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Experience-dependent changes in cerebral activation during human REM sleep

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Abstract
The function of rapid-eye-movement (REM) sleep is stiil unknown. One prevailing hypothesis suggests that REM sleep is important in processing memory traces. Here, using positron emission tomography (PET) and regional cerebral blood flow measurements, we show that waking experience influences regional brain activity during subsequent sleep. Several brain areas activated during the execution of a serial reaction time task during wakefulness were significantly more active during REM sleep in subjects previously trained on the task than in non-trained subjects. These results support the hypothesis that memory traces are processed during REM sleep in humans.

1. Introduction

The presence of sleep periods in a wide variety of animal species[1], as well as the devastating effects of a prolonged sleep deprivation' suggest a critical role for sleep processes in the survival of individuals and, consequently, in the perpetuation of the species. However, at present, the functions of sleep remain unknown[3]. In homeotherms, the presence of two different phases of sleep, non-REM sleep and REM sleep, which may or may not have similar functions, make the situation even more complex. These two types of sleep differ in many aspects, such as their circadian distribution and regulation[4], pattern of neuronal activity[5], and regional brain activity6',7. During slow-wave sleep (SWS), the deepest stage of non-REM sleep, EEG recordings characteristically show large-amplitude, low-frequency oscillations[8]. REM sleep is identified by low-amplitude, relatively fast rhythms on EEG recordings, as well as by ocular saccades and by muscular atonia[8].
One function of sleep is proposed to be maintaining or stabilizing the synaptic structure of neural networks that store material recently acquired through experience[9,10]. Many studies support this hypothesis. The immediate-early gene zif-268 is upregulated during sleep in the cerebral cortex of rats exposed to rich sensorimotor experience in the preceding waking period". Multielectrode recordings of the hippocampal formation in rats show that neurons active during wakefulness exhibit similar firing patterns during subsequent sleep, relatrve to previous sleep[12 16]. Behavioral observations in rats show that periods of learning are associated with subsequent REM sleep increases, whereas REM sleep deprivation impairs memory for previously learned material[17,18]. In humans, the functional relationships between sleep and memory processes are more complex because there are different memory systems involved[19]. In the case of implicit learning, performance improvement is not systematically related to the ability to consciously recall the memory traces[20]. Although both SWS and REM sleep may be involved in the processing of memory traces for several tasks[21], implicit learning seems particularly sensitive to REM sleep deprivation[18, 22, 23].
Using PET and $H_2{}^{15}O$ techniques, we tested the hypothesis that the distribution of cerebral activity during REM sleep would be modified by previous waking experience, in this case by sustained training on a probabilistic serial reaction time (SRT) task[24,25]. Here we were essentially interested in the task-induced acquisition of a basic visuomotor skill, simply measured by an improvement in reaction times.
The regional cerebral blood flow (rGBF), taken as a marker of local synaptic activity, was estimated in three experimental groups of subjects. The 7 subjects of group 1 were scanned during wakefulness both at rest and while they were performing the SRT task. Analysis of their data identified the brain areas activated during the task. The 6 subjects of group 2 were trained on the task during two sessions in the afternoon, then scanned during the night after training, both during waking and in various sleep stages. A third (post-sleep) training session verified that learning had occurred. The analysis of PET data looked for brain areas that were more active in REM sleep than during resting wakefulness. To ensure that this post-training REM sleep rCBF distribution differed from the pattern of 'typical' REM sleep, 5 subjects in group 3, not trained to the task, were

similarly scanned at night, both when awake and during sleep. The analysis detected brain areas that were more active in trained than in non-trained subjecLs, in REM sleep as compared to resting wakefulness. Finally, to formally test that these brain regions, possibly reactivated during REM sleep, would be among the structures that had been engaged by executing and learning the task, a conjunction analysis was done[26]. This analysis identified those regions that were both more active during REM sleep in trained subjects (group 2) compared to non-trained subjects (group 3) and activated during the execution of the task during waking (group 1). These cerebral regions, located in occipital and premotor cortices, were actually re-activated during REM sleep after training.

