaptic responses were actively
483 modulated during this sleep state.

484 We then considered that the changes in synaptic responses we observed during the
485 wake-sleep cycle could be caused by vigilance state dependent neuromodulation (i.e.
486 acetylcholine, noradrenaline or serotonin) that is known to impact synaptic transmission (Lee
487 and Dan, 2012). We therefore examined whether paired-pulse stimulation of evoked
488 responses was modulated during the sleep-wake cycle. Modulation of the paired-pulse ratio
489 (PPR) of evoked responses is a form of short-term plasticity that has been shown to depend on
490 presynaptic mechanisms of neurotransmitter release (Stevens and Wang, 1995), (Manabe et
491 al., 1993). A decrease in synaptic responses associated with an increase in PPR suggests that
492 neurotransmitter release probability decreased (due to an increased failure rate in the response
493 to the 1st stimulation of the pair). Reciprocally, an increase in synaptic responses associated
494 with a decrease in PPR, strongly suggests that neurotransmitter release probability increases
495 (due to a decrease in the failure rate to respond to the 1st stimulation). Paired-pulse
496 stimulation at 50 ms inter-stimulus interval evoked paired-pulse depression at PP-DG synapse
497 (Figure 1H) as already known (Colino and Malenka, 1993). Here, long-term recordings of
498 paired-pulse responses revealed an increase in PPR during REM compared to AW and QW
499 (Friedman test $\chi^2(3) = 13.1$, $p = 0.004$, effect size: 0.49; post-hoc Dunn's test AW vs REM p
500 $= 0.02$, QW vs REM $p = 0.04$, $n = 9$ rats). In addition, at the PP-DG synapse, synaptic slope
501 variability as assessed by computing the coefficient of variation (CV) was greater in REM
502 than in AW (Figure 1-2). The state-dependent CV modulation must be related to the increased

paired-pulse ratio observed in REM as compared to AW (see Methods). Altogether, these results suggest that presynaptic mechanisms of neurotransmitter release likely contribute to the vigilance state-dependent modulation of PP-DG synaptic responses.

Vigilance state dependent modulation of evoked responses at Schaffer Collaterals to CA1 synapse.

The slope of SC-CA1 evoked synaptic responses was also deeply modulated during the sleep-wake cycle (Figure 2B&C), with an increase during NREM and a decrease during AW and REM. The analysis from the entire group of 11 rats indicated a variation of fEPSP slopes at this synapse in the following direction: NREM > QW > [AW = REM] (Figure 2D; Friedman test, $\chi^2(3) = 27.1$, $p = 5.58e^{-06}$; post-hoc Dunn's test: NREM vs REM $p < 0.001$, NREM vs AW $p < 0.001$, NREM vs QW $p < 0.001$, REM vs AW $p = 0.2$, REM vs QW $p = 0.01$, AW vs QW $p < 0.001$; Effect size: $r=0.88$ except for REM vs AW). Thus, in contrast with the PP-DG synapse, synaptic transmission at the SC-CA1 synapse was the highest during NREM.

We then determined the time course of synaptic changes at SC-CA1 synapse during the transitions between vigilance states (Figures 2E & 1-3). A rapid modulation of synaptic responses was found at several transitions between brain states. Fast synaptic changes were thus observed during transitions from NREM to REM (a 23% decrease in 1 min, Friedman test, $\chi^2(3) = 29.72$, $p = 1.57e^{-06}$; post-hoc Dunn's test $p < 0.0001$) and from REM to QW (Friedman test, $\chi^2(3) = 29.5$, $p = 1.75e^{-06}$; post-hoc Dunn's test $p = 0.003$, Figure S3A). We also observed rapid synaptic changes for transitions between NREM and AW (Friedman test, $\chi^2(3) = 22.74$, $p = 4.56e^{-05}$; post-hoc Dunn's test $p < 0.009$). Thus, at the SC-CA1 synapse, rapid changes in fEPSP were observed during transitions between vigilance states, recalling those seen at the PP-DG synapse.

We next computed the evolution of the synaptic responses within each episode by dividing each episode by thirds (Figure S3B). During REM episodes, the synaptic responses decreased rapidly between the first third and the second third ($p = 0.0006$), as at the PP-DG synapse. The analysis by thirds did not reveal any modulation during the other states. We then examined whether paired-pulse stimulation of evoked responses was modulated during the sleep-wake cycle (Figure 1-3). A paired-pulse facilitation of synaptic response was observed at this synapse (in contrast with PP-DG synapse) that was increased during REM compared to QW and NREM (Friedman test $\chi^2(3) = 17.55$, $p = 0.0005$, effect size: 0.71; post-hoc Dunn's test: QW vs REM $p = 0.04$; NREM vs REM, $p = 0.04$, $n = 8$ rats). Moreover, an increase in paired-pulse facilitation was also found during AW compared to QW (QW vs AW, $p = 0.04$). Thus, the results are consistent with a decrease in synaptic response during REM and AW due to a presynaptic mechanism.

Vigilance state dependent modulation of evoked responses at hippocampal downstream synapses.

The fornix to medial prefrontal cortex synapse. The slope of evoked responses at the Fx-PFC synapse (P10 component, Figure 2G-H) was also significantly modulated during the sleep-wake cycle in the following direction: [NREM = QW] > [REM=AW] (Figure 2G; Friedman test, $\chi^2(3) = 9.4$, $p = 0.04$; post-hoc Dunn's test: NREM vs REM $p = 0.03$, NREM vs AW $p = 0.02$, NREM vs QW $p > 0.05$, REM vs AW $p > 0.05$, REM vs QW $p = 0.055$, AW vs QW $p = 0.008$; Effect size: 0.36, $n = 9$ rats). Then, the modulation of synaptic slopes during vigilance state transitions was analyzed (Figures 2J & 1-3). We observed a rapid decrease in the synaptic response of NREM to REM (Friedman test, $\chi^2(3) = 11.3$, $p = 0.009$; post-hoc Dunn's test: $p = 0.006$) and an increase in response from REM to QW (Friedman test, $\chi^2(3) = 10.73$, $p = 0.013$; post-hoc Dunn's test: $p = 0.02$). The evolution of the evoked responses

during each vigilance state episodes was then computed by dividing each vigilance state episode by thirds (Figure 1-3). Evoked responses in the Fx-PFC pathway were not significantly modulated within a given vigilance state episode. No modulation of paired-pulse facilitation was also found during the sleep-wake cycle (Figure 1-3, $p > 0.05$, $n = 7$ rats).

The fornix to Nucleus Accumbens synapse. The slope of evoked responses at the Fx-NAc synapse (P10 component, see Star Methods) was also modulated during the sleep-wake cycle as shown using estimation graphics from the full group of rats (Friedman test: $\chi^2(3) = 16.6$, $p = 0.0008$; effect size: 0.50; $n = 11$ rats, Fig 3B-C). In marked contrast with the PP-DG, SC-CA1 and Fx-PFC synapses, evoked responses at the Fx-NAc synapse increased during REM compared with NREM and wake (REM vs NREM: $p = 0.006$; REM vs AW: $p = 0.01$; REM vs QW: $p = 0.006$; AW vs QW: $p = 0.63$; AW vs NREM: $p = 0.21$; QW vs NREM: $p = 0.24$, Figure 3B-C). Therefore, evoked responses at Fx-NAc synapse changed during vigilance states in the following direction: REM > [AW=NREM=QW].

