

The role of sleep in the consolidation of route learning in humans: A behavioural study

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Received 31 March 2006; received in revised form 25 May 2006; accepted 17 July 2006

Available online 15 August 2006

Abstract

Considerable evidence support the role of sleep in learning and memory processes. In rodents, the relationships between sleep and memory consolidation have been extensively investigated by taking into account mainly spatial learning. On the contrary, in humans the relationship between sleep and spatial memory consolidation has so far been scarcely taken into account. Here, we investigated the importance of sleep in the consolidation of the spatial memory traces of a new route learned in a real-life unfamiliar environment. Fifty-one subjects followed a defined route in a neighbourhood they had never been to before. Then, they were tested in the laboratory in a sequence-recognition test requiring them to evaluate whether or not sequences of three views, taken along the route, represented a correct sequential order as seen while walking along the route. Participants were then assigned to one of three groups: the *sleep group* was retested after one night's sleep, the *sleep-deprived group* was retested after a night of sleep deprivation, and the *day-control group* was retested the same day after 8 h of wakefulness. At retest, performance speed increased in all groups, whereas the accuracy in the sequence-recognition task was improved only in the *sleep group*: neither sleep deprivation nor the simple passage of time gave way to any performance improvement. These preliminary findings shed more light on the role of sleep in spatial memory consolidation by extending to humans the considerable evidence found in animals.

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Keywords: Sleep; Spatial memory; Route learning; Navigation; Real environment

1. Introduction

In 1966 Moruzzi suggested that sleep plays a critical role in memory consolidation by allowing the slow recovery of "learned synapses", i.e. new contacts between neurons [11]. This early hypothesis received strong support by a large body of experimental evidence from molecular genetics, neurophysiological and behavioural studies in humans and animals [10].

Although the role of sleep in learning and memory processes has been strongly suggested [25], its specific contribution for memory remains hotly debated [21]: first, it is not clear

which aspects of memory function are affected by sleep and which processes underlie such a consolidation; second, it is not yet fully established how different types of memory are differentially influenced by the sleep stages and/or by their sequence.

In rodents, the relations between sleep and memory consolidation have been mostly studied by taking into account spatial memory, which is dependent on the hippocampus [12]. In particular, post-training spontaneous reactivations of the so-called "place cells", hippocampal neurons selectively firing when the animal occupies a specific spatial location within the environment, have been extensively investigated. At the cellular level, it has been observed that neuronal ensembles activated during the waking behaviour are then re-activated during post-training sleep [13,16,20,22,30]. Consequently, it has been hypothesised that the offline replay of hippocampal activity during NREM sleep in rodents may be involved in the consolidation of newly

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encoded spatial information, gradually transferred from short term hippocampal to long term neocortical memory stores [26].

In humans, spatial memory acquisition involves the same neuroanatomical substrate as in animals [2]. In recent years, the neural mechanisms underlying spatial navigation have been extensively investigated by means of neuroimaging techniques combined with virtual reality paradigms. Activation of the right hippocampus has been constantly shown to be strongly related to the ability to navigate within the virtual environment and to the knowledge of spatial locations within it [9]. The encoding of spatial information from the ground level perspective (route) calls upon bilateral medial temporal lobes [19]. The pattern of brain activation, however, changes as a function of the cognitive strategy used by subjects to solve a place-learning task in a virtual environment [4]. In fact, the hippocampus has been found involved only when the subjects used spatial landmarks to navigate in the early phase of training [6]. Recently, it has been shown that the hippocampal areas activated during route learning in a virtual town are then reactivated during subsequent SWS—the reactivation being correlated to the improvement in route retrieval on the next day [14]. The latter study gives strong support to the idea that spatial memory traces are processed and strengthened during sleep in humans.

