Title

Local coupling between sleep spindles and slow oscillations supports the consolidation of motor memories.

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Abstract

The precise coupling between slow oscillations (SO) and spindles is critical for sleep-dependent consolidation of declarative memories. Here, we examined whether this mechanism also operates in the stabilization of human motor memories during NREM sleep. We hypothesized that if the coupling of these oscillations is instrumental to motor memory consolidation then only SO-coupled spindles would predict long-term memory. We found that sleep enhanced long-term memory retention by 34%. Motor learning increased the density of spindles but not their frequency, duration or amplitude during NREM sleep. This modulation was manifested locally over the hemisphere contralateral to the trained hand. Although motor learning did not affect the density of SOs, it substantially modulated the spindle-SO coupling in an inter-hemispheric manner, suggesting it may rather increase the ability of slow oscillations to promote thalamic spindles. The fact that only coupled spindles predicted long-term memory points to the association of these oscillations as a fundamental signature of motor memory consolidation. Our work provides evidence in favor of a common mechanism at the basis of the stabilization of declarative and non-declarative memories.

Introduction

In the last decades, the role of sleep in memory consolidation has received extraordinary attention. There is now compelling evidence from human and non-human studies supporting a role of NREM sleep on both the stabilization and enhancement of declarative memory (e.g., Plihal & Born, 1997; Rasch et al., 2007; Diekelmann & Born, 2010; Schönauer et al., 2015), and more recently on memory persistence (Schönauer et al., 2015; Sawangjit et al., 2018).

The neural signatures of sleep dependent consolidation are rapidly being unraveled. We now know that, during NREM sleep, slow oscillations (SO, ~1 Hz) generated in the cortex (Amzica & Steriade, 1998; Timofeev et al., 2000) facilitate the occurrence of thalamic spindles (~ 10-16 Hz) during their excitable -up-state- (Steriade, 2006; Staresina et al., 2015; Schönauer & Pöhlchen, 2018). A recent study has in fact shown that the induction of thalamic spindles through optogenetics potentiates hippocampus-dependent memories when stimulation is phase locked with the up-state (active phase) of SOs, whereas spindle suppression impairs memory formation (Latchoumane et al., 2017). The precise synchrony between these oscillations in conjunction with hippocampal sharp-wave ripples appears to be key for systems consolidation in a variety of declarative tasks (Buzsaki, 2015; Maingret et al., 2016; Ladenbauer et al., 2017; Helfrich et al., 2018; Navarro-Lobato & Genzel, 2018; Muehlroth et al., 2019).

Much less is known about the neural signatures of sleep-dependent consolidation of motor memories. Growing evidence suggests that offline gains observed in humans during motor sequence learning (MSL) are associated with an increment in the density of sleep spindles (Nishida & Walker, 2007; Morin et al., 2008; Barakat et al., 2011; Boutin et al., 2018). On the other hand, a series of studies have shown that overnight savings in visuomotor adaptation are predicted by an increment in the power of slow –delta- waves (~1-4 Hz) during the early portion of NREM sleep (Huber et al., 2004; Landsness et al., 2009). Yet, whether the spindle-SO coupling is relevant for the consolidation of non-declarative motor memories remains unknown. Recent work carried out in rats using the grasp-and-reach learning paradigm described the occurrence of task-related neural replay over the motor cortex during NREM sleep, often phase locked to spindle oscillations (Ramanathan et al., 2015). A more recent study from the same lab reported a modulation of motor learning over the density of spindle-SO couplings (Silversmith et al., 2020). Yet, whether the two phenomena are linked to one another and relate to offline gains in performance remains to be established.

In this study, we examined whether the coupling between spindles and slow oscillations supports the consolidation of human motor memories. We have recently shown evidence for the

stabilization of visuomotor adaptation memories within a 6-hours period of wakefulness (Della-Maggiore et al., 2017; Albert et al., 2019; Lerner et al., 2020). We thus chose the same experimental paradigm to address whether local changes in brain activity induced by learning (Della-Maggiore et al., 2017) are further modulated by sleep. Given that the role of sleep in sensorimotor adaptation is somewhat controversial (Donchin et al., 2002; Huber et al., 2004; Doyon et al., 2009), we first conducted an experiment to confirm a benefit of sleep in our experimental paradigm. In a second experiment, we examined the impact of motor learning on the density of spindles, and on the coupling between spindles and slow oscillations. We hypothesized that if the level of coupling between these oscillations is also critical for the consolidation of motor memories then it should predict long-term memory overnight.

Results

Sleep benefits visuomotor adaptation

To examine if, like motor sequence learning, sleep influences the consolidation of adaptation memories, in Experiment 1 we manipulated the proximity between learning a visuomotor adaptation task (VMA) and sleep (Figure 1.A). For practicality, we will refer to this manipulation as PLS. This procedure has been effective in unveiling the benefit of sleep in declarative tasks (Schönauer et al., 2015; Sawangjit et al., 2018). We figured that if sleep favors consolidation of VMA then training immediately before sleep should yield greater memory retention overnight than training far from sleep. PLS was thus manipulated to vary between 14 hours and 10 min. Both groups were exposed to a 30-degree optical rotation during training for about 30 minutes (Lerner et al., 2020, see Methods for details). The PLS-14h group learned the visuomotor adaptation task in the morning and then returned to the lab about 14 hours later to sleep. In contrast, the PLS-10min group learned the adaptation task at night and went to bed about 10 minutes after training. Memory retention and persistence were assessed 24 hs (TEST1, on Day 2), and 14 days later (TEST2, on Day 15), respectively.

During training, both groups learned at a similar rate and achieved similar asymptotic performance (Figure 1.B, Welch two sample t-test, learning rate: $t(35.38)=0.79$, $p=0.43$; asymptotic performance: $t(35.43)=0.27$, $p=0.78$). Sleep architecture did not differ across groups (see Table 1 for statistics). Examination of the degree of vigilance using the Stanford Sleepiness Scale (SSS; Hoddes E., 1973) yielded scores below 3 (Day 1, Day 2 and Day 15 for PLS-10min and PLS-14h = $p>0.96$), consistent with a mental state of alertness (Berry, 2012). More detailed

information regarding the vigilance test is reported in the supplementary material (Vigilance tests, Table S1).

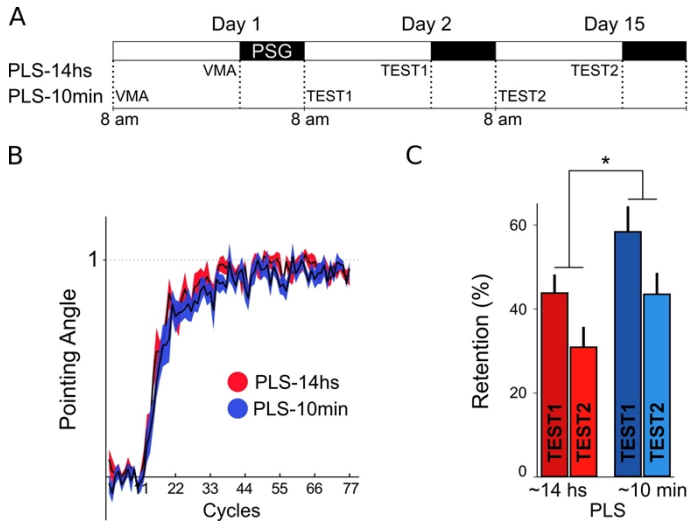

Figure 1. Sleep benefits visuomotor adaptation. A) *Experimental Design.* Participants in Experiment 1 were assigned to one of two groups in which the proximity between learning a visuomotor adaptation task (VMA) and sleep (PLS) was manipulated. Subjects in the PLS-10min and the PLS-14h groups went to sleep ~10 min and ~14 h after learning, respectively. Memory retention and persistence were assessed 24 hs and 14 days after learning (TEST1 and TEST2, respectively). Overnight sleep was monitored with polysomnography (PSG) during the first night. **B)** *Learning curves.* Shown are the median ± SE of the pointing angle corresponding to the PLS-10min group (blue shade) and the PLS-14h group (red shade). **C)** *Memory retention.* Memory retention was assessed based on error-clamp trials, and expressed as the percent relative to the asymptotic performance achieved during the learning session. Note that training in the proximity of sleep increased the level of retention at 24 hs. Shown are the mean ± SE of the pointing angle relative to the asymptote (%).