We next computed the variation of synaptic responses during vigilance state transitions (Figures 3E & S3A). We observed a fast modulation of evoked responses during transitions from NREM to REM (Friedman test, $\chi^2(3) = 19.04$, $p = 0.0003$; post-hoc Dunn's test: $p = 0.003$) and from REM to AW (Friedman test, $\chi^2(3) = 17.95$, $p = 0.0005$; post-hoc Dunn's test: $p = 0.0008$). The change in synaptic responses during vigilance state episodes was also assessed by dividing each episode by thirds (Figure 1-3). In marked contrast with the PP-DG and SC-CA1 synapses, evoked responses were not modulated during REM episodes ($p = 0.1933$ and $p = 0.0940$ respectively) at Fx-NAc synapse as at Fx-PFC synapse. Finally, no modulation of paired-pulse facilitation was found during the sleep-wake cycle (Figure 1-3, $p > 0.05$, $n = 7$ rats).

The fornix to amygdala synapse. Responses to the Fx-Amy synapse were also modulated during the sleep-wake cycle (Friedman test, $\chi^2(3) = 11.3$, $p = 0.009$, $n = 9$ rats, effect size: 0.42, Fig 3G-H). Responses decreased during NREM compared to wakefulness (AW vs QW $p = 0.074$; AW vs NREM: $p = 0.012$; QW vs NREM: $p = 0.004$; NREM vs REM $p = 0.426$; REM vs AW: $p = 0.098$; REM vs QW: $p = 0.91$). We also observed a fast modulation of evoked responses during transitions from AW to QW (Friedman test, $\chi^2(3) = 9.73$, $p = 0.02$, post-hoc Dunn's test: $p = 0.03$) and from AW to NREM (Friedman test, $\chi^2(3) = 14.1$, $p = 0.003$; post-hoc Dunn's test: $p = 0.02$, Figures 3J & S3A). The evolution of the evoked responses during each vigilance state episodes was then computed by dividing each vigilance state episode by thirds. As at Fx-NAc and Fx-PFC synapse (Figure 1-3), evoked responses in the Fx-Amy pathway were not significantly modulated during vigilance state episodes.

Pre-stimulus modulation of evoked responses by the magnitude of local oscillations.

We next considered that the modulation of evoked responses could be linked to local oscillations. Local brain states as characterized by spontaneous LFP oscillations are continuously changing on a shorter time scale (Kay and Frank, 2019). Spontaneous LFP oscillations recorded in the DG, CA1, PFC, NAc and Amy shared similarities in each vigilance state (Figure 4-1). Delta oscillations were prominent during NREM in the five areas although during REM, phasic theta waves were found in these structures that were associated with the prominent tonic theta oscillation (Figure 4-1 (Buzsáki, 2002), (Montgomery et al., 2008), (Meyer et al., 2020), (Adamantidis et al., 2019)). We determined whether synaptic slopes could be influenced by the ongoing LFP oscillation immediately preceding the electrical stimulation triggering the evoked response. We then investigated the relationship between the magnitude of pre-stimulus oscillations and the slope of the synaptic responses (Figure 4). Long-term recordings allow to compute correlations between synaptic slope and

604 pre-stimulus LFP oscillation power for each vigilance state. The power of the pre-stimulus
605 oscillations was quantified for slow oscillations (0.5-2 Hz), delta (2-4 Hz), theta (5-8 Hz),
606 sigma (9-14 Hz), low gamma (38-45 Hz) and high gamma (55-95 Hz) and then the z-scored
607 power of these oscillations was correlated with the slope of each evoked response as shown in
608 the Figure 4A2 for theta waves. To carry out multiple correlations, we used Linear Mixed
609 effect Models (LMM (Bates et al., 2015), see Methods), with the power of the frequency
610 bands as fixed effects and animals as random effects. Thus, we determined whether the power
611 of different frequency bands correlates with the modulation of the synaptic responses.

612 At the PP-DG synapse, during AW, synaptic responses were negatively correlated
613 with the magnitude of the theta oscillations ($R^2m = 0.042$, $p = 1.231e^{-06}$, $n = 10$ rats; Figure
614 4A1&D). We computed the marginal coefficient of determination (R^2m) which estimates the
615 proportion of variance explained by the fixed-effects factors (i.e. oscillation power). During
616 QW as well, synaptic slopes were negatively correlated with theta oscillations, but also with
617 slow oscillations, delta, sigma and gamma oscillations ($R^2m = 0.093$, $p = 6.166e^{-14}$) as for
618 NREM ($R^2m = 0.087$, $p = 3.026e^{-12}$). In contrast, during REM, fEPSPs were positively
619 correlated with the slow oscillations although negatively correlated with theta, sigma and
620 gamma oscillations ($R^2m = 0.073$, $p = 2.388e^{-14}$). To sum up, at this synapse, correlations
621 between synaptic responses and oscillation power were found at all vigilance states and were
622 predominantly negative.

623 At the SC-CA1 synapse, during AW, synaptic responses were positively correlated
624 with the slow oscillations although negatively correlated with the low gamma oscillations
625 ($R^2m = 0.031$, $p = 0.0047$, $n = 10$ rats; Figure 4B&D). In contrast, during REM, fEPSPs were
626 positively correlated with the slow oscillations although negatively correlated with high
627 gamma oscillations ($R^2m = 0.008$, $p = 0.010$). Thus, at this synapse, correlations between

628 synaptic responses and oscillation strength are only observed during AW and REM and the
629 level of latter correlation was low.

630 At the Fx-PFC synapse, during AW, we found a positive correlation with sigma (R^2_m
631 = 0.005 and $p = 0.0048$, $n = 9$ rats, Fig 4C&D) and, during REM, a positive correlation with
632 theta ($R^2_m = 0.019$ and $p = 0.003$). At the Fx-NAc and Fx-Amy synapses, we found no
633 significant correlation between the slope of the synaptic responses and the power of the
634 oscillations whatever the state of vigilance (Fig 4-2). Altogether, these results showed that the
635 synaptic responses of the hippocampal pathways we studied were very weakly correlated with
636 the magnitude of pre-stimulus oscillations with the exception of the PP-DG synapse.

637

638 **Correlation between the phase of theta oscillations and synaptic responses.** Since
639 theta oscillation is a predominant waveband in the brain areas we studied, we next
640 characterized changes in synaptic response related to the phase of this oscillation during AW
641 and REM (Figure 5). The graphs (Figure 5A-D) show the correlation between the pre-
642 stimulus theta phase and the synaptic slope for all rats during AW (2 cycles from -180 to 510°
643 with 30° bin size; the thick red line with the confidence interval is the fitting curve of the
644 entire dataset, the surrogates of the entire dataset are represented by a black curve) and REM.
645 At the PP-DG synapse (Fig 5A&D left), synaptic slopes increased weakly at the rising phase
646 of the theta waves during AW (phase: $-118.5 \pm 11.1^\circ$, increase in synaptic slope:
647 $100.72 \pm 0.17\%$) and REM (phase: $-92.3 \pm 13.9^\circ$ increase in synaptic slope: $101.45 \pm 0.34\%$). At
648 the SC-CA1 synapse (Figures 5B&D left), synaptic slopes increased before the top of the
649 theta waves during AW (for the phase at $-9.03 \pm 7.5^\circ$, increase in synaptic slope:
650 $101.11 \pm 0.13\%$) and REM (phase: $-3.6 \pm 7.2^\circ$, increase in synaptic slope: $101.72 \pm 0.19\%$). At
651 the Fx-NAc synapse (Figures S5B1&S5B3), synaptic slopes also increased after the wave top
652 during AW (phase: $17.71 \pm 11.7^\circ$, increase in synaptic slope: $102.48 \pm 0.5\%$) and before the

wave trough during REM (phase: $149.39 \pm 14.05^\circ$, increase in synaptic slope: $102.72 \pm 0.61\%$). In contrast, at the Fx-PFC and Fx-Amy synapses, synaptic slopes were only slightly correlated with theta phase (Fig 5C&5D right, Fig 4-2). These results thus showed the existence of links between the phase of theta oscillations and synaptic slopes, during AW and REM, especially at the SC-CA1 and Fx-NAc synapses. However, these phase-dependent modulations of synaptic slopes were small compared to that of vigilance states.