At variance with studies in rodents, evidence for relationships between sleep and spatial memory consolidation in humans are scarce. In the present study we investigated the contribution of sleep in spatial memory consolidation with respect to our continuous requirement in daily life to engaging visuospatial navigation in real surroundings. We adopted an ecological version of a virtual reality paradigm used by Wolbers and Buchel [31] to investigate the contribution of the hippocampus in the formation of a cognitive map. In that study [31], participants were required first to look at a video-clip showing, from a ground level subject perspective, the view while walking along corridors; then, they were asked to judge the relative location of two landmarks present along the route. By using functional magnetic resonance imaging (fMRI), the authors were able to show that the hippocampus was involved while performing the sequence-landmark task, suggesting its fundamental role in the formation of a spatial memory representation (cognitive map of the environment). In our study, participants were asked to follow an experimenter while walking along a route in a neighbourhood they had never been to before. Then they were tested in the laboratory in a sequence-recognition task requiring them to evaluate whether or not sequences of three pictures, taken along the route, represented a correct sequential order of places as the subjects saw them while walking along the route. For retesting in the same sequence-recognition task, the participants were divided into three different groups: the *sleep group* was retested after one night's sleep, the *sleep deprivation group* was retested after a sleep deprivation night, and the *day-control group* was retested after 8 h of wakefulness. Comparisons of accuracy and speed in the sequence-recognition task of the three groups allowed us to investigate the role of sleep in spatial memory consolidation of a newly-learned route in a real-life unfamiliar environment.

2. Materials and methods

2.1. Participants

Fifty-one male students participated in this study (mean age: 22.1 yrs, S.E.M.: 0.49). They were right-handed (score >0.8), as assessed by a standard lateral preference questionnaire [18]. None of the subjects had history of medical, neurological or psychiatric disorders. All of them had habitual sleep duration of 7–8 h per night, went to bed between 11 p.m. and midnight, and did not take naps during the day. Quality and quantity of participants' usual sleep was assessed by a sleep log: no obvious disturbances of the sleep/wake cycle along the entire week before testing were revealed, confirming for all participants a mean of 7.8 h of sleep per night (S.E.M.: 0.26). Informed consent was obtained from all participants and the study was approved by the local Ethics Committee.

The participants were randomly assigned to one of three different groups (17 subjects in each group). Subjects included in the *sleep group* (mean age: 22.5 yrs, S.E.M.: 0.66) spent the night after the route learning at home, sleeping as usual. Subjects in the *sleep-deprived group* (mean age: 22.5 yrs, S.E.M.: 0.45) stayed awake in the laboratory under the direct supervision of two experimenters: they were allowed to briefly walk around, listen to music, read, watch the television or use a computer. Lying down, sleeping and vigorous physical activity were not permitted. Light snacks were permitted, while caffeinated beverages, chocolate, alcohol, and medications that can induce sleepiness were not allowed during the deprivation protocol. Time information was available to subjects. The laboratory was constantly illuminated by neon lamps, with blinds only in part attenuating the light coming from the outside. Finally, subjects included in the *day-control group* (mean age: 21.3 yrs, S.E.M.: 0.37) spent the day pursuing their usual student activities; however, they were not allowed to do any sports or to have stimulant drinks after 4 p.m.

2.2. Real environment and route

The experiment was performed in a neighbourhood of the city of Rome (Italy) with small, narrow streets and no high buildings. In addition, the traffic in this area is allowed only to the few residents. These specific characteristics make the area quiet and comfortable to walk around in. In a screening interview participants declared to have never been in this neighbourhood. The route selected to perform the experiment was 1.2 km long, including five right and four left turns (see Fig. 1). The time taken to complete the route was about 12 min.

2.3. Stimuli and task

The stimuli consisted of 60 photographs taken along the entire route from the subject's perspective, capturing both the left and right side of the street. That is, each photograph consisted of an environmental view showing the pathway (as seen by walking and looking forward) and the landmarks available along it. No photograph was taken focusing on specific landmarks. When landmarks were present in the photographs, they were displayed in the context of the environmental view. No overlapping of views was present in the entire set of photographs. Moreover, in order to have a comparable brightness and contrast between the subjects' experience while walking along the route and the images viewed during testing, the photographs were taken in the morning (same time the participants would have been tested) and subjects were administered the learning task under similar weather conditions.

The photographs were used to create 18 sequences composed of three images each: nine sequences included images representing a correct sequential order while walking along the route, whereas nine sequences included three photographs showing an incorrect sequential order. During testing and across sequences, each photograph was presented only once. Both test and retest included the same sequences of photographs. Examples of the two types of sequences are reported in Fig. 1.

