

A Specific Deficit in Spatial Memory Acquisition in Post-Traumatic Stress Disorder and the Role of Sleep in its Consolidation

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ABSTRACT: Posttraumatic stress disorder (PTSD) is characterized by the presence of anatomo-functional hippocampal alterations. To date, the ability to orient within the environment, which relies on hippocampal integrity, has never been investigated in PTSD. We hypothesized that the ability to form a cognitive map of the environment would be impaired in PTSD. Moreover, spatial memory consolidation benefits from postlearning sleep. Because PTSD individuals often complain about sleep disturbances, we hypothesized that any sleep effect on memory performance would be hampered in these subjects. Twenty-two subjects, all survivors of the L'Aquila 2009 earthquake, were divided into a PTSD and a control group, based on clinical evaluation. After an acquisition phase, they were tested twice ("test" and "retest") on a virtual navigation task. In addition, participants were administered the Digit Span and Task Switching. Subjective sleep quality and sleep disturbances were also assessed. The two testing sessions were on consecutive mornings, interspersed with a night of sleep. During the acquisition phase, the PTSD group took more than twice as long to form a cognitive map of the environment compared to the control group. However, once this phase was successfully completed, the two groups did not differ at test, but they tendentially differed at postsleep retest. Additional analyses comparing performances between groups on test–retest difference scores confirm that sleep-dependent consolidation may be differentially affected in the two groups. Our findings are strictly confined to the navigation performance, excluding a generalized cognitive deficit. PTSD also reported more subjective sleep disturbances and shorter sleep time than controls, which were correlated to worse performance at retest. The specific deficit in the formation of a cognitive map reported in PTSD may be related to hippocampal dysfunctions as well as to the sleep disturbances experienced by these patients. The possible deficiency of sleep-dependent spatial performance improvement should however be confirmed by further studies comprising a wake control group. © 2011 Wiley-Liss, Inc.

KEY WORDS: PTSD; hippocampus; declarative memory; sleep disorders; cognitive map

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INTRODUCTION

Posttraumatic stress disorder (PTSD) is a complex clinical syndrome characterized by disabling behavioral and emotional symptoms that occur in some individuals who experienced severe psychological trauma (e.g., natural or man-made disaster, sexual or physical assault, serious accident, or injury). The typical PTSD symptoms include intrusions (e.g., flashbacks, nightmares), avoidance of thoughts, places, people, activities, and other reminders of the trauma, hyperarousal (e.g., sleep disturbances, exaggerated startle reaction), and impaired social functioning such as emotional numbing.

Emotion strongly influences memory storage because of a correlation between neuronal mechanism of both functions (Cahill and McGaugh, 1998). Alterations in several facets of memory are indeed specifically associated with PTSD. In particular, verbal declarative memory deficits in individuals with PTSD have been repeatedly demonstrated (Bustamante et al., 2001; Gilbertson et al., 2001; Vasterline et al., 2002; Yehuda et al., 2004; Yehuda et al., 2005).

It has been long hypothesized that the declarative memory impairment may be due to hippocampal abnormalities associated with PTSD (Bremner et al., 1993; Soininen et al., 1994; Bremner et al., 1995, 1997; Bremner, 1999). A recent meta-analysis of structural brain abnormalities in PTSD confirmed significantly smaller hippocampal volumes in PTSD individuals compared to controls with and without trauma exposure (Karl et al., 2006). It has been shown in monozygotic twins that also the brother that was not exposed to traumatic events had a smaller hippocampal volume, suggesting a higher vulnerability for the development of PTSD (Gilbertson et al., 2002). Indeed, because of the critical role of hippocampus in learning and memory processing as well as in stress regulation, alterations in this cerebral area have been proposed as contributing to the etiology of PTSD (Bremner, 2001).

Reduced hippocampal volume has been found to be associated with poorer memory performance (Stein et al., 1997; Tischler et al., 2006) and abnormal functional response of the hippocampus in individuals with PTSD (Bremner et al., 1999; Bremner, 2001;

Shin et al., 2004). Altogether, these findings point out that PTSD is associated with both structural alterations and abnormal functionality of the hippocampus.

Although the studies investigating the neuropsychological performance in PTSD individuals have focused primarily on the declarative memory domain (in particular, by means of verbal memory tasks), surprisingly hippocampus-dependent spatial memory has never been taken into account. Since the discovery of place cells in rodents, which signal the current allocentric location of the animal in space (O'Keefe and Dostrovsky, 1971), the pivotal role of the hippocampus for spatial navigation has been widely recognized. Cognitive map theory posits that these place cells form a cognitive map of the environment, which persists across the animal's life span, and which is necessary to support flexible navigation, such as taking shortcuts or detours (O'Keefe and Nadel, 1978).

In the last few years, the neural mechanisms underlying spatial navigation have also been extensively investigated in humans by means of neuroimaging techniques combined with virtual reality paradigms. Activation of the right and left hippocampi has been consistently reported during the formation and use of a cognitive map (e.g., Iaria et al., 2007). Then, it was demonstrated that the structural integrity of this brain region may affect the individual's ability to orient within the environment (Iaria et al., 2008).