Correlation between theta frequency and synaptic responses. We then examined whether synaptic responses were linked to the variation in theta frequency. The correlation between theta frequency and synaptic responses was computed at each synapse (Figure 6). At the PP-DG synapse, a negative correlation was found between theta frequency and synaptic slope, mainly during AW and REM (Figure 6A left and middle). The correlation was weaker in QW than in AW and REM (Figure 6A right). At the SC-CA1 synapse, a negative correlation between theta frequency and synaptic slope was also found in AW and sleep but not in QW (Figure 6B). At the Fx-PFC synapse, synaptic slopes were negatively correlated with theta frequency selectively during AW (Figure 6C). In contrast, at the Fx-NAc and Fx-Amy synapses, synaptic slopes did not appear to be linked to theta frequency whatever the state of vigilance (Figure 4-2). Thus, these results showed the existence of a low-level negative correlation between pre-stimulus theta frequency and synaptic slopes at the PP-DG, SC-CA1 and Fx-PFC synapses that contributes only weakly to explain the variance in the responses at these synapses.

Covariation of the synaptic responses at the three hippocampal efferent synapses. We next examined whether there was some degree of covariation of the responses at these synapses. We took advantage of the experimental design that evoked simultaneous responses at the three hippocampal efferent pathways to determine whether the synaptic responses at

679 these synapses covaried together at each stimulation of the fornix (i.e. Fx-PFC, Fx-NAc, Fx-
 680 Amy, see inset Fig 7A). Figure 7A shows the superimposed time course of the responses at
 681 the Fx-PFC, Fx-NAc and Fx-Amy synapses for a rat. The two-by-two correlation between
 682 these synapses revealed a high degree of correlation between the responses of the Fx-PFC and
 683 Fx-NAc synapses, in contrast to the correlations between the responses of the Fx-PFC and Fx-
 684 Amy synapses and between the responses of the Fx-NAc and Fx-Amy synapses (Fig 7A left).
 685 We next computed the correlation coefficient of the correlations of the synaptic slopes for
 686 two-by-two synapses for each vigilance state (Fig 7B). We did not observe a modulation of
 687 the covariation of synaptic responses during the sleep-wake cycle (Figure 7C). When the
 688 correlation was calculated for each animal on all synaptic responses, whatever the state of
 689 vigilance, it appeared that the correlation between the synaptic slopes of the Fx-PFC and Fx-
 690 NAc synapses was much higher than the correlation between the Fx-PFC and Fx-Amy
 691 synapses and the correlation between the Fx-NAc and Fx-Amy synapses (Figure 7D,
 692 correlation between Fx-PFC and Fx-NAc: $r = 0.88 \pm 0.15$; correlation between Fx-PFC and Fx-
 693 Amy: $r = 0.06 \pm 0.03$ and correlation between Fx-NAc and Fx-Amy: $r = 0.07 \pm 0.02$; $n = 8$ rats).
 694 We then asked what contribution a common covariation between the responses of these 3
 695 synapses could make to these correlations. To test this, we computed the partial correlation
 696 between the responses of these 3 synapses and observed that the correlation coefficients
 697 between the Fx-PFC and Fx-NAc synapses was almost identical as that was obtained
 698 previously for the two-by-two correlations (correlation between Fx-PFC and Fx-NAc: $r =$
 699 0.88 ± 0.15 ; correlation between Fx-PFC and Fx-Amy: $r = 0.03 \pm 0.03$; correlation between Fx-
 700 NAc and Fx-Amy: $r = 0.01 \pm 0.03$). To summarize, these results revealed a covariation of
 701 synaptic responses between the Fx-PFC and the Fx-NAc synapses which did not co-vary
 702 with the Fx-Amy synaptic responses and that was not modulated during the sleep-wake cycle.
 703

DISCUSSION

This work shows that brain states differentially modulate synaptic transmission of pathways projecting to, within and from the Hpc. We thus found that, during REM, synaptic transmission can be either decreased (PP-DG, SC-CA1 and Fx-PFC) or increased (Fx-NAc) depending on the synapse.

Synapse-specific modulation of responses.

Given the variability of the synaptic responses, we recorded them for very long periods of time, which allows to obtain a large sample of fEPSPs for each vigilance state. The fluctuation of the responses was not due to electrode movements since we control the fEPSPs during several days (see Methods). Synaptic responses' variability is a major feature of synaptic transmission even when synaptic potentials are recorded *in vitro* (Otmakhov et al., 1993). Brain temperature changes contribute to synaptic variability (Moser et al., 1994). However, temperature is unlikely to explain the synapse-specific modulations since in the same structure, the PP-DG and SC-CA1 synapses behave very differently.

We found that during wakefulness, responses at the PP-DG synapse were largely increased compared with sleep. This result expands the work of Winson and Abzug (1978), that did not show at the time the changes in synaptic transmission between AW and QW and between REM and NREM. Indeed, noradrenaline depletion was found to abolish the wake-NREM-dependent modulation of responses at the PP-DG synapse (Dahl et al., 1983). Given the low level of noradrenaline release during NREM compared to AW and the lack of noradrenaline during REM, our result could thus involve a noradrenergic beta receptors-dependent facilitation of synaptic transmission during wakefulness at the perforant path terminals (Haas and Rose, 1987). The rapid changes in fEPSPs during transitions between vigilance states

could be linked to fast modulation of noradrenergic signaling as observed in the thalamus (Osorio-Forero et al., 2021).

In contrast, at the SC-CA1 synapse, we found an enhancement of synaptic responses during NREM. Leung showed that SC-CA1 synaptic responses are higher during NREM than during AW, but not between NREM and QW (Leung, 1980). This author also found a decrease of SC-CA1 synaptic responses during REM compared to NREM and QW but not compared to AW. Here, with many more rats, we found that synaptic responses were the lowest during REM. Using paired-pulse stimulation, we reveal an increase in paired-pulse facilitation (PPF) in REM suggesting a presynaptic mechanism for the decrease in synaptic slope. This reduction in glutamate release could be due to the strong cholinergic activity in the Hpc during REM (Marrosu et al., 1995). This cholinergic signaling during REM would thus inhibit the hippocampal network by activating presynaptic muscarinic receptors at the Schaffer's collaterals (Hasselmo and Schnell, 1994).

Our findings also reveal for the first time a marked sleep-wake cycle dependent modulation of synaptic responses at the Fx-NAc synapse. Surprisingly, an increase in Fx-NAc transmission was observed during REM compared with the other vigilance states. This increase could be linked to postsynaptic factors since PPF is not modulated during REM. Corticosterone has been shown to increase AMPA receptor-mediated responses by a postsynaptic mechanism selectively in shell spiny neurons (Campioni et al., 2009). Since corticosterone is released during REM, it is possible that this neurotransmitter induces an increased response by a postsynaptic mechanism. Another possible explanation could arise from the increased burstiness of VTA dopaminergic neurons observed during REM (Dahan et al., 2007), which would increase dopaminergic signaling in the NAc during this state. Thus, during REM, dopamine release could activate dopamine receptors located on spiny neurons thereby enhancing AMPA mediated synaptic responses (Goto and Grace, 2008). Our result

should be linked with works suggesting an involvement of REM in reward systems including the NAc to enhance memory consolidation (Perogamvros and Schwartz, 2012).