As depicted in Figure 1.C long-term memory was benefited from sleep by 34%. Specifically, the group that slept immediately after learning showed greater retention overnight than the group that slept 14 hs post training (TEST1, mean ± SE, PLS-10min: 58.38±6.08 % vs PLS-14h: 43.79±4.42 %; TEST2, mean ± SE, PLS-10min: 43.50±5.12 % vs PLS-14h 30.90±4.86 %; LMM stats: main effect of group, $\chi^2(1)=4.34$, $p=0.037$). Of note, even though there was considerable forgetting between TEST1 and TEST2 (main effect of TEST, $\chi^2(1)=16.32$, $p=5.35e-5$), the degree of memory decay was comparable across groups (group x test interaction, $\chi^2(1)=0.10$, $p=0.74$), suggesting that sleep benefited long-term memory but not memory persistence.

It is important to emphasize that in manipulating the time interval between learning and sleep, subjects in each group were trained at different phases of the circadian rhythm. In order to examine whether this factor may have influenced our results, we carried out an additional analysis based on a large database from the lab, in which we computed the correlation between time of training and overnight memory retention. To this aim, we pooled together data from 8

VMA studies carried out using the same experimental paradigm and similar visuomotor rotations (30 to 45 degrees). Subjects considered for this analysis were trained at time points spread between 8 AM and 10 PM (Caffaro et al., 2014; Lerner et al., 2020, and unpublished data), and tested for memory retention 24 hs later (see supplementary material for further details). Note that training and test were carried out at the same time of day for each subject. The results based on a sample of 155 participants yielded no significant correlation between the time of training/test and overnight memory retention (Supplementary Figure S1; Pearson correlation: r=0.1, p=0.2), suggesting no obvious circadian modulation of memory formation.

In sum, the results from Experiment 1 suggest that sleep benefits the consolidation of visuomotor adaptation memories for at least two weeks.

	Experiment 1						Experiment 2							
	PLS-14hs		PLS-10min		Mann-Whitney U test		Familiarization		CTL		VMA		Friedman test	
Measure	Mean	SD	Mean	SD	W	p	Mean	SD	Mean	SD	Mean	SD	Chi-sq	p
Total Sleep Time (min)	443.11	33.45	432.90	36.16	218.0	0.44	376.40	75.81	386.10	28.20	386.85	43.52	2.60	0.27
Sleep Effiency (%)	89.75	6.69	90.60	6.13	175.0	0.69	81.90	16.69	87.36	6.92	86.57	9.86	0.80	0.67
Sleep latency (min)	18.92	8.90	27.15	24.48	169.0	0.56	18.20	15.66	18.40	13.75	16.05	10.75	0.20	0.90
REM latency (min)	118.87	45.74	101.72	35.89	220.0	0.41	132.60	65.80	105.00	31.27	123.85	49.53	0.60	0.74
Total Wake Time (min)	51.24	34.23	44.83	29.06	209.5	0.59	80.35	77.47	54.80	30.59	58.75	45.80	0.20	0.90
WASO (min)	22.50	25.18	15.97	16.27	214.0	0.51	42.95	63.03	33.10	28.29	29.50	20.24	1.08	0.58
NREM1 (min)	52.50	25.06	37.50	12.15	257.5	0.06	43.35	23.51	53.30	30.63	53.35	16.27	0.60	0.74
NREM2 (min)	158.84	33.71	160.80	44.13	194.0	0.92	157.30	55.89	157.25	36.30	150.15	46.48	0.60	0.74
NREM3 (min)	117.26	33.46	126.95	30.87	157.5	0.37	100.25	38.80	100.15	23.56	105.90	23.49	1.40	0.50
REM (min)	114.50	32.77	107.65	26.99	217.5	0.45	75.50	34.54	75.40	29.18	77.45	26.84	0.60	0.74

Table 1. Sleep Architecture. Shown are the mean, standard deviation (SD), statistics and *p* values corresponding to the sleep measures listed in the first column for all conditions of Experiments 1 and 2. All measures are depicted in minutes except for Sleep Efficiency, defined as the percentage of total sleep time relative to the time interval between lights-off and lights-on (%). WASO: wake after sleep onset.

Motor learning modulates the density of sleep spindles and the spindle-SO coupling

The results from Experiment 1 indicate that the consolidation of visuomotor adaptation memories is modulated by sleep. To explore the neural signatures at the basis of this phenomenon, in Experiment 2 we quantified the occurrence of sleep spindles, slow oscillations and their association during the period of NREM sleep following training on the *PLS-10min protocol*.

The experimental design of Experiment 2 is summarized in Figure 2.A. A new set of subjects went through an initial familiarization session followed by either a session of

visuomotor adaptation, in which subjects compensated for a visual rotation (VMA), or a control session (CTL), in which the visual rotation was not applied. During the VMA and CTL sessions participants performed the motor task both before and after a full night of sleep. Memory retention was assessed overnight before the second practice session using error-clamp trials (Test).