Interestingly, spatial memory traces seem to be processed and strengthened during sleep in humans, giving way to performance improvements (Peigneux et al., 2004; Ferrara et al., 2006, 2008; Rudoy et al., 2009; Wamsley et al., 2010). The mechanisms underlying such a beneficial sleep effect may be related to internally generated memory reactivation. Neurophysiological studies in rodents have demonstrated that patterns of hippocampal place cells activity first seen during waking exploration are later reexpressed during postlearning sleep (e.g., Wilson and McNaughton, 1994; Ji and Wilson, 2007). In humans, a PET study (Peigneux et al., 2004) has shown that the hippocampal areas activated during route learning in a virtual town are then reactivated during subsequent slow-wave sleep (SWS). The reactivation was correlated to the improvement in route retrieval on the next day, which confirms the critical role of sleep in spatial memory consolidation and hippocampal-dependent cognitive skills.

Recently, by using a virtual navigation task, we have documented in healthy subjects that spatial performance improvement is only observed when spatial learning is followed by a period of sleep, but not when it is followed by a period of sleep deprivation or by 10 h of daytime wakefulness (Ferrara et al., 2008).

On the basis of these premises, we hypothesized that the ability to use a hippocampus-dependent landmark-based strategy to form a cognitive map of the environment would be impaired in patients with PTSD. Therefore, in this study, we used a virtual navigation task (Iaria et al., 2007) to test whether the ability to create a cognitive map and to use it for subsequent orientation is preserved in PTSD.

To control for the specificity of spatial memory deficits in PTSD patients, and to exclude a possible general cognitive

impairment, all participants underwent two additional tests: the Digit Span and the Task Switching. The former is a short-term (immediate) memory task, which has been shown to be hippocampus-independent, remaining preserved even after damage to the human hippocampus (Cave and Squire, 1992). The latter is a measure of executive functions and involves the recruitment of prefrontal and parietal cortical networks (Sohn et al., 2000; Braver et al., 2003).

Finally, we evaluated whether PTSD subjects exhibit a sleep-dependent improvement of spatial performance, as already documented in healthy subjects (Ferrara et al., 2008). Because PTSD individuals often complain about sleep disturbances and fragmentation, we hypothesized that any sleep effect on memory performance would be hampered in these subjects.

MATERIALS AND METHODS

Subjects

The study included 22 participants, all survivors of the L'Aquila 2009 earthquake. Eleven subjects (*PTSD group*; 10 women, mean age: 22 ± 2.7 years) were affected by PTSD. The remaining 11 subjects (*Control group*; 10 women, mean age: 23 ± 4.4 years), although present in the L'Aquila area during the earthquake, did not show the PTSD symptoms at clinical evaluation.

The participants were first administered the Davidson Trauma Scale (DTS), that comprises three subscales, assessing Intrusion, Avoidance/Numbing, and Hyperarousal (Davidson et al., 1997). After this preliminary screening, all participants underwent the clinician administered PTSD scale CAPS (Version DX) (Blake et al., 1995). Participants were assigned to the PTSD group if they matched the PTSD current DSM-IV criteria, according to CAPS 1–2 scoring rules. A symptom was considered if it was present with at least occasional frequency and moderate intensity, and a diagnosis was assigned only if the subject's score was higher than the CAPS cut-off (Blake et al., 1995).

Individuals were excluded from the study if any of the following applied: history of head injury associated with loss of consciousness of more than 15-min duration or overnight hospitalization, current use of psychotropic medication.

All participants underwent a clinical evaluation through the following instruments: the State-Trait Anxiety Inventory (Spielberger and Vagg, 1984; Italian validation: Moroni et al., 2006) and the Beck Depression Questionnaire (BDQ, Italian validation: Vidotto et al., 2010), a partially modified version of the Beck Depression Inventory (Beck et al., 2009).

The STAI measures both trait (T) and state (S) anxiety. Trait anxiety is assumed as a predisposition to perceive situations as potentially threatening, possibly leading to an increase in state anxiety. Both the state and trait sections of this questionnaire comprise 20 questions, with a total score ranging from 0 to 60. Both scales has shown good psychometric qualities (Chronbach α : STAI-S = 0.92; STAI-T = 0.91; Moroni et al., 2006).

TABLE 1.

Psychological Assessment

	PTSD (SD)	Controls (SD)	<i>U</i>	<i>P</i>
STAI-state	43.82 (11.43)	23.36 (10.08)	10.0	0.0009
STAI-trait	43.54 (7.50)	21.81 (10.84)	7.0	0.0004
BDQ	3.54 (1.03)	1.27 (1.27)	11.5	0.001
DTS intrusion	21.54 (4.08)	8.63 (7.68)	9.5	0.0008
DTS avoidance	27.45 (15.37)	9.90 (10.99)	20.0	0.008
DTS hyperarousal	27.09 (7.77)	13.00 (11.16)	19.0	0.006

Mean scores (and standard deviations) to the psychological tests separately for PTSD and control subjects. The results of the statistical comparisons (Mann–Whitney *U*, and probability) are also shown. STAI: State-Trait Anxiety Inventory; BDQ: Beck Depression Questionnaire (Italian adaptation); DTS: Davidson Trauma Scale.