Altogether, our results suggest that vigilance states might help organize the transfer of information in networks upstream and downstream the Hpc critically involved in memory (Figure 4-2). Synaptic slope is a key factor contributing to control the spike firing probability as well as the speed and temporal precision of their emission, a parameter quantified in information efficacy (London et al., 2002). Thus, during NREM, the information transfer would be facilitated by the increase in synaptic transmission at the SC-CA1 synapse. In contrast, during REM, transmission would be greatly reduced everywhere, at the exception of the Fx-NAc synapse. Following the most frequent sequence of vigilance states (i.e. wakefulness-NREM-REM), the information might be transferred faster from the entorhinal cortex to the DG during wakefulness and then, within the Hpc (SC-CA1) during NREM. Finally, the information flow would be facilitated to the NAc during REM, while the Hpc-PFC transmission would be enhanced during NREM. In contrast, at the Fx-Amy synapse, the information flow would be facilitated, albeit faintly, during AW.

Correlation between synaptic responses and LFP oscillations

We also revealed correlations between synaptic responses and pre-stimulus oscillations, as proposed by the Communication Through Coherence hypothesis. PP-DG synaptic responses seem to be more modulated by local oscillations power than other synapses. At this synapse, several types of waves except slow oscillations were negatively correlated with synaptic slopes. Correlations were found for the theta band during all vigilance states, and especially during REM. Granular cell recordings show that spontaneous EPSPs, that are mainly generated at the PP-DG synapse, are coherent with theta (Pernia-Andrade and Jonas, 2014). Since the PP-DG responses are characterized by a paired-pulse depression, it is likely that the increase in theta power, corresponding to higher excitatory

drive at this synapse, leads to a depression of the subsequent synaptic responses. Theta-dependent synaptic modulation may contribute to the integration of different information conveyed by theta waves in granular cells. In contrast, we found that the slow oscillation power was positively correlated with synaptic responses during REM at the PP-DG synapse but also at the SC-CA1 synapse. This effect may seem surprising given that slow waves are not predominant during this state. However, at the beginning of REM episodes, DG and CA1 slow waves show a higher power than later (middle and end periods) during these episodes (Figure 4-1). This transient substate at the beginning of REM episodes, that we have clearly separated from intermediate sleep, also corresponds to the period when synaptic responses are greater (Figures 1G&1-3). This result suggests that the last two-thirds of a REM episode may exert a specific role, perhaps of reorganizing excitability, that could be related to the redistribution of interneuron activity (Grosmark et al., 2012).

We also reveal that the responses at the SC-CA1 synapse reached their maximum at the peak of the theta during AW and REM. This phase-dependent modulation of synaptic responses suggests that pre-stimulus oscillations create periodic windows that can facilitate transmission. This modulation of the synaptic slope at theta peak coincides with the minimum discharge for pyramidal cells and the maximum discharge for several types of interneurons (Klausberger and Somogyi, 2008). Thus, the modulation of excitatory and inhibitory neuron activity in CA1 could contribute to enhance the driving force for SC-CA1 fEPSPs evoked at peak theta compared to those evoked at trough. Our result contrasts with a study in anesthetized rats where responses at this synapse is maximal during the descending phase of theta (Schall et al., 2008). One possible explanation could lie in key differences between theta oscillations in the anesthetized and awake animals (Buzsáki, 2002). We also found theta phase-dependent modulations of synaptic transmission at the Fx-PFC, Fx-NAc, and Fx-Amy synapses. These modulations of responses related to theta phase may allow the encoding of

information as observed between the Hpc and the PFC. It is of interest to note that the connection between the Hpc and the NAc (Fx-NAc) presents a periodic theta increase in responses during AW (peak) and REM (trough). This phase-dependent synaptic modulation may further enhance the role of REM at the Fx-NAc synapse during memory processing.

Covariation of synaptic responses.

Our results also reveal a covariation of synaptic responses at the Fx-PFC and Fx-NAc pathways. In contrast, we did not observe any covariation between the Fx-Amy synapse and the Fx-PFC and Fx-NAc synapses whatever the state of vigilance. Interestingly, it has been shown that pyramidal cells in the ventral Hpc send axons that bifurcate into multiple branches that can reach the prelimbic area of the PFC, the shell of the NAc, and the basolateral amygdala, the areas in which we recorded synaptic responses (Ciocchi et al., 2015). Therefore, a variation in excitability at one of these multi-branch axons could explain the covariation of synaptic responses we observed. The covariation of synaptic responses between Fx-PFC and Fx-NAc pathways may underlie a synchronization of neuronal activity in the PFC and the NAc, a factor that may help the information transfer from the Hpc to these structures.

To summarize, in contrast with hypotheses proposing homogenous synaptic modulations during vigilance state changes, our findings reveal that the five hippocampal pathways behave differently. Local oscillations also contribute to this differential modulation, albeit at a weaker level. These modulations in the synaptic responses may allow a sequential integration of information in the hippocampal network driven by behaviors during wakefulness and offline memory processing during sleep.

829 **Data availability:** Data are available via reasonable requests to the corresponding author.

830 **Author contributions:** Conception and design of the study: JC, RP and PAS. Data

831 acquisition: MR, MM and JC. Data analysis MR, MM and PAS. Analysis software: JCC.

832 Drafting the manuscript: GM and PAS. All authors reviewed and accepted the final draft of

833 the manuscript.

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Figure Legends

Figure 1. The response at the perforant path-dentate gyrus (PP-DG) synapse is increased during waking compared to sleep states. **A.** Sagittal section of the rat brain illustrating the schematic locations of recording and electrical stimulation sites. In one group of rats, synaptic responses were evoked at the perforant path (PP) to the dentate gyrus (DG) synapse and in another group of rats, the synaptic responses were evoked at the Schaffer collaterals (SC) to CA1 area of the dorsal Hpc synapse and at the fornix (Fx) to the medial prefrontal cortex (PFC), the nucleus accumbens (NAc) and the amygdala (Amy) synapses. **B.** To evoke responses of the PP-DG synapse, stimulating electrodes were located in the PP (close to the medial entorhinal cortex) and an array of 8 recording electrodes were placed in the superior blade of the DG of the dorsal Hpc. **C.** Top: typical single fEPSP trace during the four vigilance states. Right: enlargement of the initial part of the single fEPSPs showing their slopes (superimposed traces). Scales: 0.2mV; 2.5ms. Middle: Dynamics of the vigilance states during one hour of recordings (diurnal period). Bottom: Modulation of the synaptic responses in the same animal during the same period. Thick arrows indicate increase in synaptic response, observed during AW, while dashed arrows show a decrease in synaptic responses, usually observed during REM. Data were normalized to the average of the synaptic slopes obtained during a continuous 24h period. **D.** Average of synaptic responses for AW, QW, NREM and REM during 24h of continuous recording in one animal. Scale bars: 0.2mV;

2.5ms. **E.** During wakefulness synaptic responses increased compared to sleep (Friedman test, $\chi^2(3) = 30$, $p = 1.38 \times 10^{-6}$, $n = 10$ rats). During REM, synaptic responses drop significantly compared to all other vigilance states. The number of fEPSPs analyzed was 5044 for AW, 4089 for QW, 7595 for NREM and 2241 for REM. **F.** The slope of the synaptic responses changed rapidly during transitions between two distinct vigilance states. The normalized slope of synaptic responses was averaged at the four points of each sequence. Synaptic transmission rapidly decreased within 30 seconds during the transitions AW-QW, QW-NREM and NREM-REM and increased during the transition REM-AW. Transitions between vigilance states were first selected and then the synaptic responses were averaged for each rat at the four points of each sequence 30 seconds apart. Only the most frequent transitions are illustrated (mean \pm SEM). **G.** Intra-episode modulation of synaptic response at the PP-DG synapse. Slope quantification was obtained by subdividing each vigilance state episode in three bouts. During REM, synaptic responses rapidly decreased while synaptic responses were not significantly modulated during the other vigilance state episodes. **H.** Modulation of paired-pulse depression during vigilance states. Paired-pulse depression decreased during REM compared to wakefulness suggesting that presynaptic mechanisms could be involved in the modulation of synaptic slopes.