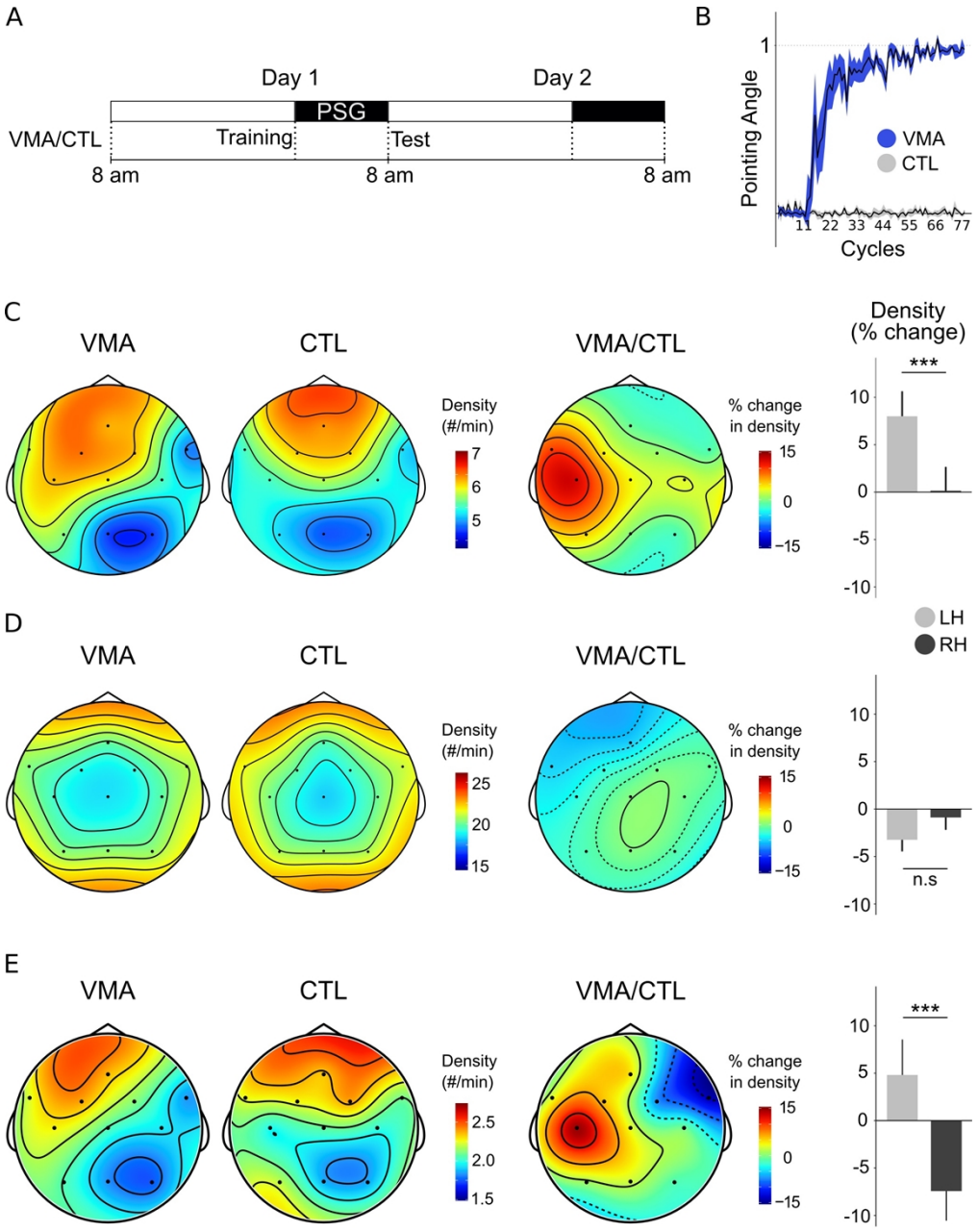

Figure 2. Motor learning modulates the density of spindles and spindle-SO couplings. A) *Experimental design*. Subjects in Experiment 2 were evaluated following the PLS-10min protocol on the VMA and CTL tasks in a counterbalanced order, over a period of two weeks. Memory retention was assessed overnight before re-adaptation using error-clamp trials (Test). After practice on Day 2, subjects were washed out to avoid carry over effects into the next session. Sleep was monitored with polysomnography (PSG) overnight. **B)** *Behavioral performance*. Median ± SE

of the pointing angle for the VMA (blue shade) and CTL (light gray shade) conditions for Day 1. **C)** *Local modulation of sleep spindle density*. Shown are the topographic plots for sleep spindle density (number by minute) corresponding to the VMA session, the CTL session and their relative difference ((VMA-CTL)/CTL*100). The barplot on the right depicts the relative difference in sleep spindles density (mean ± SE) collapsed across the electrodes of the left hemisphere (LH) and right hemisphere (RH). **D)** *Sleep did not impact on the density of slow oscillations*. Shown are the topographic plots for slow oscillations density corresponding to the VMA and CTL sessions and their relative difference. The barplot on the right depicts the relative difference in slow oscillations density (mean ± SE) for the LH and RH. **E)** *Local modulation of spindle-SO coupling.* Shown are the topographic plots for spindle-SO density corresponding to the VMA and CTL sessions and their relative difference. The barplot on the right depicts the relative difference in spindle-SO density (mean ± SE) for the LH and RH. Note that both the density of spindles and the density of spindles associated with SOs were significantly modulated by learning in an inter-hemispheric manner. Colorbars represent the density of these metrics for the VMA and CTL conditions, and their percent change, respectively.

As in Experiment 1, we found no significant differences in sleep architecture across sleep sessions for any of the computed measures (see Table 1 for scores and corresponding *p* values). Examination of the degree of vigilance using the Stanford Sleepiness Scale yielded scores below 3 (Vigilance tests, Table S1; Day 1 and Day 2 for sessions CTL and VMA = $p>0.5$), consistent with a mental state of alertness. All volunteers learned to compensate the visual rotation during the VMA condition (Figure 2.B) and, on average, retained 56±10.5 % (mean ± SE) overnight. Importantly, this level of retention was comparable to that exhibited by the PLS-10min group of Experiment 1 (Welch two sample t-test, $t(15.27)=-0.19$, $p=0.84$). In the CTL condition, in which no perturbation was applied, visuomotor error oscillated around zero.

Due to the known inter-subject variability in various metrics of spindles and slow oscillations (Purcell et al., 2017; Cox et al., 2018), the impact of motor learning on these measures and their coupling was quantified relative to the control condition (i.e. (VMA-CTL)/CTL). To appreciate the spatial distribution of the effects across the 11 EEG channels, we report the results for these measures in topographic plots. Yet, to explore the possibility of a local –hemispheric- modulation of learning (Nishida & Walker, 2007; Johnson et al., 2012; Della-Maggiore et al., 2017; Geva-Sagiv & Nir, 2019), statistical analyses were conducted on data pooled across the channels of the left hemisphere (LH) and right hemisphere (RH). Given that the midline may capture electrical activity from both hemispheres it was not included in these analyses. Thus, unless stated otherwise, all statistical analyses that follow were conducted on the relative measure described above (VMA-CTL)/CTL) for each hemisphere.

Visuomotor adaptation modulates brain oscillations during NREM sleep

We first looked at the impact of visuomotor adaptation on the intrinsic features of spindles, that is frequency, duration and peak-to-peak amplitude across NREM2 and NREM3. No statistical

differences were found for frequency (LMM stats, main effect of hemisphere; NREM2: $\chi^2(1)=2.24$, $p=0.13$; NREM3: $\chi^2(1)=0.04$, $p=0.84$), duration (LMM stats, main effect of hemisphere; NREM2: $\chi^2(1)=0.15$, $p=0.7$; NREM3: $\chi^2(1)=2.68$, $p=0.10$), or amplitude of sleep spindles (LMM stats, main effect of hemisphere; NREM2: $\chi^2(1)=0.36$, $p=0.55$; NREM3: $\chi^2(1)=0.74$, $p=0.39$).

We then examined the effect of learning on spindle density. We found that adaptation to a visual rotation increased the density of spindles (Figure 2.C). Interestingly, this effect was observed during NREM3 over the electrodes contralateral to the trained hand (relative change in density, mean ± SE: NREM2: LH=-2.9±4.1 %, RH=1.6±4.6 %; NREM3: LH=8.0±2.6 %, RH=0.1±2.5 %; LMM stats: main effect of sleep stage: $\chi^2(1)=2.16$, $p=0.14$; main effect of hemisphere: $\chi^2(1)=0.47$, $p=0.49$; sleep stage x hemisphere interaction: $\chi^2(1)=3.79$, $p=0.05$; one sample t-test for the LH vs zero: $t(24.2)=1.76$, $p=0.04$). Figure 2.C illustrates the topographic plots for spindle density during NREM3. As depicted in the bar graph, the left hemisphere drove this effect entirely (main effect of hemisphere: $\chi^2(1)=12.34$, $p=0.0004$; one sample t-test for the LH vs zero: $t(11.7)=2.06$, $p=0.031$). Further qualitative information regarding the individual electrodes driving this effect are provided in Figure S2.A (Supplementary material), showing that this effect was mostly driven by C3, the electrode placed over the sensorimotor cortex contralateral to the trained hand.