The normative scores (mean ± standard deviation (SD)) in the 15–25 years age range are as follows: males STAI-S: 39.2 ± 9.8, STAI-T: 42.1 ± 8.5; females STAI-S: 40.1 ± 9.9; STAI-T: 42.9 ± 9.4.

The Beck Depression Inventory is a measure of severity of self-reported depression in adults. In the Italian adaptation (BDQ) used in this study (Vidotto et al., 2010), it is scored by summing the ratings for each of the 24 symptoms. Each symptom is rated with a dichotomic response and total score can range from 0 to 24. The scale has shown good psychometric qualities (Chronbach α: 0.87). The normative scores (mean ± SD) in the 15–25 years age range are as follows: males = 4.4 ± 9.8; females = 4.4 ± 4.2).

Table 1 shows the scores to the above tests, separately for the two groups. PTSD subjects reported significantly higher scores than controls to all the considered anxiety, depression and trauma-related scales. According to the normative data of the Italian sample, six participants with PTSD (54.5% of the sample) had comorbid state-trait anxiety disorder. None of the participants had comorbid depression.

As far as the assessment of sleep characteristics is concerned, all subjects were administered the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI consists of 19

questions assessing a wide variety of factors relating to sleep quality in the preceding month (estimates of sleep duration and latency and of the frequency and severity of specific sleep-related problems). A global score >5 is considered as an indicator of relevant sleep disturbances (Buysse et al., 1989).

Moreover, the participants filled in the PSQI-Addendum (PSQI-A) for PTSD (Germain et al., 2005). This questionnaire consists of seven items that focus on the frequency of seven disruptive nocturnal behaviors in the preceding month (hot flashes; general nervousness; memories or nightmares of traumatic experience; severe anxiety or panic not related to traumatic memories; bad dreams not related to traumatic memories; episodes of terror or screaming during sleep without fully awakening; and episodes or acting out dreams). A PSQI-A score >4 has is highly predictive for discriminating between subjects with and without PTSD (Germain et al., 2005).

Each subject was asked to maintain a regular sleep-wake cycle during the experiment: compliance was controlled by sleep diary filled in upon each morning awakening.

Table 2 shows the PSQI and PSQI-A scores, as well as the self-reported total sleep time (TST), number of awakenings (AW) and sleep latency (LAT) during the first (1, prelearning) and second (2, postlearning) sleep nights, separately for the two groups. The PTSD individuals reported higher PSQI and PSQI-A scores compared to the control groups, indicating an overall worse sleep quality and a higher presence of trauma-related sleep disturbances. Interestingly, control subjects had mean PSQI-A scores slightly above the critical threshold (Germain et al., 2005), indicating that also this group experienced a form of trauma-related sleep disturbance. TST in both nights tended to be shorter in the PTSD group (see Table 2 for more details).

Behavioral Testing: Virtual Environment and Control Tasks

Participants performed a computerized 3D virtual navigation task, created by using the editor of a three-dimensional game software (Game Studio A6, LA Mesa, CA), in which they navigated by using three different key-buttons of the computer keyboard, each button corresponding to movement in one of three directions: forward, left and right (Iaria et al., 2007).

TABLE 2.

Subjective Sleep Measures

	PSQI	<i>U</i> (<i>P</i>)	TST1	<i>U</i> (<i>P</i>)	AW1	<i>U</i> (<i>P</i>)	LAT1	<i>U</i> (<i>P</i>)
PTSD	7.72 (3.0)	23.0 (0.01)	397.5 (73.3)	34.0 (0.08)	1.18 (1.25)	59.5 (0.95)	24.0 (26.1)	41.0 (0.32)
Controls	4.63 (2.5)		456.4 (81.9)		1.09 (0.94)		19.6 (22.5)	
	PSQI-A	<i>U</i> (<i>P</i>)	TST2	<i>U</i> (<i>P</i>)	AW2	<i>U</i> (<i>P</i>)	LAT2	<i>U</i> (<i>P</i>)
PTSD	8.36 (4.0)	27.0 (0.03)	390.4 (55.8)	33.5 (0.07)	1.50 (1.91)	49.0 (0.42)	26.5 (24.5)	51.0 (0.77)
Controls	4.36 (3.9)		454.3 (79.5)		0.70 (0.90)		26.2 (27.2)	

Mean scores (and standard deviations) to the Pittsburgh Sleep Quality Index (PSQI), the PSQI-Addendum (PSQ-A), and the subjective evaluation of total sleep time (TST), number of nocturnal awakenings (AW) and sleep latency (LAT) during the pre- and postlearning nights (1, 2). The scores are reported separately for PTSD and control subjects.

The results of the statistical comparisons (Mann–Whitney *U*, and probability) are also shown.

The virtual navigation task evaluates the ability to orient within the environment. The task first requires that subjects learn about the environment by forming a mental representation of it (i.e., a cognitive map). Then, participants are required to rely on that mental representation to travel between different landmarks locations within the virtual environment.

The virtual city includes four clearly identifiable landmarks: a fast food, a hotel, a cinema and a flower shop (see below for more details).