2. RESULTS

2.1.Task performance and sleep

Reaction times in group 2 significantly decreased across sessions (A, 568 ms; B, 533 ms; C, 444 ms, $F_{2,10}$ = 87.45, $p < 0.0001$) and within sessions (24 blocks, ANOVA, $F_{23,115} = 10.63$, $p < 0.0001$; Fig. 1). The interaction between block and session factors was significant ($F_{46,230}$ — 5.14, $p < 0.0001$), showing that reaction-time improvements differed across sessions. Separate analyses showed that reaction times significantly improved within blocks during sessions A and C ($p < 0.0001$), but not during session B ($p > 0.18$). *Post-hoc* Tukey HSD tests revealed significant reaction-time differences between sessions A and B ($p < 0.05$) and highly significant RT differences between post-sleep (C) and each pre-sleep (A, B) session ($p < 0.0005$), suggesting that subjects refined their task-dependent visuomotor capabilities overnight. Sleep in groups 2 and 3 was comparable in all respects; no significant differences could be found in terms of any sleep parameter (Table 1). Thus, any differences in brain activity between the two groups must be due to the prior training session in group 2.

2.2. PET results

In group 1 (waking SRT group), as compared to rest, execution of the SRT task was related to significant rCBF increases, in bilateral striate and extrastriate, premotor and superior parietal cortices and in the left primary sensorimotor cortex, supplementary motor area, precuneus, anterior cingulate cortex and cerebellum (Table 2; Fig. 2a). In group 2 (trained sleep group), during REM sleep as compared to wakefulness, significant rCBF increases were observed in bilateral striate, extrastriate, motor, premotor and superior parietal cortices as well as in the supplementary motor area, anterior cingulate cortex, pons, mesencephalon and cerebellum (Table 3; Fig. 2b). In group 3 (non-trained sleep group), during REM sleep as compared to wakefulness, significant bilateral rCBF increases were observed in striate, extrastriate, motor and superior parietal cortices as well as in supplementary motor area and anterior cingulate cortex (Table 4; Fig. 2c). Although both groups were scanned in comparable conditions, a significant group (trained versus non trained) by condition (REM sleep versus wakefulness) interaction was found bilaterally in the cuncus and adjacent striate cortex, the left premotor cortex, the inferior part of the left thalamus and the mesencephalon (Table 5; Fig. 2d). These brain areas were more active in trained than in non-trained subjects during REM sleep. The conjunction between the group-by-condition interaction and the waking results (group 1) was significant in the cuneus and adjacent striate cortex bilaterally, left premotor cortex, and mesencephalon (Table 6; Fig. 2e). These regions are both more active during REM sleep in the trained subjects (group 2) compared to the non-trained subjects (group 3) and activated by task performance during waking (group 1).

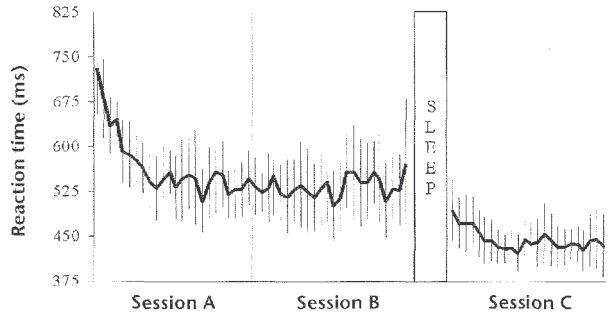

Fig. I. Average reaction times (and standard deviations) for pre- and post-sleep sessions (group 2). Global reaction time improves within sessions A and C, as well as overnight, between sessions.

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Table I. Sleep parameters on the third night.

Sleep parameter	**Group 2 Mean ± s.d.**	**Group 3 Mean ± s.d.**	***P***
Total recording period (TRP, min)	417 + 52	403 ± 10	0.46*
Total sleep time (TST, min)	352 ±46	339 ± 29	0.58*
Stage Il duration (min)	185 + 43	184 ±29	0.86*
SWS duration (min)	106 + 59	91 ±49	1.00*
REM sleep duration (min)	61 ±21	64 ± 15	1.00*
Stage Il latency (min)	I7± 13	I6± 18	1.00*
REM sleep latency (minus awake, min)	112 + 51	107 + 53	0.58*
Sleep efficiency (TST/TRP)	0.85 ±0.1 3	0.84 ± 0.07	0.36*
Sleep quality (SWS+REM sleep/TST)	0.48 + 0.06	0.46 ± 0.09	0.85*
REM density in REM sleep	17+ 17	I2± 13	O_{30}**
REM density in wakefulness	24 ±21	I6± I I	0.26**
Theta power in REM sleep (μV^2)	4.88 ± 2.77	6.22 ±4.19	0.22**

Mann-Whitney U test; **unpaired two-tailed Student's t-test

3. DISCUSSION

In group 1, task performance was accompanied by significant activation of occipital, parietal, anterior cingulate, motor and premotor cortices and the cerebellum. This pattern is consistent with engagement of several mental processes necessary for the task, such as visual and spatial perception[27], spatial attention[28], mental motor representation[29], upper limb movements[30], timing processes[31] and pointing[32].