The 18 trials were randomly presented on a 14 in. computer screen. For each sequence, the three photographs appeared on the screen one at a time for 2 s each. At the end of each sequence, a question mark was presented and the subjects were asked to judge whether or not the sequence was shown in the correct order as experienced while walking along the route. Participants performed the task by

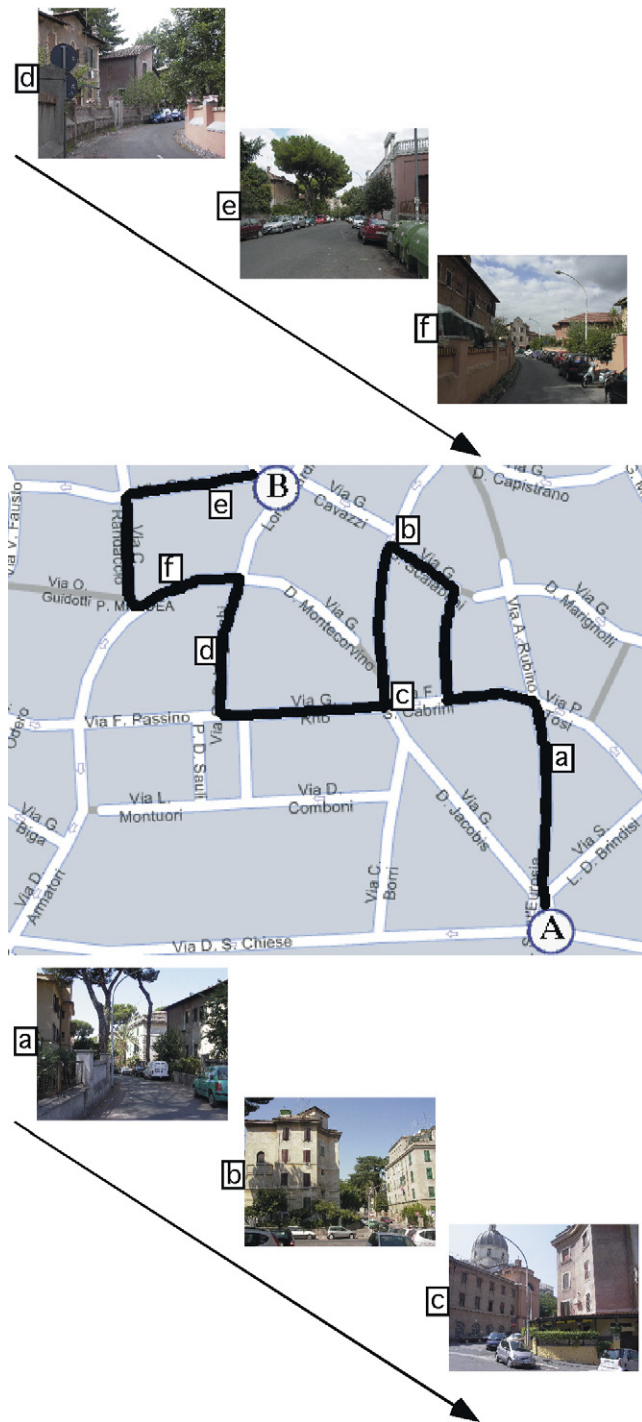


Fig. 1. The upper panel of the figure shows one of the nine incorrect sequences administered during the sequence-test and retest tasks: the order of the photographs (d, e, f) shown within the sequence does not correspond to the real sequence experienced along the route (d, f, e). The middle panel shows the route followed by the subjects from the starting point (A) to the final location (B). The lower panel shows a correct sequence in which the order of the photographs corresponded to the real order of the views seen while walking along the route (a–c).

using two response buttons indicated on the computer keyboard: reaction times and errors were recorded.

Before testing, in order to give the instructions and to practice the motor aspects of the task, the subjects underwent a training session. This session consisted of sequences including photographs different from the experimental ones:

these photographs showed three views taken at the beginning, middle and final part of the route.

2.4. Procedure

The participant was driven from the Psychology Department to the area where the learning phase of the route would take place. At the starting point (see Fig. 1), the subject was informed regarding the nature of the sequence-test that would be performed later at the laboratory. Then he was instructed to follow the experimenter while walking along the route, scanning the entire scene and trying to memorize the route in order to better perform the sequence-recognition task. No further specific instructions were given to the subjects while performing the learning phase.