The Digit Span (based on the WAIS-III subtest) was used to measure short-term memory. In this simple task, the subject has to repeat a sequence of numbers in the order and in the reverse order in which the numbers were stated by the experimenter. The first part of this test (Digit Span Forward) consists of pairs of increasingly longer strings of numbers; each number in a string is read to the patient at a rate of one digit per second. The patient is asked to repeat the string of numbers in exactly the same order as presented. After failing both items for a given string length, the patient is presented with another set of increasingly longer strings of numbers and asked to recite the string of numbers in reverse order (Digit Span Backward). Administration is discontinued when both items from a given pair are failed. A correct response to a single string of a pair is scored 1, while a correct response to both strings of a pair is scored 2.

The Task Switching is a measure of the executive functions (Monsell, 2003): two different tasks are performed in rapid succession and according to a random sequence of task presentation, so that the to-be-executed task can change from one trial to the next (*switch* trial), or can be repeated (*repetition* trial). Task switches are usually slower and less accurate than task repetitions, and this difference is often referred to as the task *switch cost* (SC). This cost is thought to reflect the time needed for the executive control processes to reconfigure the cognitive system for the execution of a new task (Monsell, 2003). Thus, the switch cost is considered an operational measure of the executive control.

In this task, while the subject looks at the center of a computer monitor (fixation point), a cue is presented on each trial which indicates the task to perform on the subsequent target stimulus. The two tasks consisted of judging if a digit stimulus was odd or even, or if it was smaller or larger than 5. Task cues stimuli consisted of outlined white squares or diamonds, indicating the even-odd and smaller-larger-than-5 tasks, respectively. Participants used their left and right index fingers for responding: odd digits and smaller-than-5 digits were mapped onto the left index finger response; even digits and larger-than-5 digits were mapped onto the right index finger response. The same two response keys on the computer keyboard (for left and for right index finger) were used for both tasks (for more details, see Couyoumdjian et al., 2010). Stimuli presentation and responses recording were managed by means of a custom software (Superlab version 2.1 for Windows).

Procedure

All subjects reported to the laboratory at 10 a.m. to undergo the behavioral testing.

Before starting, all subjects underwent a practice session in which they were free to move as long as they wanted, until they felt at ease in the virtual environment. Then, to ensure that the subjects had proficient motor skills, they were asked to perform three control tasks. These tasks required the subject to complete a predetermined route, indicated by arrows, within the same virtual environment in which s/he performed the practice session. When the subjects were competent to follow the arrows without making any stops along the route and were able to proceed along the pathway without wavering from side to side, they were administered the experimental tasks, namely the cognitive map learning (acquisition phase) and retrieval task, which were performed in a different virtual environment.

In the acquisition phase, the subjects were requested to form a cognitive map by moving in the environment to learn where the four landmarks were. During this phase, the subjects were free to move through the environment using whatever path and strategy s/he chose. Whenever the subject said s/he had learned where the landmarks were, the accuracy of the acquired cognitive map was assessed by asking her/him to report the respective locations of each landmark that s/he could remember on a 2D top-view outline of the city map. If s/he did not report the four landmarks precisely, the subject was allowed to continue to explore the city for another 2 min session. The learning task ended when the subject correctly reported on the map the four locations of four landmarks with an accuracy of 100%. During this phase, the total time (in seconds) for learning the locations of the landmarks was recorded.

After the acquisition phase, the subjects were administered the retrieval task consisting of 12 trials. Six of 12 trials were included in the so-called test phase, that immediately followed the acquisition phase. The remaining six trials were included in the “retest phase” taking place after 24 h, following one night of sleep. In each trial the subjects were required to make use of the cognitive map to reach different locations as quickly as possible and using the shortest possible route.

For all the 12 trials (test and retest) the task was the same, but the starting point and the landmarks to be reached were always different. In this phase we recorded the time (in seconds) the subject took to reach the specific location of the landmark on each trial, as well as the exact route chosen to reach the landmark. The choice of the shortest possible route to reach a target landmark is used as an indication of the subject’s navigation performance accuracy.

After completing the navigation task, all subjects underwent the Digit Span test, which was verbally administered by an experimenter. This task lasted about 5 min.

Finally, the subjects performed the Task Switching. The task included a training session, consisting of a series of 12 blocks of trials. The aim of this phase was to bring the subjects as close as possible to their asymptotic performance. There was no time constraint on this phase, and it was stopped only when the subject told the experimenter s/he felt s/he had understood the task. Therefore, the subjects completed one task switching session comprising 40 trials, lasting about 7 min.