In group 2, intensive pre-sleep training on the SRT task presumably engaged this set of cerebral areas. On the behavioral level, performance improved within session A and C, as well as across night. During the learning of perceptual-motor skills, the experience of sequences of some external stimuli is proposed to lead to the formation of novel sequences of muscle activity[33]. Consequently, speed of motor execution is improved without any deterioration in accuracy. During this process, the system acquires a new capability, which is more than the simple functional adaptation of any pre-existing property of the network[33]. Our data suggest that similar processes may occur during REM sleep, as they show a temporal association between the subjects' performance improvement across the night and the experience-dependent rCBF modifications during intervening sleep.

In REM sleep, as compared to resting wakefulness, some brain areas are more active in trained than in non-trained subjects. In addition, the conjunction analysis demonstrates that these areas are a subset of the regions activated during SRT task-performance during wakefulness. These results support therefore the hypothesis of an experience-dependent re-activation of brain areas during post-training REM sleep. These rCBF increases may reflect higher rates of local synaptic activity[34] during post-training REM sleep than in 'typical' REM sleep. Their localization in regions activated during SRT task performance, and the subjects' performance improvement in the post-sleep session, support the idea that some processing of memory traces may occur in REM sleep and suggest the optimization of neural networks necessary for performing a newly learned task.

We should emphasize that memory traces are not processed exclusively during sleep periods. For both perceptual and motor skills, performance gains may appear after several hours of either wakefulness[35-37] or sleep[14,21-23]. In our experimental protocol, we cannot disentangle the respective influence of post-training sleep and waking periods on the improvement in subjects' performance. Further research is needed to identify the specific role of sleep periods in memory trace processing. Likewise, we do not rule out the possible involvement of non-REM sleep episodes in the processing of memory traces, although our data do not yet allow us to show any significant experience-dependent modifications in rCBF during SWS.

The cellular mechanisms that cause local increases in synaptic activity during post-training REM sleep remain largely unknown.

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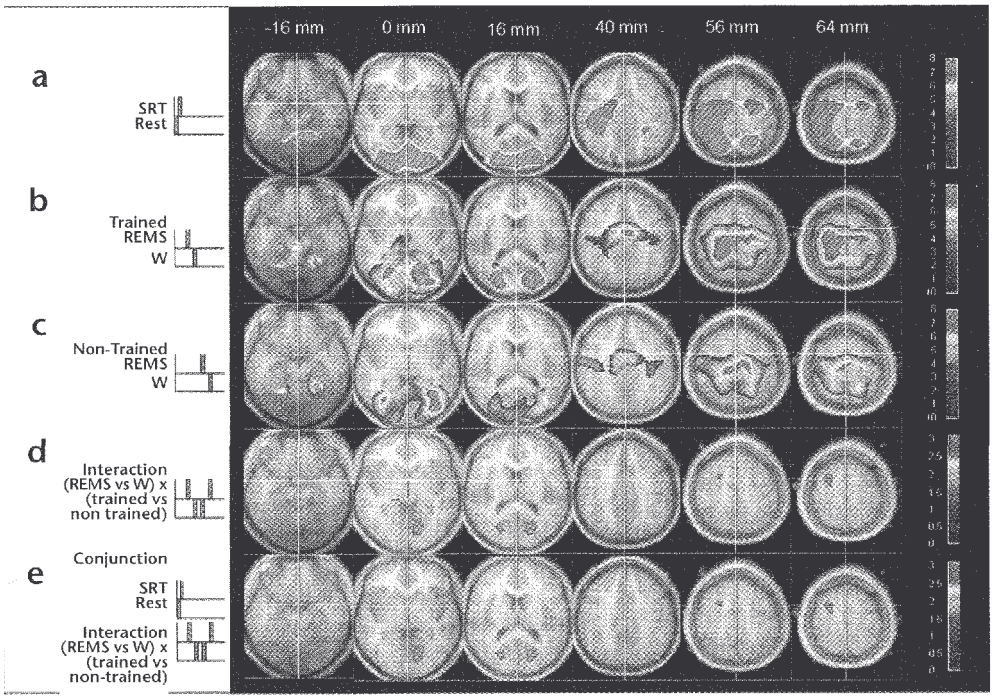