Figure 2. Schaffer collaterals-CA1 and fornix-medial prefrontal cortex evoked synaptic responses are increased during NREM sleep and quiet wake compared to active wake and REM sleep. A. To evoke responses at the Schaffer collaterals to CA1 (SC-CA1) synapse two stimulating electrodes were placed in the stratum radiatum of area CA3 of the dorsal Hpc. In the same rats, two recording electrodes were placed in the CA1 area of the dorsal Hpc. **B.** Modulation of SC-CA1 synaptic responses during the sleep-wake cycle. Top: Single fEPSP trace during AW, QW, NREM and REM. Right: enlargement of the initial part of the single

1020 fEPSPs showing their descending slopes (superimposed traces). Scales: 0.5mV; 10ms.
 1021 Middle: dynamics of the vigilance states during one hour of recordings during the diurnal
 1022 period. Bottom: modulation of the normalized synaptic responses in the same animal during
 1023 the same period. Thick arrows indicate increase in synaptic slope, observed during NREM,
 1024 while dashed arrows show a decrease in synaptic transmission, more specifically observed
 1025 during REM. **C.** Average of synaptic responses at CA3-CA1 synapse during 24h (same rat as
 1026 in A). Scale: 1mV; 2.5ms. **D.** Each state of vigilance corresponds to a specific modulation of
 1027 synaptic responses at CA3-CA1 synapse. During NREM, synaptic responses were increased
 1028 compared to the other states although during REM, synaptic responses decrease significantly
 1029 compared to all other vigilance states. The large circles represent the average (with SEM) of
 1030 individual data from each rat (indicated by small circles). The number of fEPSPs analyzed
 1031 was 6987 for AW, 7126 for QW, 9345 for NREM and 2937 for REM, n=11 rats). **E.** Synaptic
 1032 responses changed rapidly during transitions between vigilance states at CA3-CA1 synapse.
 1033 An increase in fEPSP was observed between the transition from AW to QW, the transition
 1034 from QW to NREM and the transition from REM to AW. On the other hand, the synaptic
 1035 response decreased sharply from NREM to REM. **F.** To evoke responses at the fornix to the
 1036 PFC (Fx-PFC) synapse, two stimulating electrodes were placed in the fornix and two
 1037 recording electrodes were placed in the prelimbic area (PL) of the PFC. **G.** Modulation of Fx-
 1038 PFC synaptic responses during the sleep-wake cycle. Top: Single fEPSP trace during AW,
 1039 QW, NREM and REM. Right: enlargement of the initial part of the single fEPSPs showing
 1040 their descending slopes (superimposed traces). Middle: dynamics of the vigilance states
 1041 during one hour of diurnal period. Bottom: the time course of synaptic responses in the same
 1042 animal during the same period. Thick arrows indicate an increase in synaptic response in QW
 1043 and NREM and a decrease in AW and REM. **H.** Average of Fx-PFC synaptic responses
 1044 during 24h (same rat as in G). Arrow indicates the synaptic response (P10 positive response at

10 ms). Scale: 0.2mV, 5ms. **I.** At the Fx-PFC synapse, responses during NREM were increased compared to AW and REM. Responses at this synapse were also increased during QW compared to AW (n = 9 rats). **J.** At the Fx-PFC synapse, a decrease in evoked responses was observed during transition between NREM and REM. For each transition between states represented, the slope of the fEPSP was computed for the two last responses of a given state, and for the two first responses of the following state for each animal.

Figure 3. Responses at the fornix-nucleus accumbens and fornix-amygdala synapses were modulated during the sleep-wake cycle. **A.** To evoke responses at the fornix to the NAc (Fx-NAc) synapse, two stimulating electrodes were placed in the fornix and two recording electrodes were placed in the shell of the NAc. **B.** Top: Single fornix-nucleus accumbens synaptic response trace during AW, QW, NREM and REM. Arrows indicate the P10 and P25 evoked responses (positive responses respectively at 10 and 20-30 ms). Right: enlargement of the initial part of the single fEPSPs showing their slopes (superimposed traces). Middle: dynamics of the vigilance states during one hour of recordings during the diurnal period. Bottom: the time course of synaptic responses in the same animal during the same period. Thick arrows indicate an increase in synaptic response during REM. Data were normalized to the average of the slope of the synaptic response obtained during a continuous 24h period. **C.** Average of the fornix-nucleus accumbens synaptic responses during 24h (same animal as in A). **D.** The Fx-NAc synaptic responses were increased during REM compared to wakefulness and NREM (n=11 rats). **E.** Responses changed rapidly during transitions between vigilance states at the fornix-nucleus accumbens synapse. A rapid increase in fEPSP slope was observed during transitions between NREM and REM although a decrease was found at the transition between REM and AW. **F.** To evoke responses at the fornix to the amygdala (Fx-Amy) synapse, two stimulating electrodes were placed in the fornix and two

recording electrodes were placed in the basolateral amygdala. **G.** The slopes of synaptic responses tend to increase during AW. Top: Single fornix-amygdala synaptic response trace during AW, QW, NREM and REM. Arrows indicate the P10 and P25 evoked responses (positive responses respectively at 10 and 20-30 ms). Right: enlargement of the initial part of the single fEPSPs showing their slopes (superimposed traces). Middle: dynamics of the vigilance states during one hour of recordings during the diurnal period. Bottom: the time course of synaptic responses in the same animal during the same period. Thick arrows indicate frequent increases in synaptic response during AW. **H.** Average of the Fx-Amy synaptic responses (same animal as in G). Arrow indicates the P10 synaptic response. **I.** The Fx-Amy synaptic responses were increased during wakefulness compared to NREM (n= 9 rats). **J.** Modulation of synaptic responses at the Fx-Amy synapse during transitions between vigilance states. A decrease in synaptic slope was observed during transitions between AW and QW. Transitions between vigilance states were first selected and then the synaptic responses were averaged at the four points of each sequence for each animal. Scale bars: 0.2mV, 5ms.