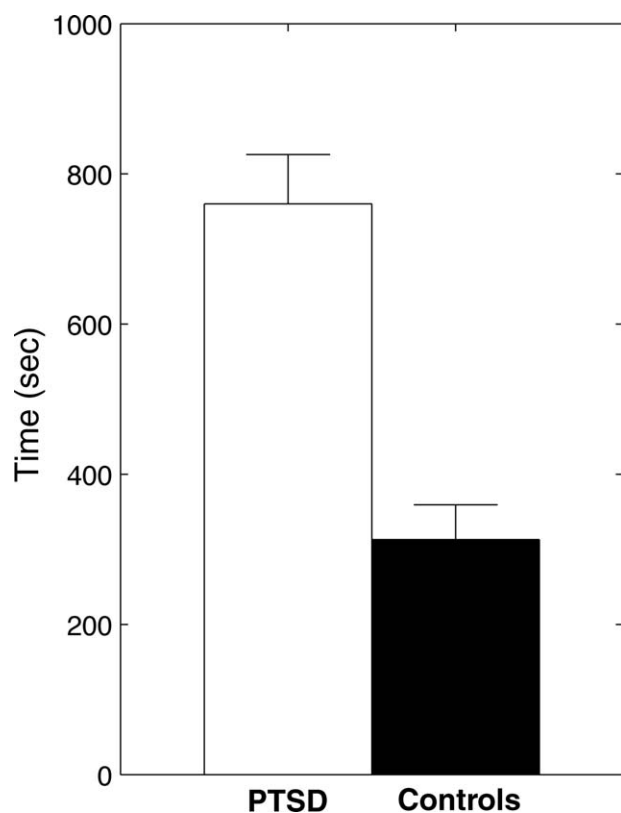


FIGURE 1. Creation of the cognitive map. Mean time and SEM (in seconds) needed by the PTSD and the Control group to form the cognitive map of the virtual environment in the acquisition phase.

The retrieval phase of the navigation task, the Digit Span and the Task Switching session were identically carried out on two consecutive mornings, before (Test session) and after (Retest session) one night of sleep, always starting at about 10 a.m.

Data Analysis

For the spatial navigation task, the time (in seconds) the subject took to reach the specific landmark location on each trial was used as a *speed* measure. Moreover, as an *accuracy* measure, we calculated the number of times the subject chose the shortest possible route to reach a target landmark (ranging between 0 and 6).

For the Digit Span test, the dependent variable was the total number of correct sequences of digits (Digit Span Forward + Digit Span Backward: range 0–28).

Finally, for the Task Switching we used as dependent variable the switch cost (in milliseconds).

Given the relatively small sample size, the large variability of CMT data (particularly during the learning phase of the spatial navigation task), the narrow range of variation and a substantial deviation from normality and homoschedasticity of some variables (e.g., the number of short routes), nonparametric statistics were used. Specifically, for all the behavioral and subjective

variables differences between groups were assessed by means of Mann–Whitney U, while between conditions differences were evaluated by means of Wilcoxon signed-rank test. Finally, to further assess whether sleep-dependent consolidation is differentially affected in the two groups, Mann–Whitney U-test was performed on the retest–test difference values of each variable.

RESULTS

Virtual Navigation Task

The PTSD group took more than twice as long to form a cognitive map of the environment during the learning phase compared to the control group (mean \pm standard error of mean (SEM): PTSD = 760 \pm 65.7 s, controls = 313 \pm 46.4 s; $U = 4$; $Z = -3.71$; $P = 0.0002$; see Fig. 1).

Nevertheless, once the acquisition phase was successfully completed, the two groups did not differ at test (mean \pm SEM: PTSD = 174.6 \pm 20.1 s; controls = 164.7 \pm 18.6 s; $U = 48$; $Z = -0.49$; $P = 0.62$; PTSD group $n = 10$, one subject was discarded as outlier). The between group difference at postsleep retest performance was close to significance (mean \pm SEM: PTSD = 173.7 \pm 17.4 s; controls = 131.1 \pm 12.7 s; $U = 28.5$; $Z = -1.87$; $P = 0.06$; see Fig. 2), due to the fact that only the control group improved from test to retest ($Z = -2.57$; $P = 0.009$), while the PTSD group showed unchanged performance ($Z = -0.15$; $P = 0.88$).

The between group comparison on the retest–test difference scores was significant ($U = 25$; $Z = -2.11$; $P = 0.03$), coherently with an interpretation in terms of a sleep-dependent consolidation which differentially affected the two groups.

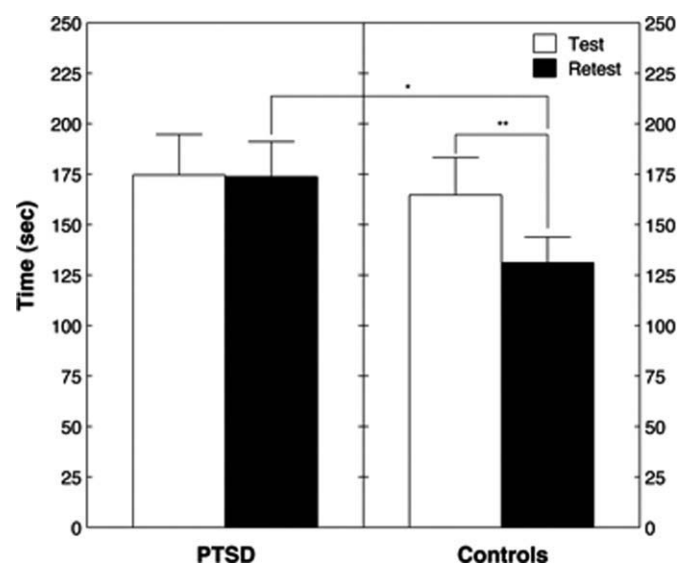


FIGURE 2. Spatial navigation performance. Mean performance (and SEM) during test and retest sessions for the PTSD and the Control group. The dependent variable is the median time (in seconds) needed to complete the test and retest trials. * $P = 0.06$; ** $P < 0.01$.