After studying sleep spindles activity, we explored the impact of motor learning on slow oscillations. Slow oscillations are the hallmark of NREM3 sleep, therefore, here we quantified their density during NREM3 as an index of SO activity (Riedner et al., 2007; Mölle et al., 2011). As illustrated in Figure 2.D, we found no effect of visuomotor adaptation on SO density (relative change in density, mean ± SE: LH = -3.2±1.2 %, RH = -0.9±1.3 %; LMM stats: main effect of hemisphere: $\chi^2(1)=2.84$, $p=0.1$; one sample t-test for the LH vs zero: $t(12.2)=-1.77$, $p=0.10$; RH vs zero: $t(12.2)=-0.48$, $p=0.64$), suggesting that this parameter was not modulated by learning.

So far, we have shown an inter-hemispheric modulation of motor learning on the density of spindles but not SOs. We know, however, that the coupling of these oscillations may be critical in the consolidation of declarative memories (Buzsaki, 2015; Maingret et al., 2016; Ladenbauer et al., 2017; Navarro-Lobato & Genzel, 2018; Helfrich et al., 2018; Muehlroth et al., 2019). To explore the relevance of this coupling in the consolidation of motor memories, we quantified the amount of spindles that occurred phased locked to a SO during NREM3. We found that the density of spindles coupled with a SO was modulated by VMA (Figure 2.E), in such way that it increased over the contralateral hemisphere but decreased over the ipsilateral hemisphere to the trained hand (relative change in density, mean ± SE: LH = 5.0±3.9 %, RH = -

7.7±3.2 %; LMM stats: main effect of hemisphere: $\chi^2(1)=11.35$, $p=0.0008$). Qualitative assessment of this effect (Figure S2.B, Supplementary material) suggests that the up-regulation of the coupling was mostly driven by the electrode C3.

To examine whether the increment in spindle-SO coupling in fact promoted memory consolidation, we next correlated the relative change in the density of spindles during NREM3 phase locked to a SO with overnight memory retention. To evaluate the specificity of this phenomenon, we contrasted this result with that obtained from correlating *uncoupled* spindles with memory retention. As observed in Figure 3 only spindles associated with a SO predicted long-term memory overnight (Pearson correlation: *Coupled spindles*: r1= 0.89, p=0.001; *Uncoupled spindles*: r2=0.09, p=0.81; comparison r1 vs. r2: Williams' t, t (6) = 2.56, p-value = 0.04).

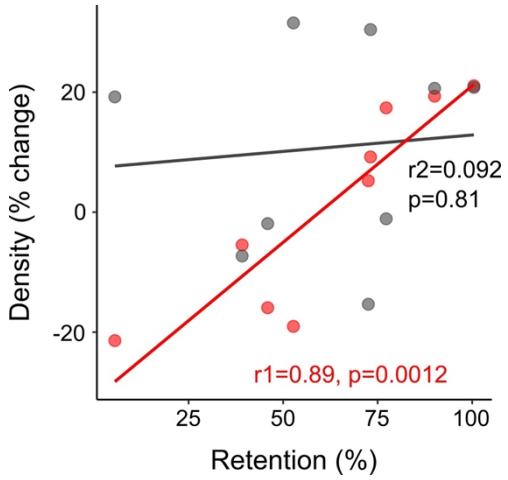

Figure 3. The density of SO-coupled spindles predicts motor memory consolidation. Correlation between memory retention and the % change in density ((VMA-CTL)/CTL*100) of SO-coupled spindles (red) versus uncoupled spindles (dark gray). Only SO-coupled spindles predicted long-term memory. Shown are the dots representing the mean across all 4 electrodes of the left hemisphere, and the corresponding regression lines.

In sum, we found that sensorimotor adaptation modulates the density of spindles but not their frequency, duration or amplitude during NREM sleep. This modulation was specific to NREM3, and was manifested as an increase in spindle density over the hemisphere contralateral to the trained hand. Although VMA did not affect the density of SOs, it substantially modulated the spindle-SO coupling, suggesting that motor learning may rather increase the ability of slow oscillations to promote thalamic spindles. The fact that only coupled spindles predicted long-term memory points to the association of these oscillations as a fundamental signature of motor memory consolidation.

Visuomotor adaptation does not affect the level of synchrony between SOs and spindles

Previous studies have shown that learning may influence the degree of synchrony between SO and spindles, which is reflected in the level of grouping (or variance) of spindles around the active phase of slow oscillations (Mölle et al., 2009, 2011). To investigate whether the modulation of the spindle-SO coupling observed in Figure 2.E was accompanied by a change in the degree of synchrony, we determined the phase of the SO at which the spindle yielded its maximum peak-to-peak amplitude, and contrasted the level of grouping of spindles around the mean phase for the VMA and CTL sessions.

We found a consistent phase relationship between SOs and spindles for both the CTL and VMA conditions (Rayleigh non-uniformity test. CTL: r=0.69, p=4.9e-03; VMA: r=0.89, p=7.93e-06). As illustrated in Figure 4, spindles occurred mainly during the active phase of the slow oscillation, close to its positive peak (Steriade & Amzica, 1998a; Amzica & Steriade, 1998; Rasch & Born, 2013). This is in line with previous studies from declarative memory (Ladenbauer et al., 2017; Helfrich et al., 2018; Muehlroth et al., 2019). Yet, the preferred synchronization phase between these oscillations (Watson's Large-sample Nonparametric Test. VMA vs. CTL: χ^2=0.35, p=0.56) and the grouping around the mean phase (Wallraff's Nonparametric Test. VMA VS. CTL: V=25, p=0.85) were similar in both conditions, suggesting that motor learning did not modulate these parameters.

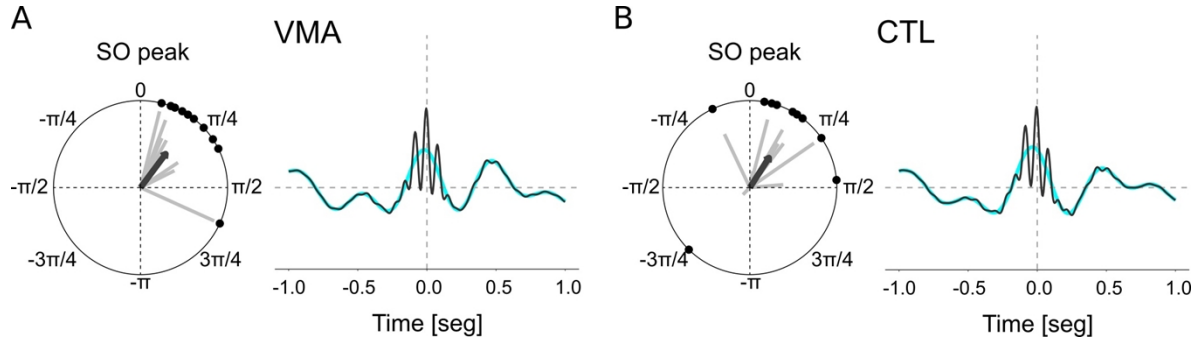

Figure 4. Spindle-SO synchrony in the VMA (A) and CTL (B) sessions. (Left) Polar plots illustrate the mean coupling phase between spindles and slow oscillations for each subject (gray lines/black points) and all subjects (black arrow), corresponding to the left hemisphere. (Right) Grand average EEG for spindle-SO coupling events locked to the spindle maximum peak-to-peak amplitude. The cyan line is the signal filtered in the slow oscillations frequency band (0.5-1.25 Hz) and the black line is the signal filtered in the spindles band (10-16 Hz).