Fig. *2. Statistical parametric maps of different contrasts. Maps are displayed at 6 different brain levels (from 16 mm below to 64 mm above the bicom-missural plane), superimposed on the average (coregistered and normalized) MRI image of the sleeping subjects. All maps were thresholded at $p < 0.001$ (uncorrected), except for (a), which was thresholded at voxel-level-corrected $p < 0.05$). (a) Brain regions activated during performance of the SRT task during wakefulness (SRT - rest), (b) Brain regions activated during REM sleep in trained subjects (REM sleep - wakefulness), (c) Brain regions activated during REM sleep in non-trained subjects (REM sleep - wakefulness), (d) Brain regions activated more in trained subjects than in non-trained subjects during REM sleep (that is, condition (REM sleep versus wakefulness) by group (trained versus non- trained) interaction), (e) Brain regions that showed a common activation in subjects scanned while performing the task during wakefulness and that were activated more in trained than in non-trained subjects scanned during REM sleep (that is the conjunction of (SRT - rest) with the condition (REM sleep versus wakefulness) by group (trained versus non-trained) interaction).*

Table 2. Brain regions activated during the SRT task (SRT - rest).

Side	Region	X	*Y*	*Z*	t value
Left	Striate cortex	-18	-90	-2	10.73
Left	Lingual gyrus	-20	-92	-6	10.66
Left	Cuneus	-4	-88	18	8.48
Left	Primary sensorimotor cortex	-32	-18	58	15.74
Left	Premotor cortex	-22	-6	54	14.15
Left	Superior parietal cortex	-26	-52	56	14.18
Left	Supplementary motor area	-6	-4	56	8.71
Right	Striate cortex	16	-82	8	9.67
Right	Lingual gyrus	12	-86	-8	8.87
Right	Cuneus	22	-78	18	9.92
Right	Premotor cortex	28	-6	54	11.42
Right	Superior parietal cortex	20	-58	56	10.24
Right	Precuneus	2	-60	62	6.62
Right	Anterior cingulate cortex	8	0	36	4.92
	Cerebellum	12	-56	-16	14.97

All results are significant at $p < 0.05$ (voxel level corrected).

Table 3. Brain regions activated during REM sleep in trained subjects (REM sleep - wakefulness).

Side	Region	X	*Y*	Z	t value
Left	Striate cortex	-26	-66	10	8.65
Left	Lingual gyrus	-26	-86	-4	5.86
Left	Cuneus	-24	-80	IS	8.60
Left	Primary sensorimotor cortex	-12	-30	60	8.81
Left	Premotor cortex	-24	-14	66	8.77
Left	Superior parietal cortex	-28	-52	S8	5.77
	Supplementary motor area	0	-22	62	8.84
Right	Striate cortex	26	-66	10	9.73
Right	Lingual gyrus	22	-62	6	9.55
Right	Cuneus	22	-74	16	9.26
Right	Motor cortex	40	-20	56	6.74
Right	Premotor cortex	14	-16	66	7.81
Right	Superior parietal cortex	22	-50	60	6.04
Right	Anterior cingulate cortex	8	-4	40	7.81
	Cerebellum	2	-42	-10	5.19
	Mesencephalon	-2	-30	-16	6.19
	Pons	0	-26	-20	6.11

All results are significant at $p < 0.001$ (uncorrected).

One possible hypothesis pertains to long-term memory consolidation. Memory consolidation concerns the processes by which new memories, initially in a fragile state, become less easily disrupted by the learning of other information, after a time ranging from hours to years[38]. Memory consolidation would rely on protein-synthesis-dependent mechanisms, which eventually lead to augmented synaptic transmission[39,40] and increased synaptic density[41]. These processes are remarkable manifestations of the substantial plasticity of the adult brain. REM sleep might be a privileged period for mammalian brain plasticity, not only during development[42] but also in adult subjects in learning situations. REM sleep is characterized by high activity of cholinergic neurons while noradrenergic and serotonergic neurons are totally silent[43]. The high level of cholinergic activity during which the memory-related processes take place is probably essential for brain plasticity. Indeed, increasing cholinergic drive promotes cortical plasticity in adult mammals. In rats, local application of acetylcholine increases the receptive field of barrel field neurons during sensory—sensory conditioning[44].
Nucleus basalis stimulation has similar effects on primary auditory cortex neurons[45]. In contrast, depletion of acetylcholine prevents the normal expansion of topographic maps in somatosensory cortex after digit amputation in cats[46]. In conclusion, pre-sleep experience exerts a sizeable influence on regional cerebral activity during REM sleep in humans.