Figure 4. Correlation between the synaptic responses and the magnitude of pre-stimulus oscillations. **A.** Correlations between pre-stimulus oscillation power and synaptic slope at the PP-DG synapse during the sleep-wake cycle (from left to right: AW, QW, NREM and REM). **A1.** The color code corresponds to the correlations between the different frequency bands (SO, slow waves: 0.5-2 Hz, δ (delta): 2-4 Hz, θ (theta): 5-8 Hz, σ (sigma): 9-14 Hz, γ_L (low gamma): 38-45 Hz; γ_H (high gamma): 55-95 Hz) and the synaptic slope. Measurement of the power of the filtered LFP was carried out over a pre-stimulus period of 2s for slow wave, 1s for delta oscillations, 500ms for theta and sigma and 250ms for low and high gamma oscillations. The different regression lines (lm function of R, grey lines) correspond to the

correlation (linear fitting curve and confidence interval) obtained for each rat (24h recordings). At the PP-DG synapse, during AW, synaptic slopes were negatively correlated with the magnitude of theta oscillations ($R^2m = 0.042$, $p = 1.23e^{-06}$; beta estimate (β): normalized synaptic slope (%)/oscillation power, $\beta = -2.35$; $n = 10$ rats). During QW as well, fEPSPs were negatively correlated with theta oscillations, but also with delta, sigma and gamma oscillations ($R^2m = 0.093$, $p = 6.16e^{-14}$; for delta: $\beta = -5.28$, theta: $\beta = -4.12$, sigma: $\beta = -5.06$, low gamma: $\beta = -2.93$, high gamma: $\beta = -2.98$) as for NREM ($R^2m = 0.087$, $p = 3.02e^{-12}$, delta: $\beta = -2.62$, theta: $\beta = -3.91$, sigma: $\beta = -3.86$, low gamma: $\beta = -1.91$, high gamma: $\beta = -2.82$). In contrast, during REM, fEPSP slopes were positively correlated with the slow oscillations although negatively correlated with theta, sigma and gamma oscillations ($R^2m = 0.073$, $p = 2.38e^{-14}$, SO: $\beta = 3.97$, theta: $\beta = -5.35$, sigma: $\beta = -3.27$, low gamma: $\beta = -3.89$, high gamma: $\beta = -5.35$). **A2.** Detailed observation of A1: the correlation between synaptic slopes at the PP-DG and the magnitude of theta during REM. The different grey regression lines correspond to the results obtained for each animal and the black regression line corresponds to the regression line obtained for the entire dataset. The correlation was negative for all rats. **B.** At the SC-CA1 synapse, during AW, synaptic slopes were positively correlated with the slow oscillations although negatively correlated with the low gamma oscillations ($R^2m = 0.031$, $p = 0.0047$, for SO: $\beta = -1.01$ and for low gamma: $\beta = 1.204$; $n = 10$ rats). In contrast, during REM, fEPSPs were positively correlated with the slow oscillations although negatively correlated with high gamma oscillations ($R^2m = 0.008$, $p = 0.010$, for SO: $\beta = 2.204$ and for high gamma: $\beta = -2.53$). **C.** At the Fx-PFC synapse, during AW, we found a positive correlation with sigma ($R^2m = 0.005$ and $p = 0.0048$, for sigma: $\beta = 6.25$; $n = 9$ rats) and, during REM, a positive correlation with theta ($R^2m = 0.019$ and $p = 0.003$; for theta: $\beta = 7.07$). **D.** Matrix representing the beta parameters of the significant correlations between the synaptic slopes and the power of the different frequency bands for the three cortical

synapses. Estimates in blue are negative while estimates in red are positive. The intensity of the color scale indicates the level of the beta estimates.

Figure 5. Correlation between the phase of theta oscillations and the synaptic responses.

A. At the PP-DG synapse, modulation of the synaptic slope by the pre-stimulus theta phase during active wake (AW, purple) and REM sleep (REM, green). Top: superimposed single traces representing the raw data (black), the filtered data in the theta band (blue) and the theta phase (red). The black arrows indicate the time of the electrical stimulation and synaptic response. Bottom: Superimposed correlations (grey dots) between the theta phase (from -180° to 540°) and the synaptic slopes of data acquired over 24h ($n=10$ rats) during AW (left) and REM (right). On the same graphs, average correlation of the entire data set (purple dots for AW and green dots for REM) and the superimposed fitting curve (red). The theta phase randomized surrogate data generation of the entire data set is represented by a dark line and the confidence interval by the thickness of this line (500 randomizations). Fitting of the correlation results indicates that the period of the sinusoid is $175.5 \pm 11.1^{\circ}$ ($R^2 = 0.48$, $p = 0.003$) and $189.4 \pm 13.9^{\circ}$ ($R^2 = 0.42$, $p = 0.01$) for AW and REM respectively. **B.** Same as in A for the SC-CA1 synapse. Fitting of the correlation results indicates that the period of the sinusoid is $175.5 \pm 11.1^{\circ}$ ($R^2 = 0.48$, $p = 0.003$) and $189.4 \pm 13.9^{\circ}$ ($R^2 = 0.42$, $p = 0.01$) for AW and REM respectively. Fitting of the correlation results indicates that the period of the sinusoid is $175.5 \pm 11.1^{\circ}$ ($R^2 = 0.48$, $p = 0.003$) and $189.4 \pm 13.9^{\circ}$ ($R^2 = 0.42$, $p = 0.01$) for AW and REM respectively. **C.** Same as in A and B for the Fx-PFC synapse. The correlation of the entire data set was fitted by a sinusoid (period: $90.1 \pm 2.8^{\circ}$, $R^2 = 0.42$, $p = 0.003$) for AW. During REM, the correlation between theta phase and synaptic slope was not fitted by a sinusoidal function ($R^2 = 0.15$, $p = 0.85$). ns: non-significant. **D.** The 2 graphs show where the phase relationship of the synaptic slope maximum to the 180° period sinusoid (PP-DG and

1145 SC-CA1) or 90° period sinusoid (Fx-PFC connected by a dashed line) in AW (purple dots)
 1146 and REM (green dots). The mean of the maximum synaptic slope is also shown (y:±SEM)
 1147 relative to the surrogate (dark gray dots). At the PP-DG synapse, synaptic slopes tend to
 1148 increase weakly at the rising phase of the theta waves during AW (phase: $-118.5 \pm 11.1^\circ$,
 1149 increase in synaptic slope $100.72 \pm 0.17\%$ (surrogate: $99.8 \pm 0.2\%$)) and REM (phase: -
 1150 $92.3 \pm 13.9^\circ$ increase in synaptic slope $101.45 \pm 0.34\%$ (surrogate: $100.7 \pm 0.3\%$)). At the SC-
 1151 CA1 synapse, synaptic slopes tend to increase weakly at the top of the theta waves during AW
 1152 (phase: $-9.03 \pm 7.5^\circ$, increase in synaptic slope: $101.11 \pm 0.13\%$ (surrogate: $99.9 \pm 0.21\%$)) and
 1153 REM (phase: $-3.6 \pm 7.2^\circ$, increase in synaptic slope $101.72 \pm 0.19\%$ (surrogate: $99.9 \pm 0.24\%$)).
 1154 At the Fx-PFC synapse, synaptic slopes tend to increase weakly at two phases of the theta
 1155 waves during AW (phase: $-167.29 \pm 7.9^\circ$ and increase in synaptic slope: $102.2 \pm 0.49\%$
 1156 (surrogate: $99.9 \pm 0.6\%$) and phase: $12.3 \pm 7.8^\circ$, (surrogate: $100.9 \pm 0.5\%$)). Scale bars: 250 ms
 1157 and 0.1mV.