In sum, we showed that spindles occurred mainly during the active phase of SOs independently of the condition (CTL or VMA). Even though VMA increased the coupling between slow oscillations and spindles, it did not influence their level of synchrony nor the mean

coupling phase, suggesting that those parameters may not provide relevant information regarding motor memory consolidation.

Effect of VMA on the power of delta activity

Previous studies from Huber and collaborators (Huber et al., 2004; Landsness et al., 2009; Wilhelm et al., 2014) have shown that visuomotor adaptation (reaching) induces a local increase in delta activity (1-4 Hz) over the anterior and medial portion of the posterior parietal region, as assessed by the average EEG power density during the beginning of NREM sleep. The authors have interpreted this finding within the frame of the synaptic homeostasis hypothesis (SHY) (Tononi & Cirelli, 2003), according to which synaptic weights potentiated during wake, are downscaled by sleep. Empirically, SHY would manifest as an increment in the power of delta during the beginning of sleep that decreases as the night progresses (Tononi & Cirelli, 2006).

To test this hypothesis in our data, we followed the same preprocessing steps (Huber et al., 2004, 2006, refer to Methods for details) and computed the mean power of delta activity during the first 20 minutes of NREM sleep for VMA relative to the CTL. Figure 5 depicts a significant inter-hemispheric modulation of the relative change in delta power, consisting of an increase in the LH and a decrease in the RH (relative change in power, mean ± SE: LH=4.9±3.8 %; RH=-8.1±3.4 %; LMM stats: main effect of hemisphere: $\chi^2(1)=6.47$, $p=0.01$).

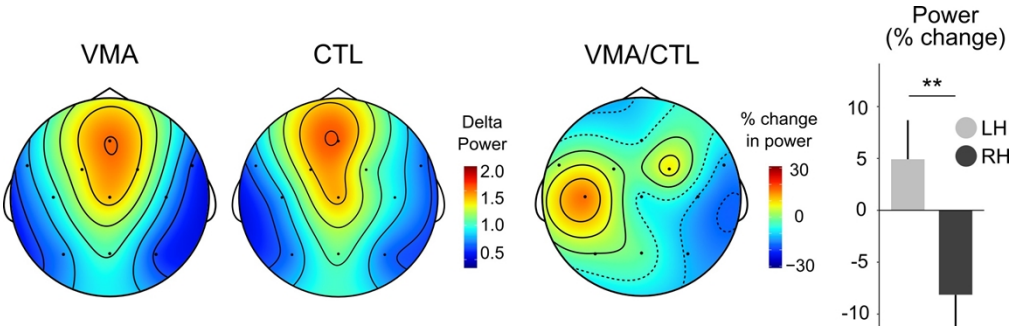

Figure 5. Sleep modulates the power of delta activity early during NREM sleep. Topographic plots for normalized delta (1-4Hz) power at the beginning of NREM sleep (first ~20 min) for VMA and CTL sessions, and their relative difference ((VMA-CTL)/CTL*100). The barplot on the right depicts the relative difference in delta power (mean ± SE) collapsed across the electrodes of the left (LH) and the right (RH) hemispheres. Sleep modulated the power of delta oscillation in an inter-hemispheric manner. Colorbars represent the normalized delta power for the VMA and CTL conditions, and the percent change, respectively.

As for the density of spindle-SO coupling, the modulation of delta power appeared to be driven by the electrode C3 (Figure S2.C, Supplementary material). Note however, that no

significant correlation was observed between the delta power increase in the LH and long-term memory retention (Pearson correlation: r=0.29, p=0.41).

In sum, despite some major differences regarding the experimental design and paradigm, in agreement with Huber and collaborators (2004) we observed an effect of visuomotor adaptation on the power of delta activity at the beginning of NREM sleep consistent with SHY. We did not find, however, a significant correlation between delta power modulation and overnight memory retention.

Discussion

The degree of coupling between slow oscillations (SO) and spindles is critical for sleep-dependent consolidation of declarative memories. Here, we examined whether this mechanism also operates in the stabilization of motor memories. To this aim, we measured the impact of learning a visuomotor adaptation task on the density of slow oscillations, spindles and their coupling during NREM sleep. Adaptation modulated both the spindle density and the degree of spindle-SO coupling locally in an inter-hemispheric manner during NREM3. Critically, only the density of spindles associated with slow oscillations predicted memory retention overnight.

Abundant literature suggests that MSL benefits from sleep consolidation (Stickgold, 2005; Nishida & Walker, 2007; Doyon et al., 2009; Debas et al., 2010; Albouy et al., 2013a). This effect is thought to be mediated by the hippocampus (Albouy et al., 2013b; Albouy et al., 2015; Boutin et al., 2018; Schapiro et al., 2019). A couple of papers (Huber et al., 2004; Landsness et al., 2009) have also shown evidence supporting a role of sleep in stabilizing savings overnight following training in a VMA reaching paradigm. This finding has, however, been challenged more recently. Specifically, work from Doyon and collaborators (Doyon et al., 2009; Debas et al., 2010) has shown no benefit of sleep in a VMA task, whereas Donchin and colleagues (Donchin et al., 2002) found no effect of sleep deprivation on savings associated with force-field adaptation. Based on these data the authors have claimed that, unlike motor skill learning, consolidation of adaptation memories depends solely on the passage of time (Donchin et al., 2002; Doyon et al., 2009), a hypothesis in line with the preponderant view that only hippocampal tasks benefit from sleep (Shadmehr et al., 1998; Doyon et al., 2009; Thürer et al., 2018). One possible explanation of this discrepancy may lie on the dissimilarities between tasks and experimental procedures. For example, Doyon and colleagues asked subjects to track elliptic trajectories under a 180-degree perturbation (Doyon et al., 2009; Debas et al., 2010). Mirror perturbations are learned and consolidated through different mechanisms than small

rotations (< 60 degrees), like the one used in our study (Bédard & Sanes, 2011; Gutierrez-Garralda et al., 2013; Telgen et al., 2014). Another critical factor may relate to the time interval elapsed between training and sleep (PLS), which was not manipulated in force-field adaptation (Donchin et al., 2002) and was key to our findings. As revealed by Experiment 1, sleeping immediately after learning significantly increased the level of retention over that observed when training occurred much earlier.