4. METHODS

SRT task[24, 23]. Participants faced a computer screen where six permanent position markers were displayed. A keyboard with six spatially compatible response keys was within reach of the right hand. Subjects were asked to react as quickly and accurately as possible to the appearance of a stimulus below one of the markers by pressing the spatially corresponding key. The computer emitted a short beep on incorrect responses. The next stimulus was then displayed after a fixed 200-ms response-stimulus interval, until a block of 205 trials had been completed. Unknown to the subjects, the sequential structure of the stimulus material was manipulated. Stimuli were generated based on a probabilistic finite-state grammar that defines legal transitions between successive trials. The task is designed to explore the implicit acquisition of complex sequential knowledge[24,25]. However, during the task, subjects also acquire simple visuomotor capabilities (reflected by the improvement in reaction times). This paper essentially deals with the latter skill, because the main difference between the two sleep groups was the visuomotor activity during the four-hour training session.
Experimental protocol. The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liege. Written informed consent was obtained from all subjects. Subjects were young (mean 22.9 ± 3.5 years), healthy, right-handed males.
Group 1 subjects underwent six experimental scans while performing the SRT task and six control scans while awake, at rest with eyes closed. The order of the conditions was alternated and counterbalanced over subjects. One block (205 trials) was presented during each SRT scan.
In group 2, volunteers were polygraphically monitored during three consecutive nights spent in the scanner. The

first two nights accustomed the subjects to the experimental settings and allowed us to check for any abnormality in sleep (insomnia, sleep fragmentation, REM sleep onsets and so forth). Subjects were selected for the third night if they could maintain 20 minutes of continuous stage II sleep, SWS and REM sleep on both acclimatization nights. Before the third night, they were trained on the SRT task, between 16:00 and 20:00 (2 sessions, A and B, of 24 blocks each, that is, 9840 trials) and, on the following day, between 16:00 and 18:00 (one session, C, of 24 blocks, 4920 trials). Behavioral analyses included all three sessions (A, B and C). During the intervening night, 12 scans were performed both during waking and during various stages of sleep. Sleep scans were performed when polysomnography showed steady characteristic sleep patterns. Waking scans were obtained at rest with eyes closed in complete darkness. In all subjects, we obtained at least two waking, two stage II sleep, two slow wave sleep and three REM sleep scans. Because of the physiological architecture of human sleep, SWS and REM sleep scans were usually obtained respectively in the first and second half of the night.

Table 4. Brain regions activated during REM sleep in non-trained subjects (REM sleep - wakefulness).

Side	Region	X	Y	Z	t value
Left	Striate cortex	-12	-92	0	4.17
Left	Lingual gyrus	-30	-74	-8	7.36
Left	Cuneus	-8	-92	16	4.37
Left	Primary sensorimotor cortex	-52	-10	52	4.95
Left	Superior parietal cortex	-14	-42	62	5.78
Left	Anterior cingulate cortex	-10	-8	40	5.08
	Supplementary motor area	0	-22	62	7.21
Right	Striate cortex	14	-96	0	3.19
Right	Fusiform gyrus	40	-76	-10	8.16
Right	Cuneus	10	-92	16	3.39
Right	Motor cortex	36	-24	52	4.31
Right	Superior parietal cortex	18	-48	62	6.30

All results are significant at $p < 0.001$ (uncorrected).

Table 5. Condition (REM sleep versus wakefulness) by group (trained versus non-trained) interaction.

Side	Region	X	Y	Z	t value
Left	Cuneus	**-18**	**-80**	24	**3.33**
Left	Premotor cortex	-24	**4**	64	3.63
Right	Cuneus	**22**	-70	**16**	5.30
Left	Thalamus	**-14**	**-28**	-4	3.29
	Mesencephalon	**-IO**	-30	-10	3.17

All results are significant at $p < 0.001$ (uncorrected).