As far as the choice of the short routes is concerned, again the two groups did not differ at test (mean \pm SEM: PTSD = 3.70 ± 0.47 ; controls = 3.54 ± 0.53 ; $U = 51.5$; $Z = -0.25$; $P = 0.80$), and the controls showed a tendency toward choosing a higher number of short routes at retest compared to PTSD individuals (mean \pm SEM: PTSD = 3.70 ± 0.47 ; controls = 4.91 ± 0.37 ; $U = 30$; $Z = -1.76$; $P = 0.08$). This difference was due to the fact that only in the control subjects there was a significantly increased choice of short routes from test to retest ($Z = -2.40$; $P = 0.02$). Such an increase was not found in the PTSD group ($Z = -0.28$; $P = 0.78$).

Also in this case, the between group comparison on the retest–test difference values was significant ($U = 25.5$, $Z = -2.08$, $P = 0.04$).

Control Tasks

Digit Span

The two groups do not differ at both the test (mean \pm SEM: PTSD = 16.6 ± 0.6 ; controls = 16.2 ± 0.9 ; $U = 52$; $Z = -0.56$; $P = 0.57$) and retest sessions (mean \pm SEM: PTSD = 17.5 ± 1.0 ; controls = 17.1 ± 1.0 ; $U = 51.5$; $Z = -0.59$; $P = 0.55$). Moreover, there was no difference between test and retest performance in both groups (PTSD: $Z = -0.77$; $P = 0.44$; controls: $Z = -1.44$; $P = 0.15$).

The between group comparison on the retest–test difference scores was not significant ($U = 58$; $Z = -0.16$; $P = 0.87$), given that both groups showed no performance improvement between test and retest.

Task Switching

The analysis on switch costs (in msec) showed again that the two groups did not differ both at test (mean \pm SEM: PTSD = 271.75 ± 28.3 ; controls = 221.0 ± 46.6 ; $U = 47$; $Z = -0.89$; $P = 0.37$) and at retest (mean \pm SEM: PTSD = 173.1 ± 42.8 ; controls = 137.77 ± 60.4 ; $U = 37.5$; $Z = -1.51$; $P = 0.13$). Indeed, both PTSD subjects ($Z = -2.76$; $P = 0.006$) and controls ($Z = -1.99$; $P = 0.05$) showed a decrease of switch costs from test to retest.

The between group comparison on the retest–test difference scores was not significant ($U = 49$; $Z = -0.75$; $P = 0.45$), because both groups similarly improved their performance from test to retest.

Correlations between Subjective Sleep Variables and Spatial Performance

Because the PTSD subjects reported more sleep disturbances than controls (see Table 2), we asked whether the different performance levels in the two groups were correlated with the subjective sleep variables that somehow differentiated the same groups (i.e., PSQI and PSQI-A scores, as well as TST1 and TST2, the variables in Table 2 showing a $P < 0.10$).

The correlations (Pearson r) in the whole sample ($N = 22$) showed that total sleep time in the prelearning night (TST1) was not significantly related to the learning performance

($r = -0.30$, $P = 0.18$). Similarly, PSQI scores ($n = 22$, $r = 0.31$, $P = 0.16$) and PSQI-A scores ($n = 22$, $r = 0.38$, $P = 0.08$) were not significantly correlated with the virtual navigation performance at learning in the whole sample. As far as the latter close-to-significance correlation is concerned, a closer look at the relation between PSQI-A scores and learning performance separately for the two groups indicated that it disappeared both in the PTSD individuals ($n = 11$, $r = -0.07$, $P = 0.84$) and in the control subjects ($n = 11$, $r = 0.18$, $P = 0.59$).

No significant correlation emerged also between spatial performance at test and the above subjective sleep variables (TST1: $r = -0.14$, $P = 0.54$; PSQI: $r = -0.14$, $P = 0.54$; PSQI-A: $r = 0.08$, $P = 0.71$).

On the other hand, the estimated total sleep time on the postlearning night (TST2) of the whole sample was significantly correlated with CMT performance at retest ($n = 22$, $r = 0.42$, $P = 0.05$), indicating that shorter sleep times are related to worse performance at retest. The evaluation of this correlation separately for each group shows that it is absent in the PTSD group ($n = 11$, $r = -0.04$, $P = 0.90$, see Fig. 3, panel A), while it is close to significance in the control group ($n = 11$, $r = -0.55$, $P = 0.08$). Similarly, higher PSQI-A scores in the whole sample were associated to lower levels of performance at retest ($n = 22$, $r = 0.42$, $P = 0.05$). Also in this case, the PTSD subgroup showed no correlations between PSQI-A scores and retest performance ($n = 11$, $r = -0.02$, $P = 0.95$), while in the control group the correlation was significant ($n = 11$, $r = 0.69$, $P = 0.02$, see Fig. 3 panel B).

PSQI scores showed no significant correlation with postsleep spatial performance ($n = 22$, $r = 0.30$, $P = 0.17$).