The results from Experiment 1 are against the hypothesis that adaptation depends solely on the passage of time. Our data rather shows a strong modulation of VMA memories by sleep that was maintained through two weeks. Given that the level of memory retention for the PLS-14h group was not assessed before bed time, we cannot ascertain whether sleep actually improved memory retention or simply stabilized it after performance was degraded during wake (Brawn et al., 2010). Further studies will be needed to discern between these factors. It is important to emphasize that, like Huber and collaborators (2004), we found both a benefit of sleep on memory retention and a local increment in the power of delta activity (~1-4 Hz) during the first 20 min of NREM sleep. The authors interpreted this finding in the context of the synaptic homeostasis hypothesis (SHY; Tononi & Cirelli, 2003), according to which synaptic weights potentiated during wake, are globally downscaled during sleep. This process is thought to improve the signal-to-noise ratio for strongly potentiated synapses. An alternative hypothesis, is the active systems consolidation, according to which newly encoded memories initially stored in hippocampal and cortical networks, are reactivated during slow wave sleep and gradually integrated with existing memories at the systems level. This process is thought to depend on the close synchrony between slow oscillations, sleep spindles and hippocampal ripples (Rasch & Born, 2007; Diekelmann & Born, 2010). Our results are consistent with both hypotheses as we found that adaptation modulated both delta activity early during NREM sleep, and the coupling between spindles and slow oscillations. The reproducibility of Huber's findings (2004) is noticeable despite the substantial differences regarding the effector involved in the task (fingers vs arm), the perturbation type (abrupt vs steps of 15 degrees) and the density of EEG electrodes (11 vs 256 channels). Yet, critically, subjects in both studies were exposed to a relatively small visuomotor rotation (< 60 degrees) and performed the task *immediately* (minutes) before sleep.

Our results showed a strong association between the increase in the number of spindles coupled with SOs and the ability to retain information overnight. The fact that uncoupled spindles were not related to long-term memory suggests that adaptation enhanced the capacity of slow oscillations to generate thalamic spindles and, that this coupling, in turn, promoted

synaptic plasticity. How may the enhanced coupling between slow oscillations and spindles drive motor memory consolidation? The mechanism by which the spindle-SO association may favor memory consolidation has been explored by Niethard and collaborators using two-photon imaging (2018). The authors found that cortical pyramidal neurons are more active, their dendrites disinhibited and, thus, more sensitive to excitatory inputs during the coupling of these oscillations than during their occurrence alone. This mechanism may facilitate dendritic plasticity during NREM sleep, when newly encoded representations are reactivated in the presence of spindle-SO events (Steriade et al., 1998b). The findings from Niethard and collaborators, consistent with the active systems consolidation theory mentioned above (Rasch & Born, 2007; Diekelmann & Born, 2010), are further supported by a recent optogenetic study showing that the induction of spindles in phase with the upstate of the slow oscillation potentiates hippocampal memories, whereas its suppression impairs consolidation (Latchoumane et al., 2017). Critically, here we observed that the induction of uncoupled spindles was ineffective in modulating memory formation. We speculate that these mechanisms may be at play in the overnight improvements in performance reported in our study.

One consistent finding we observed in our study is the inter-hemispheric modulation of brain oscillations: the two hemispheres appear to be engaged in an antagonistic manner. Given that subjects performed the task with their right hand, this inter-hemispheric modulation stresses the specificity of our results. There is growing evidence sustaining that both SO, spindle activity and their coupling develop locally during sleep rather than globally (Massimini et al., 2004; Andrillon et al., 2011; Nir et al., 2011; Cox et al., 2018). In motor skill learning, for example, local modulation has been observed in humans for sleep spindles (Nishida & Walker, 2007; Johnson et al., 2012) and more recently in rats for spindle-SO coupling (Silversmith et al., 2020). This focal effect suggests that sleep may promote the consolidation of memory representations in local networks that may be active during learning (Klinzing et al., 2019). This hypothesis is supported by neuroimaging and transcranial magnetic stimulation from our and other labs pointing to the involvement of contralateral motor and posterior parietal cortex in the acquisition and diurnal consolidation of sensorimotor adaptation memories (Della-Maggiore et al., 2004; Richardson et al., 2006; Hadipour-Niktarash et al., 2007; Landi et al., 2011; Villalta et al., 2015; Della-Maggiore et al., 2017).

Previous studies have shown that learning a declarative task (Mölle et al., 2009, 2011; Rasch & Born, 2013) may influence the level of synchrony between slow oscillations and spindles. Our results go along with this evidence as we found that spindles were phase-locked to the active state of the SOs in both the learning and control conditions (Steriade & Amzica,

1998a; Amzica & Steriade, 1998). It has been suggested that learning may enhance the level of synchrony of these signals (grouping of spindles around the active phase of the SO) promoting plastic changes in cortico-thalamic feedback loops that underlie the consolidation of neocortical memory traces (Mölle et al., 2009). Here, we found that the level of synchrony was not modulated by learning. Further examination using a larger sample size may be necessary to address the modulation of this metric.

In conclusion, we have shown that motor learning modulates the density and the level of coupling between spindles and slow oscillations in an inter-hemispheric manner during NREM3. Critically, only spindles associated with slow oscillations predicted memory retention overnight, pointing to a role of this coupling in motor memory consolidation. Our findings provide compelling evidence for a role of the spindle-SO coupling in the stabilization of motor memories, and open the possibility of a common mechanism operating at the basis of procedural and declarative memory.

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Materials and Methods

Participants

Fifty-six normal volunteers (28 females, age: (mean ± SD) 24.1±3.3 years old) were recruited for this study. All subjects were right-handed as assessed by the Edinburgh Laterality Questionnaire (Oldfield, 1971), and none of them declared neurological nor psychiatric disorders. All potential participants were asked to fill the Pittsburgh Sleep Quality Questionnaire (Buysse et al., 1989) and were evaluated on the Epworth Drowsiness Scale (Johns, 1991). Only subjects fulfilling the criteria for good sleep quality based on the last two measures were included in the study. Participants were instructed to maintain a regular sleep schedule and to avoid drinking alcohol and coffee during the duration of the experiment. This was monitored through self-recorded spreadsheets provided for that purpose.

All volunteers signed the informed consent approved by the Ethics Committee of the Hospital de Clínicas, University of Buenos Aires (approved on Nov, 24, 2015), which complies

with the Declaration of Helsinki in its latest version (Fortaleza, 2013), and with the National Law on the Protection of Personal Data.

Experimental paradigm

The visuomotor adaptation (VMA) task has been described in detail elsewhere (Villalta et al., 2015; Lerner et al., 2020) and will be briefly described here. Subjects performed a center-out task consisting of moving a cursor from a start point in the center of a computer screen to one of 8 visual targets arranged concentrically at 45º from each other, using a joystick controlled with the thumb and index finger of the right hand. Vision of the hand was occluded. Participants were instructed to make a shooting movement to the target. One cycle consisted of eight trials, in which subjects made pointing movements to each of the eight targets, whereas there were 11 cycles in each block.

Subjects performed three different types of trials throughout the study. During perturbed trials a clockwise visual rotation was imposed to the cursor relative to the movement of the hand. During null, i.e., unperturbed trials in which no visual rotation was applied, the movement of the cursor directly mapped onto the hand movement. Finally, during error-clamp (EC) trials, visual feedback was manipulated to provide fake “straight” paths to the target (mean=0°, SD=10°). Error-clamp trials were used to assess memory retention, and served to estimate the state of the motor system while preventing participants from continuing to learn from error (Criscimagna-Hemminger & Shadmehr, 2008). The VMA task was implemented in MATLAB (The MathWorks, Inc, MA) using the Psychophysics Toolbox v3 (Brainard, 1997; Kleiner et al., 2007).