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1159 **Figure 6. Correlation between the theta frequency and the synaptic responses. A.** At the
 1160 PP-DG synapse, theta frequency and synaptic slope were negatively correlated. Top-left:
 1161 sample data with the raw trace (black) and the filtered theta band (red) and bottom-left the
 1162 correlation between theta frequency and synaptic slope during AW for one rat. Arrow shows
 1163 the synaptic response. Middle, the correlations were calculated with the entire dataset (AW: r
 1164 $= -0.10$, $p = 4.6e^{-15}$; QW: $r = -0.03$, $p = 0.02$; NREM: $r = -0.03$, $p = 0.003$; REM: $r = -0.11$, p
 1165 $= 8.0e^{-09}$; $n = 10$ rats). Only the linear fitting curves (and their confidence interval) are shown
 1166 for the different vigilance states. Right: the correlation coefficient (corrected with Fisher z-
 1167 transformation) of all rats was weaker in QW than in AW and REM (Friedman test, $\chi^2(3) =$
 1168 10.92 , $p = 0.0018$, followed by post-hoc Dunn's test, AW vs QW $p = 0.03$; REM vs QW $p =$
 1169 0.04). **B.** At the SC-CA1 synapse, a negative correlation between theta frequency and

synaptic slope was found in AW and sleep but not in QW. Left: Correlation between theta frequency and synaptic slope during REM for one rat. Middle, correlations during AW: $r = -0.08$, $p < 2.2e^{-16}$; QW: $r = -0.006$, $p = 0.2$; NREM: $r = -0.04$, $p < 2.2e^{-16}$; REM: $r = -0.09$, $p < 2.2e^{-16}$, $n = 11$ rats. Right: the correlation coefficient (corrected with Fisher z-transformation) of all rats was weaker in QW than in AW and REM (Friedman test, $\chi^2(3) = 21.44$, $p = 8.54e^{-5}$, post-hoc Dunn's test, AW vs QW $p = 7.27e^{-4}$; REM vs QW $p = 8.74e^{-4}$). C. At the Fx-PFC synapse, responses were negatively correlated with theta frequency in wakefulness but not in sleep. Left : correlation between theta frequency and synaptic slope during AW for one rat. Middle: correlations during AW: $r = -0.04$, $p < 0.006$; QW: $r = -0.03$, $p = 0.01$; NREM: $r = -0.009$, $p = 0.4$; REM: $r = -0.03$, $p = 0.15$, $n = 9$ rats. Right : a difference in correlation coefficients was observed between AW and NREM (Friedman test, $\chi^2(3) = 10.73$, $p = 0.013$, post-hoc Dunn's test $p = 0.02$).

Figure 7. Covariation of the synaptic responses between the three hippocampal efferent pathways. A. Correlation of the synaptic slopes between pairs of synapses during the sleep-wake cycle. The rationale for the experiment is presented in the inset (top) on a sagittal section of the rat brain that illustrates the site of electrical stimulation in the fornix corresponding to the hippocampal axons that connect neurons in the PFC, the NAc and the Amy. Left top to bottom: time course of synaptic slopes (normalized) for the 3 efferent pathways of a rat for 50 minutes. The evolution of the synaptic slopes is superimposed to illustrate the covariation of the responses. Covariations are indicated by arrows. Right and from top to bottom, the graphs show the correlations between the slope of Fx-PFC and Fx-NAc synapses (top), between the slope of Fx-NAc and Fx-Amy synapses (middle) and between the slope of Fx-PFC and Fx-Amy synapses (bottom) and the linear fitting curve with the confidence interval (same data as in left). B. The dark gray linear fitting curves correspond

to two-by-two correlations of the slopes of the 3 synapses from one rat during the vigilance states (AW, QW, NREM and REM). The colored curves are the linear fitting curve (with the confidence interval, the Pearson correlation coefficient (r) and the p value) of the data correlations obtained from 8 rats. **C.** The correlation coefficients (r coefficient corrected with Fisher z-transformation; Fisher transformation explains why values are higher than 1) were not modulated by the sleep-wake cycle ($p > 0.05$, Friedman test, $n = 8$ rats). From left to right, for each vigilance state, the slope of the linear fitting curves of the correlations between the responses of Fx-NAc and Fx-PFC synapses, between Fx-Amy and Fx-PFC synapses, and between Fx-NAc and Fx-Amy synapses. **D.** comparison of the correlations of the synaptic slopes between the 3 pairs of synapses regardless of the vigilance states (correlation between Fx-PFC and Fx-NAc synapses ($r = 0.88 \pm 0.15$); correlation between Fx-PFC and Fx-Amy synapses ($r = 0.06 \pm 0.03$); correlation between Fx-NAc and Fx-Amy synapses ($r = 0.07 \pm 0.02$), $n = 8$ rats, 14016 responses for the 3 synapses). The level of correlation was much higher for the Fx-NAc/Fx-PFC pair than for the Fx-Amy/Fx-PFC and Fx-NAc/Fx-Amy pairs (Friedman test, $\chi^2(2) = 12.56$, $p = 0.0018$, followed by post-hoc Dunn's test, $p = 0.002$ between the correlation Fx-PFC and Fx-NAc synapses and the correlation Fx-PFC and Fx-Amy synapses; $p = 0.016$ between the correlation Fx-PFC and Fx-NAc synapses and the correlation Fx-NAc and Fx-Amy synapses).

Figure 1-1. Histological verification of electrode implantations. **A.** Electrode implantation at the PP-DG synapse. Left: Location of the stimulation electrodes in the PP for individual rats. Right: location of the recording electrode arrays in the DG for individual rats. **B.** Microphotography of a coronal brain section showing the location of the perforant path stimulation electrodes. **C.** Location of the recording electrodes in the dentate gyrus of the dorsal hippocampus. **D.** location of the stimulation (CA3) and recording (CA1) electrodes at

the CA3-CA1 synapse. **E.** location of the stimulation electrodes in the fornix. **F.** Location of the recording electrodes in the PFC (prelimbic area). **G.** Location of the recording electrodes in the NAc (shell). **H.** Location of the recording electrodes in the Amy (basolateral amygdala) in individual rats. **I.** Location of the stimulation (CA3) and recording electrodes (CA1) in a coronal section of the dorsal hippocampus. **J.** Location of a stimulation electrode in the fornix. **K.** Location of recording electrodes in the PFC (prelimbic area). **L.** Location of recording electrodes in the NAc (shell). **M.** Location of recording electrodes in the Amy (basolateral area).

Figure 1-2. Row A-E. graphs illustrating the quantification performed successively for PP-DG, SC-CA1, Fx-PFC, Fx-NAc and Fx-Amy synapses. **Column 1 Left and Middle:** Analysis of the entire dataset using estimation statistics (with DABEST package under R (Ho et al., 2019)) leads to similar results as computed per rat (Figures 1-3). **Left:** Estimation graphic with the plot of the entire datasets for each vigilance state, the standard deviation (SD) for each group (vertical dark bars) and the mean value (gap in the vertical dark bar). **Middle :** the 95% confidence interval of the mean difference between vigilance states was obtained by performing bootstrap resampling (black vertical bars). The black dots represent the mean difference between AW and the other vigilance states. The zero level of these graphs corresponds to the synaptic slope values in AW. The curves show the resampled distribution of the mean difference. **Column 2:** Variability of synaptic slopes assessed by the coefficient of variation (CV, $CV = SD/mean$) at each synapse. At the PP-DG synapse, the CV is greater in REM than in AW. At the SC-CA1 synapse, the CV is higher in AW than in QW and NREM. The CV is also higher in REM than in NREM. At the Fx-PFC synapse the CV is higher in AW than in QW and NREM. At the Fx-NAc synapse the CV is higher in AW than