DISCUSSION

Here we showed that PTSD is characterized by a specific deficit in the formation of a cognitive map of a virtual environment. However it is of note that, once the spatial map was successfully acquired, in the test phase the PTSD subjects were able to use it as properly as the normal controls. Although preliminary, our results also suggest a possible differential role of sleep in supporting the consolidation of spatial memory in PTSD. In fact, the direct comparison between groups with respect to the differential retest–test performance measures suggests that PTSD individuals may not benefit from postlearning sleep as normal controls. Nevertheless, the lack of a wake control group, controlling for the mere passage of time, necessarily limits our findings. Therefore, further studies on patients with PTSD would assess whether or not this kind of memory performance benefits from the simple passage of time in wakefulness.

The effects here reported were specifically related to the hippocampus-dependent spatial memory system. In fact, PTSD individuals did not seem to show a general cognitive impairment, since they performed at the control group level on either

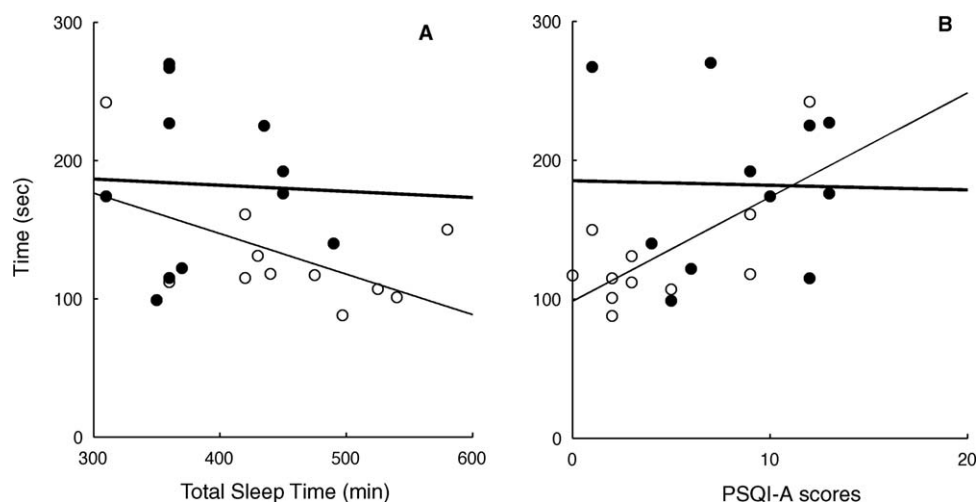


FIGURE 3. Correlations among navigation performance, total sleep and PSQI-A scores. Scatterplot of the individual correlations between the navigation performance at retest and the total sleep time (panel A) and PSQI-A scores (panel B) for the

PTSD (filled circles) and the Control group (open circles). The regression lines are plotted separately for the two groups (see Results for more details). The bold regression lines refer to the PTSD group.

the Digit Span and the Task Switching. Therefore, these effects can be tentatively explained by the anatomo-functional abnormalities typically reported by PTSD in the hippocampal region (Bremner et al., 2003; Shin et al., 2004; Karl et al., 2006).

About half of our PTSD sample also showed a comorbid state-trait anxiety disorder. The presence of cognitive deficits related to anxiety disorders among young adults is disputed (Airaksinen et al., 2005; Walkenhorst and Crowe, 2009). Although our subjects showed well preserved short-term memory and task switching performance compared to controls, others reported that state-trait anxiety symptoms may negatively affect memory performances (Walkenhorst and Crowe, 2009). Therefore, given that, to the best of our knowledge, the influence of anxiety disorders on spatial memory has never been evaluated, further studies are needed to exclude that the effects of anxiety symptoms have played a significant role on the relationship between PTSD and cognitive performance.

As expected, the PTSD group had higher general (PSQI) and trauma-related (PSQI-A) sleep disturbances, and they slept tendentially less than normal controls in both nights. This finding confirms that this is a core feature of this disorder (Spoormaker and Montgomery, 2008). Interestingly, virtual navigation performance at retest was significantly correlated with total sleep time in the postlearning night, indicating that the longer the subjects slept, the better they performed. Similarly, higher PSQI-A scores, indicating the presence of disruptive nocturnal behaviors (such as trauma-related nightmares, nocturnal intrusive memories, distressing dreams, sleep terrors, nocturnal panic attacks, dream enactment behaviors) were related to worse performance at retest. On the other hand, these relations were not significant considering total sleep time of the prelearning night and virtual navigation performance at test. Together, these findings suggest that the lack of sleep-dependent performance improvement may be also related to the sleep

disturbances experienced by the PTSD participants in the the postlearning night.

PTSD Is Characterized by a Specific Deficit in the Formation of a Spatial Cognitive Map

We hypothesized that PTSD would show a specific deficit in a spatial navigation task. The present results support the idea that the functioning of the hippocampus-dependent memory system is impaired in PTSD subjects, by adding the first empirical evidence to date on a specific deficit in the formation of a cognitive map of the environment. Because of the specificity of our task, the hippocampus-dependent instructions suggested for task solution and the previous findings reporting the critical contribution of the hippocampus for solving it (Iaria et al., 2007), we can assume that any delay in reaching a target location selectively reflects the strength of consolidation of the cognitive map and, consequently, the ensuing ability to make use of it (i.e., a hippocampus-dependent declarative memory).