Experimental Design

Experiment 1: Sleep benefits visuomotor adaptation

Experiment 1 was conducted to examine whether sleep benefits visuomotor adaptation. To this aim, we manipulated the proximity between learning and sleep, an experimental manipulation we will refer to as PLS from now on. Each participant was randomly assigned to one of two groups (Figure 1.A). Participants in the PLS-14hs group (n=23) arrived to the sleep lab in the morning of Day 1 (between 8 and 9 am) to perform the VMA task, and returned ~14 hour later (13.7 ± 0.6 hours post learning) for a polysomnographic recording session obtained through a

night of sleep (PSG; see below). Participants were instructed not to nap during the daytime. Participants in the PLS-10min group (n=23) arrived to the sleep lab the night of Day 1 (between 9 and 10 pm), performed the VMA task and went to sleep ~10 min later (9.78 ± 5.5 minutes post learning). A PSG recording was also obtained throughout the night of sleep. Both groups returned to the lab 24 hs (TEST1 on Day 2) and 14 days (TEST2 on Day 15) post training to obtain measures of long-term memory retention and persistence, respectively.

During the VMA task on Day 1 all subjects performed one block of null trials followed by six blocks of perturbed trials with an imposed clockwise (CW) visual rotation of 30º. The task took approximately 35 minutes to complete. TEST1 and TEST2 consisted of two cycles of error-clamp trials to measure memory retention and persistence. In all cases, before performing the task, participants completed the Stanford Sleepiness Scale (SSS; Hoddes E., 1973) to assess their degree of vigilance.

Experiment 2: Motor learning modulates the density of sleep spindles and the spindle-SO coupling

To identify the neural signatures mediating the beneficial effect of sleep on VMA we carried out a second experiment, in which we quantified the impact of sensorimotor adaptation on slow oscillations (SO), sleep spindles and the spindle-SO coupling. Experiment 2 consisted of three sessions separated by 7 days each: a familiarization session during which subjects performed the center-out task in the absence of the visual rotation, a visuomotor adaptation session in which subjects adapted to a visual rotation (VMA), and a control session in which subjects performed the center-out task in the absence of the optical rotation (CTL). After the familiarization session, subjects were randomly assigned to the VMA or the CTL condition (Figure 2.A), each of which took place on a different day and week. The order was counterbalanced so that half of the volunteers performed the VMA condition in the second session and half in the third session. Subjects were washed out after each session to avoid carry over effects. In all sessions, subjects performed the motor task following the protocol of the PLS-10min group which yielded the greatest memory retention in Experiment 1. Given that subjects have an internal bias for movement direction, adaptation may even take place in the control condition (e.g. Della-Maggiore et al., 2017). The familiarization session thus served as a first approximation to practice with the joystick and the experimental paradigm in the sleep lab (Tamaki et al., 2016).

Participants (n=10) arrived to the sleep laboratory at 9 pm and electroencephalography (EEG) electrodes were placed over their scalp following the 10-20 montage (see below). During the familiarization session, subjects performed seven blocks of the center-out task without any perturbation. Next, they went to bed for a full night of sleep. During the VMA and CTL sessions, subjects performed the task before (Day 1) and after (Day 2) a full night of sleep. In the VMA session they performed one block of null trials followed by six blocks of perturbed trials (Training) on Day 1. On Day 2, they performed two cycles of error-clamp trials (EC) to assess retention (Test), followed by 6 blocks of perturbed trials and three blocks of null trials (washout). The CTL session followed the same experimental protocol but the visual rotation was not applied. In all cases, the level of vigilance before performing the task was assessed using the Stanford Sleepiness Scale (Hoddes E., 1973). EEG signals were registered throughout sleep.

Polysomnographic recordings (PSG)

Eleven surface electroencephalogram (EEG) electrodes were placed over prefrontal, motor and parietal areas (FC1, FC2, FC5, FC6, C3, C4, P3, P4), and over the midline (Fz, Cz, Pz). Electrodes were mounted following the standard 10-20 arrangement (Modified Combinatorial Nomenclature; Oostenveld & Praamstra, 2001). Both mastoids were used as reference. In addition to EEG electrodes, two electrodes were placed over the periorbital area of both eyes and two additional electrodes over the chin, to measure electrooculography (EOG) and electromyography (EMG), respectively. All signals were acquired at 200 Hz, using the Alice 5 (Philips Respironics, PA, EEUU) and BWmini (Neurovirtual, FL, EEUU) EEG devices.

EEG processing

EEG signal was bandpass-filtered between 0.5 and 30 Hz using a FIR filter (*eegfiltnew* function) from the MATLAB's toolbox EEGLAB (Delorme & Makeig, 2004), and processed with the Artifact Subspace Reconstruction algorithm (ASR, Mullen et al., 2015) to remove transient and large-amplitude artifacts (*clean_rawdata* function from EEGLAB; threshold= 30). EOG and EMG signals were also bandpass-filtered in order to facilitate sleep scoring (filter cutoff frequencies: EOG = 0.5-15 Hz; EMG = 20-99 Hz). All PSG recordings were sleep staged manually, according to standard criteria of the American Academy of Sleep Medicine (AASM; Iber, 2004). Namely, 30-second epochs were classified as either Wake (W), Non Rapid Eye Movement (NREM1, NREM2 and NREM3), or Rapid Eye Movement (REM) stage. Stage classification was

carried out by two independent scorers and a concordance criterion was used to define the stage of each epoch. After stage classification, sleep architecture was determined based on the metrics mentioned below (Data Analysis). Movement artifacts on the filtered EEG signal were detected by visual inspection and manually rejected.

Slow oscillations (0.5-1.25 Hz) and sleep spindles (10-16 Hz) were automatically identified from the EEG signal corresponding to the stages NREM2 and NREM3, using previously reported algorithms (see below).

Detection of Slow oscillations (SO)

The algorithm implemented to detect SOs was based on that reported by Mölle and collaborators (2011), and Antony & Paller (2016). EEG signal was bandpass-filtered between 0.5 and 2.25 Hz. To quantify SOs, we first identified zero crossings of the EEG signal and labeled them as positive-to-negative (PN) or negative-to-positive (NP). Next, those EEG segments between two NP zero crossings were considered a slow oscillation if: i) they lasted between 0.8 and 2 seconds, ii) their maximum amplitude was positive, and iii) their minimum amplitude was negative. This algorithm was used for each channel of each PSG recording (Experiment 2). Only slow oscillations with a peak-to-peak amplitude greater than the median amplitude of the corresponding channel were kept for subsequent analysis (Mizrahi-Kliger et al., 2018).

Sleep spindles detection

The algorithm implemented to detect sleep spindles was based on that reported by Ferrarelli and collaborators (2007), and Mölle and collaborators (2011). It was run along each channel for each PSG recording of Experiment 2. First, EEG signal was bandpass-filtered between 10 and 16 Hz before calculating the instantaneous amplitude (IA) and instantaneous frequency (IF), by applying the Hilbert Transform (Tort et al., 2010). The IA was used as a new time series and smoothed with a 350 ms moving average window. Next, those segments of the IA signal that exceeded an upper magnitude threshold (90th percentile of all IA points) were labeled as potential spindles. The beginning and end of potential spindles were defined as the points in which the signal dropped below a lower threshold (70th percentile of all IA points). Finally, potential spindles with a duration between 0.5 and 3 seconds were labeled as true spindles. Mean frequency, duration and maximum peak-to-peak amplitude were calculated for each true spindle.