Table 6. Conjunction of (SRT - rest) with (condition (REM sleep versus wakefulness) by group (trained versus non-trained) interaction).

Side	Region	X	*Y*	Z	T value
Left	Cuneus	-18	-80	24	3.33
Left	Pretnotor cortex	-24	4	64	3.63
Right	Cuneus	22	-70	16	5.30
	Mesencephalon	0	-30	-16	3.16

All results are significant at $p < 0.001$ (uncorrected).

Subjects in group 3 followed exactly the same protocol, except that, before the third night, between 16:00 and 20:00, tliev were asked to remain in the laboratory and to have no intensive and continuous activity. Polysomnography acquisition and analysis. Polysomnography was recorded with a Synamp (Ncuroscan, NeuroSoft, Sterling, Virginia), at 500 Hz, with a bandwidth 0.15 to 100 Hz and A_1 as reference. For the third night, twenty-eight scalp channels were placed according to the 10-20 system. Vertical and horizontal electro-oculograms, chin elec-tromyogram and electrocardiogram were recorded on bipolar montages. Polygraphic recordings were scored using standard criteria[8]. Mean power spectra for each scan were computed on Cz over the 90 s of PET acquisition. Spectral power densities were computed with a FFT routine written in MATLAB (Mathworks, Sherbom, Massachusetts) using the average of consecutive 4-s periods overlapping by 1 s, a square window and a bandwidth from 0.75 to 20 Hz. Average theta (4-7 Hz) power density was computed for REM

sleep scans.
PET acquisition and analysis. The subject's head was stabilized by a thermoplastic facemask secured to the head holder (Truscan Imaging, Annapolis, Maryland), and a venous catheter was inserted in a left antebrachial vein. A transmission scan was performed to allow a measured attenuation correction. Cerebral blood flow was estimated during twelve emission scans. Each of them consisted of 2 frames: a 30-second background frame and a 90-second frame. The slow intravenous water ($H_2{}^{13}O$) infusion begun just before the second frame to observe the head curve rising within the first 10 seconds of this frame. Six mCi (222 MBq) were injected for each scan, in 5 *cc* saline, over a period of 20 seconds. The infusion was totally automated in order not to disturb the subject during the scanning period. Data were acquired on a Siemens CTI 951 R 16/31 scanner in three-dimensional mode, reconstructed using a Han-ning filter (cutoff frequency, 0.5 cycle/pixel) and corrected for attenuation and background activity. Structural Tl -weighted MRI scans (0.96 x 0.96 x-1.50 mm voxel size) were obtained on a 1.5 T Magnetom scanner (Siemens, Erlangen, Germany) for the subjects of groups 2 and 3.
PET data were analyzed using statistical parametric mapping[47] (SPM99; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) implemented in MATLAB. For each subject, all scans were realigned to the mean PET image, and the MRI scan was coregistered to the same image. This mean image was normalized into a standard space[48], and the same transformations were applied to each PET and MRI image. PET images were smoothed using a Gaussian kernel of 16 mm full width at half maximum. The condition and subject (block) effects were estimated according to the general linear model at each voxel. Global flow adjustment was done by proportional scaling. Areas of significant change were determined using linear contrasts of condition estimates. First, primary contrasts estimated the main effect of task versus rest (group 1) and of REM sleep versus wakefulness (group 2 and group 3). Second, the condition (REM sleep versus wakefulness) by group (trained versus non trained) interaction was assessed, to identify brain areas that were more active in trained than in non-trained subjects in REM sleep as compared to wakefulness. Finally, to ensure that the activated areas were among the cerebral structures activated during the execution of the task, a conjunction was performed between this interaction and the main effect of the task in the waking group. This analysis relies on a fixed-effect model. In consequence, the results pertain only to the sampled population. The results should be extended to the general population with caution. The resulting set of voxel values for each contrast constituted a map of the (statistic, SPM(T), thresholded *at* $p < 0.001$ ($f > 3.14$). The results of group 1 served to identify the brain areas that could possibly be reactivated in REM sleep. In this group, statistical inferences were obtained at the voxel level (in terms of peak height at $p < 0.05$, corrected for multiple comparisons). For the remaining analyses, as we had an *α priori* hypothesis concerning the brain areas of interest, we set the significance at the level of p (uncorrected) < 0.001 ($f \geq 3.14$).

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