in NREM and REM. The CV is also higher in QW than in REM. At the Fx-Amy synapse the CV is higher in AW than in NREM and REM.*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Figure 1-3. A. Sleep-Wake cycle transitions. Modulation of synaptic slope during transitions between QW and AW, AW and NREM, NREM and AW, REM and QW and finally between NREM and QW. These transitions were less frequent than the transitions shown in Figures 1-3. There were several significant changes in synaptic slope during the transitions, particularly at the PP-DG and SC-CA1 synapses. At these 2 synapses the change in slope is large and sometimes rapid within 30s. We also observe slope changes at the Fx-PFC, Fx-NAc and Fx-Amy synapses for some transitions. **B.** Intra-episode modulation of synaptic slopes at the SC-CA1 synapse. Slope quantification was obtained by subdividing each vigilance state episode in three bouts. During NREM, synaptic slopes increased while during REM, synaptic responses rapidly decreased. Intra-episode modulation of synaptic efficacy at the Fx-PFC, Fx-NAc and Fx-Amy synapses. No modulation of synaptic slope was observed during the vigilance states. **C.** Modulation of Paired-Pulse Facilitation (PPF) at the SC-CA1 synapse (inter-stimulus interval 50ms) by vigilance states. Paired-pulse ratio increased during REM compared to wakefulness. At this synapse, paired-pulse ratio also increased during AW compared to QW and decreased during NREM compared to REM. In contrast, no modulation of paired-pulse ratio at the Fx-PFC and Fx-NAc synapses was found during the sleep-wake cycle. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$. Scale bars: 10ms, 0.5mV.

Figure 4-1. Ongoing local field potentials during the sleep-wake cycle. **A.** Top: Bouts of LFP recording during the sleep-wake cycle in the 5 structures studied (DG, CA1, PFC, NAc and Amy). Bottom: traces of EMG recordings during the sleep-wake cycle. **B.** Spectral analysis (mean \pm SEM) in DG, CA1, PFC, NAc and Amy during wakefulness and sleep.

NREM was characterized by delta oscillations although AW and REM were identified by prominent theta oscillations. **C.** Spectral analysis of LFP in DG and CA1 at the beginning, middle and end of the REM episodes (n = 6). **D.** Simultaneous recordings of LFP bouts of phasic theta during REM recorded in CA1, PFC, NAc and Amy. **E.** Percentage of vigilance state amount in a group of rats before and after 24 hours of electrical stimulation of CA3 area and fornix (n=15). No change in the amount of vigilance states was observed after continuous electrical stimulation. IS: intermediate sleep.

Figure 4-2. A. Correlation between oscillation power and the synaptic slope at the Fx-NAc and at the Fx-Amy synapses (related to Figure 4). **A1.** At the Fx-NAc synapse, no correlation was found in AW ($R^2_m = 0.001$, $p = 0.8$; 9 rats), QW ($R^2_m = 0.003$, $p = 0.8$), NREM ($R^2_m = 0.001$, $p = 0.1$) and REM ($R^2_m = 0.009$ and $p = 0.4$). **A2.** No significant correlation was also found at the Fx-Amy synapse in AW ($R^2_m = 0.002$, $p = 0.051$; 9 rats), QW ($R^2_m = 0.002$, $p = 0.9$), NREM ($R^2_m = 0.007$, $p = 0.06$) and REM ($R^2_m = 0.002$ and $p = 0.9$). **B1.** Correlation between theta phase and the synaptic slope at the Fx-NAc synapse (related to Figure 5). Fitting of the correlation results indicates that the period of the sinusoid is $176.6 \pm 11.7^\circ$ ($R^2 = 0.43$, $p = 0.003$) and $176.5 \pm 12^\circ$ ($R^2 = 0.44$, $p = 0.002$) for AW and REM respectively. **B2.** Correlation between theta phase and the synaptic slope at the Fx-Amy synapse. Fitting of the correlation results indicates that the period of the sinusoid is $91.13 \pm 2.1^\circ$ ($R^2 = 0.63$, $p = 3.6 \times 10^{-5}$) and $90.1 \pm 1.5^\circ$ ($R^2 = 0.76$, $p = 5.5 \times 10^{-7}$) for AW and REM respectively. **B3.** The graph shows where the phase relationship of the synaptic slope maximum to the 180° period sinusoid (Fx-NAc) or 90° period sinusoid (Fx-Amy connected by a dashed line) in AW (purple dots) and REM (green dots). The mean of the maximum synaptic slope is also shown ($y \pm \text{SEM}$) relative to the surrogate (dark gray dots). At the Fx-NAc synapse, synaptic slopes tend to increase weakly at the top of the theta waves during AW (phase: $-17.71 \pm 11.7^\circ$, increase in synaptic

1294 slope: $102.48 \pm 0.5\%$ (surrogate: $100.09 \pm 0.57\%$)) and at the trough of the theta waves during
 1295 REM (phase: $149.39 \pm 14.05^\circ$, increase in synaptic slope: $102.72 \pm 0.61\%$ (surrogate:
 1296 $100.73 \pm 0.65\%$)). At the Fx-Amy synapse, synaptic slopes tend to increase weakly at the rising
 1297 phase of the theta waves during AW (phase: $-75.36 \pm 5.65^\circ$, increase in synaptic slope:
 1298 $101.22 \pm 0.19\%$ (surrogate: $99.68 \pm 0.31\%$) and at the decaying phase of the theta waves
 1299 ($107.9 \pm 5.6^\circ$ (surrogate: $100.37 \pm 0.31\%$)). During REM, synaptic slopes tend to increase
 1300 weakly at the top of the theta waves (phase: $-25.11 \pm 3.35^\circ$, increase in synaptic slope:
 1301 $101.46 \pm 0.17\%$ (surrogate: $100.29 \pm 0.29\%$) and at the trough of the theta waves ($156.3 \pm 3.35^\circ$
 1302 (surrogate: $100.47 \pm 0.29\%$)). **C. Correlation between theta frequency and the synaptic slope**
 1303 (related to Figure 6). **C1.** No correlation was found between the theta frequency and the
 1304 synaptic slope at the Fx-NAc synapse (AW: $r = 0.015$, $p = 0.24$; QW: $r = -0.002$, $p = 0.9$;
 1305 NREM: $r = 0.006$, $p = 0.5$; REM: $r = 0.02$, $p = 0.14$; $n = 11$ rats). No significant correlation
 1306 was observed at this synapse between vigilance states (Friedman test, $\chi^2(3) = 0.71$, $p = 0.87$).
 1307 **C2.** No correlation was found between the theta frequency and the synaptic slope at the Fx-
 1308 Amy synapse (AW: $r = -0.003$, $p = 0.74$; QW: $r = -0.03$, $p = 0.06$; NREM: $r = -0.005$, $p = 0.6$;
 1309 REM: $r = 0.03$, $p = 0.09$; $n = 9$ rats). No significant correlation was observed at this synapse
 1310 between vigilance states (Friedman test, $\chi^2(3) = 4.06$, $p = 0.25$). Scale: 0.5mV, 500ms. **D.**
 1311 Schematic representation of the main results. This diagram, which represents a summary of
 1312 the main results, shows that the 2 states of wakefulness and sleep exert very different roles on
 1313 synaptic slopes. REM decreases synaptic responses at all synapses except the one between the
 1314 hippocampus and the nucleus accumbens (Fx-NAc synapse) where it is increased. NREM
 1315 increases synaptic responses at the SC-CA1 synapse and the synapse between the
 1316 hippocampus and the prefrontal cortex. This suggests a facilitation of information transfer to
 1317 these 2 synapses during this sleep state according to a hypothesis (Rasch and Born, 2013).
 1318 Finally, the responses of the 3 cortical synapses (PP-DG, SC-CA1 and Fx-PFC), were more

1319 modulated by pre-stimulus LFP oscillations than the 2 subcortical synapses (Fx-NAc and Fx-
1320 Amy).

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