Coupling between slow oscillations and spindles

After identifying spindles and SOs, we looked for spindles that occurred during a SO. We quantified spindle-SO coupling according to the following criterion: if a spindle had its maximum peak-to-peak amplitude during the course of a SO it was counted as a spindle-SO coupling.

In order to further characterize this coupling we explored the phase of the SO at which the spindle occurred using the method reported by Tort et al. (2010) and Niknazar et al. (2015). To this end, the instantaneous phase (IP) of each SO was first obtained through the Hilbert transform. The IP of an oscillation varies in a range of ±π radians, so we arbitrarily fixed the SO's positive peak to 0 radian and the negative peak to either + π or -π radians (PN and NP zero crossings occurred at +π/2 and -π/2 radians, respectively). The phase relationship for each spindle-SO coupling was defined as the phase of the SO at which the spindle developed its maximum peak-to-peak amplitude. This algorithm was applied to each channel of each PSG recording from Experiment 2.

Data analysis

Behavior

For each trial of the center-out task, the pointing angle was computed based on the angle of motion of the joystick relative to the line segment connecting the start point and target position. Trials in which the pointing angle exceeded 120 degrees were excluded from further analysis. All trial-by-trial data were converted into cycle-by-cycle time series by computing the median pointing angle for each cycle and each subject. We computed each subject's learning rate by fitting a single exponential function ($y[n] = \alpha*\exp(-\beta*n) + c$) to the sequence of pointing angles, where $y[n]$ represents the pointing angle on cycle n, α and c determine the initial bias and the asymptote of the exponential, and parameter β represents the learning rate of the subject. To assess memory retention, the median of error-clamp cycles was first transformed to percentage relative to the median of the last block of learning (asymptote). Next, the mean was computed across the two error-clamp cycles for each TEST.

EEG signal

- Sleep architecture

Sleep architecture was determined based on the following measures, expressed in minutes: total sleep time, sleep latency (latency to NREM1), REM latency, total wake time, WASO (wake

after sleep onset), time in NREM1, NREM2, NREM3 and in REM. Sleep efficiency was also computed as the percentage of total sleep time relative to the time interval between lights-off and lights-on (%).

-SO and Spindle measures

As described above, in Experiment 2, SOs and spindles were automatically identified from the EEG signal previously classified as NREM2 and NREM3. Given that the EEG signal from some channels deteriorated due to friction as the night progressed, we focused the EEG analysis on the first sleep cycle. The following measures were computed for sleep spindles: duration (msec), mean frequency (Hz), peak-to-peak amplitude (μV) and density (number of sleep spindles/minute of NREM2 or NREM3 sleep). Density was also computed for SOs (number of SOs/minute of NREM3 sleep). To characterize the spindle-SO coupling we computed the density of spindles coupled with a SO (number of spindle-SO couplings/minute of NREM3 sleep), and their coupling phase.

To assess how these measures differed between VMA and CTL we computed their relative difference according to the equation ((VMA-CTL)/CTL*100) for each EEG channel and each subject. Topographic maps ('topoplot' function in 'eegUtils' R package; Craddok, 2019) were implemented to illustrate the spatial distribution for each measure and each condition, and the relative differences between VMA and CTL. For statistical analysis we pooled the data from the four channels of each hemisphere (Left hemisphere: FC1, FC5, C3, P3; Right hemisphere: FC2, FC6, C4, P4).

In order to study the level of synchrony between spindles and SOs we determined the phase of the SO at which the spindle yielded its maximum peak-to-peak amplitude and contrasted the level of grouping of spindles around the mean phase for the VMA and CTL sessions. Specifically, we first computed the mean coupling phase for each subject and across subjects in polar coordinates, and displayed them in circular plots. The level of synchrony was then assessed by comparing the variance of the individual coupling phase around the grand mean across sessions.

To visually illustrate the synchrony and phase relationship between slow oscillations and spindles, the grand average of the EEG signal filtered for the slow oscillations frequency band (0.5-1.25 Hz) and the grand average of the sleep spindles frequency band (10-16Hz) were graphically overlaid, time locked to the spindle's maximum amplitude.

-Delta power

To contrast our results with those by Huber and collaborators (2004) in which they report an increment in delta power induced by visuomotor adaptation using a reaching paradigm, we assessed this measure following their method. To this aim, the EEG power density for the first 20 minutes of artifact-free NREM sleep (Huber et al., 2006) was averaged for the frequencies of the delta band (1-4 Hz). This was carried out for each channel and each condition (VMA and CTL). The value corresponding to each channel was then normalized by the average of all channels. Finally, the relative change between VMA and CTL was computed.

Statistical analysis

Statistical analyses were carried out using R (version 3.4.1; R Core Team, 2017) in RStudio (Rstudio Team, 2015). Statistical differences were assessed at the 95% level of confidence. Prior to statistical testing, outliers for most behavioral and EEG measures were detected based on a threshold of 2.5 median absolute deviations (MAD) from the group median, and removed from the corresponding analyses (Leys et al., 2013). Outliers for the correlations computed between spindles and long-term memory retention were detected with the squared Mahalanobis distance, using the Minimum Covariance Determinant, and were removed based on a threshold of 99.9% quartile of the distance probability distribution (Leys et al., 2018).

When the variables of interest followed normality and homogeneity of variance, statistic were carried out by fitting a Linear Mixed Model (LMM, using the 'lmer' function implemented in the 'lme4' package in R, Bates et al., 2015). Random intercepts of LMM were estimated for each subject to take into account the repeated measures. For Experiment 1, the response variable was the percentage of memory retention, the fixed effects were the groups (PLS-10min or PLS-14hs), the memory test (TEST1 or TEST2), and the group by test interaction. For Experiment 2, the response variable was the relative difference between sessions, and the fixed effect was hemisphere (left/right hemisphere). To assess the statistical significance of fixed effects, we used a step-up strategy starting with an empty model (global mean of the response variable) and then we successively added potential predictors (fixed effects). We used the *Likelihood Ratio Test* to compare the fitted models ('anova' function in R).

In cases where the statistical distributions failed tests for normality or homogeneity of variance data was analyzed using non-parametric tests. For repeated measures designs, the Mann-Whitney U test was used to compare two conditions, whereas the Friedman test was used in the case of having three or more conditions.

In cases where the statistical test indicated a significant main effect or interaction ($p < 0.05$), we compared the estimated marginal means (EMMs, Searle et al., 1980) using a t-test corrected for multiple comparisons following a Bonferroni correction (using 'emmeans' R package; Lenth, R., 2020).

In cases where two circular distributions were compared, we used the Watson's Large-sample Nonparametric Test for assessing common mean direction, and the Wallraff's Nonparametric Test for circular concentration (homoscedasticity). The Rayleigh test was used to assess unimodal departure from uniformity for each circular distribution. All tests are implemented in the 'circular' R package (Agostinelli & Lund, 2017).

Finally, to examine if the density of SO-coupled and uncoupled spindles correlated with long-term memory, a Pearson correlation was calculated for each measure and contrasted using the Williams's t test (Williams, 1959), which allows the comparison of two dependent correlations with an overlapping variable. This test is implemented in the 'cocor' R package (Diedenhofen & Musch, 2015).

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