In a pilot experiment we found that, after walking along the route only once, the subjects performed the sequence-test very badly. For this reason, we decided to perform the route twice before administering the sequence-test at the laboratory. After the first trip, the subject was driven from the arrival point to the same starting location in order to follow the route again. At the end of the second trip, the subject was driven back to the Department to perform the sequence-test. In order to avoid confounding views similar to the ones seen along the route, the subjects were always blindfolded while moving from (and to) the Department and all the way back to the starting point in order to perform the route for the second time.

All subjects learned the new route at 11 a.m., and were subsequently tested in the sequence-recognition task at noon. At the end of the sequence-test performed in the laboratory, the subjects were randomly assigned to one of three different groups. Subjects included in the *sleep* and *sleep-deprived* groups were retested on the sequence-test 24 h later (again at noon), while subjects included in the *day-control* group were retested the same day at 8 p.m.

2.5. Statistics

Number of errors and reaction times while performing both test and retest sequences were used for statistical analyses, as accuracy and speed measures, respectively. Thus, data were submitted to a mixed design ANOVA (*group* (sleep, sleep-deprivation, day-control) \times *session* (test, retest)). *Post hoc* comparisons (LSD tests) were performed to assess the main effects or interactions.

3. Results

3.1. Accuracy measure

The mean errors made in the test and retest session for the three experimental groups are reported in Fig. 2. The mixed design ANOVA showed a significant *group* \times *session* interaction ($F_{2,48} = 3.42, p = 0.04$). LSD *post hoc* comparisons revealed that only the performance of the *sleep* group improved while performing the retest session ($p = 0.01$). In the retest session, the *sleep* group performance was better than the ones from the *day-control* ($p = 0.03$) and *sleep-deprivation* groups ($p = 0.0005$). The main effects of *group* ($F_{1,48} = 1.06; p = 0.35$) and *session* ($F_{1,48} = 1.70, p = 0.20$) were not significant.

The *sleep* group showed a test-retest decrease in number of errors (mean decrease = -1.53 , S.E.M. = 0.44), corresponding to the 21% of mean performance improvement. Looking at the individual data, in this group 12 out of 17 subjects (71%) showed a decrease in the number of errors while performing the retest session (mean increase in accuracy: 31%). Only two subjects increased their number of errors in the retest session (decrease in accuracy).

The *day-control* group showed only a slight decrease of errors (mean decrease = -0.35 , S.E.M. = 0.60), corresponding to a 5%

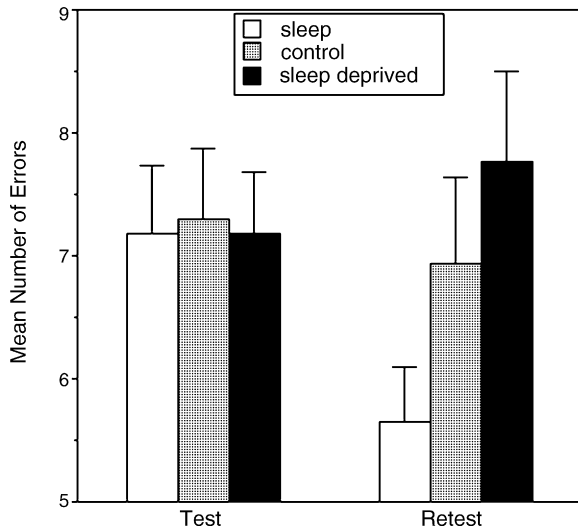


Fig. 2. Mean number of errors (accuracy measure) of the three experimental groups in the sequence-task while performing the first (test) and second (retest) session.

performance improvement. In this case, 8 out of 17 subjects (47%) improved their performance (mean improvement = 31%). However, 7 subjects (41%) showed an increase of errors in the retest session.

Finally, the *sleep-deprived group* showed a slight increase of errors in the retest session (mean increase = 0.59, S.E.M. = 0.66), equal to an 8% performance impairment. Individual data revealed that in this group, only 6 out of 17 subjects (35%) improved the accuracy of their performance (mean improvement: 31%). Of note, 10 subjects (59%) increased their number of errors in the retest session.