It is interesting to note, however, that after having successfully acquired the map itself, the PTSD subjects showed an intact ability to orient themselves in the environment by going from one place to another in the test phase, when they performed at the same level of the controls. A previous study using the same spatial task indicated that different networks are involved in the acquisition and use of the cognitive map (Iaria et al., 2007). Future neuroimaging studies should focus on these networks, to evaluate whether their anatomo-functional integrity is differentially affected by PTSD.

It is worth pointing out that, based on the present finding, the specific spatial memory deficit in PTSD is not to be ascribed to a generalized cognitive impairment. In fact, PTSD and controls did not differ as to the Digit Span and Task Switching performance. Although the memory span is a basic

and simple ability that is independent from the hippocampus (Cave and Squire, 1992), the task switching is a particularly demanding paradigm that has been widely used to investigate the executive control of cognition, recruiting various prefrontal and parietal cortical regions (Sohn et al., 2000; Braver et al., 2003). Therefore, at least part of the executive control processes, namely those involved in the shift between different cognitive tasks, adjusting behavior rapidly and flexibly to changing environmental demands, are not compromised in patients with PTSD.

The Relation Among Sleep, Sleep Disturbances, and Spatial Performance in PTSD

This study confirmed that, in normal subjects, sleep benefits spatial memory performance (Ferrara et al., 2006, 2008). We also reported the first indications that such a sleep-dependent spatial memory improvement may be not warranted in patients with PTSD. However, as recognized earlier, the small sample size and the lack of a wake control group make this finding preliminary, awaiting further confirmation.

The possible deficiency of a sleep effect on spatial memory in PTSD can be tentatively accounted for by two different (maybe interacting) causes. This effect may be related to the anatomo-functional hippocampal deficits repeatedly shown in these individuals (Bremner et al., 2003; Shin et al., 2004; Golier et al., 2006; Karl et al., 2006; Tischler et al., 2006; Wang et al., 2010). It has been hypothesized that the consolidation of newly encoded spatial information, gradually transferred from short-term hippocampal stores to long-term neocortical memory stores, requires the offline replay of hippocampal activity during sleep (Sutherland and McNaughton, 2000). This idea is supported by the finding that the hippocampal areas that are activated during route learning in a virtual town are then reactivated during subsequent sleep, the extent of reactivation during slow-wave sleep being correlated with the improvement in route retrieval on the next day (Peigneux et al., 2004). Therefore, it can be speculated that a decrease of the anatomical and/or functional integrity of brain regions that are critical to spatial memory processes would hinder any sleep-dependent declarative memory consolidation.

However, we cannot overlook the possibility that the spatial memory deficits in PTSD individuals may be related to their sleep disturbances, more than to hippocampal dysfunctions. Unfortunately, we did not have the possibility to record sleep EEG in these patients, and our sleep analyses are limited to subjective reports. Nevertheless we found a significant relation between total sleep time during the postlearning night and virtual navigation performance at retest. In particular, in the control group a longer sleep was accompanied by a better performance, while this relation disappeared in the PTSD group (Fig. 3, panel A). Therefore, the subjective estimates of sleep confirm the general relation between sleep and navigation tasks in healthy subjects (Ferrara et al., 2008), while the lack of the same relation in PTSD subjects may suggest that sleep (length and possibly quality) exerts a beneficial influence on memory

consolidation only when the neuroanatomical machinery underlying the consolidation processes is structurally and functionally intact. It is noteworthy that either the learning performance and the navigation performance at test in the two groups did not correlate with total sleep time in the prelearning night. In such way, we can reasonably exclude an “aspecific” effect of sleep disturbances on spatial memory.

Interestingly, also trauma-related sleep disturbances (i.e., PSQI-A scores) were correlated with retest performance, and again the relation was significant only in the control group. The finding that the incidence of disruptive nocturnal behaviors during sleep in control subjects (exposed themselves to the same trauma, but not developing manifest PTSD symptoms) is related to worse performance levels, again supports the importance of sleep quality and continuity for the sleep-dependent memory consolidation processes. The null correlation in the PTSD subgroup may be related to the absence of a significant postsleep performance improvement, as well as to a ceiling effect in PSQI-A scores.

The lack of sleep-dependent spatial performance improvement in PTSD further supports the high specificity of the observed effects, that are strictly related to the hippocampus. In fact, the same effect was not present on task switching performance, that, on the contrary, confirmed and extended to PTSD individuals the postsleep improvement recently reported in normals (Couyoumdjan et al., 2010).

In conclusion, these findings indicate that PTSD is accompanied by an impressive deficit in forming (but not in using) a cognitive map of the environment. These effects at the behavioral level can be related to possible anatomo-functional hippocampal abnormalities that have been repeatedly reported in patients with PTSD (but not directly assessed in this study). Such hippocampal dysfunctions, together with the sleep disturbances observed (by subjective reports) in our PTSD group, may lead to impaired sleep-dependent spatial memory consolidation, to be confirmed by future studies.

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