3.2. Speed measure

The mixed design ANOVA with reaction times as dependent measure showed a significant main effect of *session* ($F_{1,48} = 20.30$; $p = 0.0001$ (Fig. 3)): the three groups

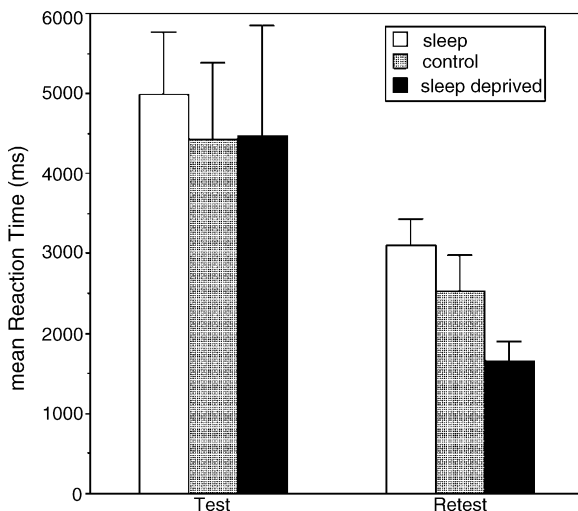


Fig. 3. Mean reaction times (speed measure) of the experimental groups performing the sequence-task at test and retest sessions.

all increased their speed while performing the retest session (mean increase = 48%; *sleep group* = 43%; *day-control group* = 38%; *sleep-deprived group* = 63%). The main effect of *group* ($F_{1,48} = 0.54$; $p = 0.59$) and the *group* \times *session* interaction ($F_{2,48} = 0.39$, $p = 0.68$) were not significant.

4. Discussion

The relationship between sleep and spatial memory has been investigated in rodents by several neurophysiological studies showing a critical role of sleep for the consolidation of memory for spatial locations within the environment [13,16,22,30]. However, the relations between sleep and memory skills for navigation in humans has so far received little attention. Aubrey et al. reported that total sleep deprivation negatively affects memory for a simple route through the stacks of a university library [1]. More recently, a virtual reality environment was used to show that the hippocampal areas activated during route learning in a virtual town are reactivated during the ensuing SWS, and that the amount of reactivation is correlated to the improvement in route retrieval the next day [14]. Thus, a link between SWS and spatial memory consolidation in humans was strongly suggested, in agreement with previous findings indicating that other memory tasks benefit from SWS [e.g., 15].

In the present study, we investigated the relationship between sleep and spatial memory for human navigation in a real-life environment. We found that after exploring a new environment by following a defined route, subjects who slept as usual during the ensuing night showed a better accuracy than the sleep-deprived subjects when retested on a sequence-recognition task. In addition, the subjects in the *sleep-group* performed significantly better than the participants who were retested during the same day before sleep. These results are a preliminary piece of evidence in support of the hypothesis that sleep helps the strengthening of spatial memory also in humans. Indeed, they clearly indicate that the relationship between sleep and spatial memory can be explored experimentally, as well as that this indication requires to be refined by laboratory studies.

It is well-known that the sleep deprivation paradigm, especially in animals, may be contaminated by uncontrolled non-specific effects of the deprivation procedure (stress response, increased brain excitability, emotional–motivational modifications) that can themselves impair memory [21]. Although in humans the side-effects of the deprivation procedure seem to be fewer [5,17], a possible concern may still be the fact that subjects in the *sleep deprivation group* have been tested in a different vigilance state than the other groups. A way to control for this confounding would have been to test again all subjects 2–3 days after the recovery night, to ensure similar vigilance parameters. Unfortunately, this control has not been carried out, since a further retest with the same sequence-recognition task would have given the way to possible uncontrolled learning effects. Nevertheless, to estimate the actual advantage of sleep condition with respect to that of absence of sleep, future studies will have to assess the additional negative effect of sleep deprivation by means of more complex experimental designs.

However, although in principle the lack of accuracy improvement in the sleep-deprived group could be equally due to lack of consolidation during post-training sleep or to reduced cognitive abilities after extended wakefulness, it must also be borne in mind that, in the present experiment, the *sleep-deprivation group* concomitantly showed an *increase* of performance speed (as in the other groups). The latter result is in contrast with the expected *decrease* of speed and maintained accuracy, typically reported in the sleep deprivation literature as a consequence of the decreased levels of vigilance [e.g., 8]. This result contributes to partly ruling out the possibility that the observed effect could be due to unspecific confounding effects of the sleep deprivation procedure, such as tiredness or hypovigilance.

Moreover, the presence of a *day-control group* (non-sleep-deprived) in our paradigm allows us to fairly attribute the reported effects to sleep itself, although the circadian factors were not controlled for. In fact, the *day-control group* was retested at a different circadian phase (8 p.m. instead of noon) with respect to the other two groups. However, in sleep experiments it is almost impossible to control for the passage of time and circadian factors at the same time [28]. In the present study, we ensured that all subjects learned the new route and were tested at the same circadian time. The choice of an ecological task carried out in a natural environment obviously posits more constraints.

The peculiarity of the present work is indeed the use of a spatial memory task with a high “ecological validity”. One of the main limitations in the sleep-memory consolidation literature indeed is the investigation of a small number of very simple, mainly procedural tasks. On the other hand, the relation between sleep and spatial learning has hardly been taken into account. According to a few authors, sleep does not even play a role in declarative memory consolidation [27]. Our results support the opposite view [24].

As repeatedly reported for some procedural abilities [e.g., 7], even our spatial memory task seems to undergo a time-dependent mechanism of stabilization. As a result, the behavioural performance in the *day-control group*, retested 8 h after the first test, was maintained but not improved. According to the contemporary brain-state-dependent model of memory formation [29], this effect should be linked to a process of consolidation-based stabilization, resulting in a memory representation more resistant to interference. However, even for the spatial memory domain, it seems that the additional process of consolidation-based enhancement takes place during sleep [29]. Following this, it would be interesting to assess whether a short nap is sufficient to obtain similar benefits.

It is noteworthy that the “sleep effect” we found in this study was limited to the accuracy measure, while performance speed was increased in all participants. Thus, a second experience with the same task is sufficient in increasing velocity, regardless of the length of the retention interval (8 or 24 h) and the presence of sleep. On the other hand, only the *sleep group* showed a significant accuracy improvement, in line with the results by Wagner et al. who used a very different task [28]. In that study, subjects performed a mathematical task requiring the learning of stimulus–response sequences with a hidden abstract rule

underlying all sequences. The percentage of subjects finding the “short cut” was significantly larger in the sleep group than in the wake groups. Intriguingly, the subjects who benefited from sleeping by subsequently finding the new solution showed only a marginal speeding up of reaction times across sleep as compared to the profound decrease in the non-solvers reaction times. As suggested by Stickgold and Walker [23], these results seem to indicate that “the sleeping brain can only process the information initially learned one way or the other”; which in our study means either enhancing speed (a simple strengthening of the acquired skill) or creating a better map of the newly-learned route. The outcomes of the present study suggest that the latter result requires the presence of sleep. On the basis of both the human and animal literature, it may be hypothesised that a specific part of sleep, namely the highly synchronized SWS, is important for the strengthening of spatial memory traces. Future studies should shed more light on this point, by means of sleep EEG recordings and selective SWS manipulations [e.g., 3].

In conclusion, in this study we presented preliminary evidence that new spatial memories acquired in a real environment are strengthened by a nocturnal sleep period. Sleep deprivation, instead, seems to hinder any improvement in performance accuracy. Similarly, spatial memory performance does not benefit from the simple passage of time.

It is possible to hypothesize that spatial memory may be related to SWS, since this part of sleep has been found to be particularly relevant for declarative memory formation via hippocampal-neocortical networks. Since we did not record sleep EEG parameters, this assumption remains in part speculative. In the near future further studies are needed in order to establish the role of factors presumably involved in the effect observed here, such as the overall amount of sleep, the variation in the proportions of sleep stages, the time-of-day for acquisition and recall of the information, and possible gender differences. Further steps forward in investigating this important component (spatial information) of declarative memory and the relationship between the process of consolidation of such component and sleep, will entail fMRI recordings to assess how sleep affects the brain networks underlying spatial navigation.

Acknowledgments

The authors wish to thank Matteo Martini and Antonella Mattiocco for their help in data collecting, and Prof. Luigi Piz-zamiglio for his comments on the protocol and the article. This research was partially supported by a grant to M.B. from the MIUR (PRIN 2004), and by a grant to C.G. from the European Community (FP6-NEST:Wayfinding; 12959).

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