

## Optimizing Methodology of Sleep and Memory Research in Humans

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Article

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#### Article

## **Optimizing Methodology of Sleep and Memory Research in Humans**

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**Abstract:** Understanding the complex relationship between sleep and memory is a major challenge in neuroscience. Many studies on memory consolidation in humans suggest that sleep triggers offline memory processes, resulting in less forgetting of declarative memory and performance stabilization in non-declarative memory. However, issues related to non-optimal experimental designs, task characteristics and measurements, and inappropriate data analysis practices can significantly affect the interpretation of the effect of sleep on memory. In this article, we discuss these issues and suggest constructive solutions to address them. We believe that implementing these solutions in future sleep and memory research will significantly advance this field by improving the understanding of the specific role of sleep in memory consolidation.

**Keywords:** long-term memory; declarative memory; procedural memory; sleep; consolidation; fatigue effect; circadian effect; napping; data analysis recommendations; open science



#### Introduction

There is a great interest in sleep both in the general public and the scientific community. The critical influence of sleep on health and certain aspects of cognition is well established <sup>1–3</sup>. Furthermore, modern lifestyles and technologies impact sleep habits and sleep quality, leading to an increased prevalence of sleep deprivation and poor sleep hygiene <sup>4–7</sup>. Human memory is also a subject of societal interest, encompassing education and learning on one end of the developmental spectrum, and aging and age-related memory decline on the other. Consequently, the effect of sleep on human memory has gained significant attention in psychology and neuroscience research over the past two decades, resulting in thousands of dedicated publications. Moreover, several theories and models have been developed to explain the beneficial effect of sleep on memory, e.g., <sup>8–23</sup>.

This paper primarily focuses on the effect of sleep on human declarative and non-declarative memory consolidation at the behavioral level. Specifically, we discuss issues related to examining how sleep following the acquisition of new information(e.g., new vocabulary or playing the piano) enhances subsequent memory compared to an equivalent amount of time spent without sleep. We follow *the primacy of behavioral research for understanding the brain* principle <sup>24,25</sup> as we believe that optimizing behavioral methods, including study design and task characteristics/measurements, is crucial in assessing the effect of sleep on memory using neuroscience techniques. Due to the scope of this article, we do not discuss the biological mechanisms or neural substrates underlying memory consolidation. However, we do address some issues arising from physiological factors that may potentially impact the effect of sleep on the behavioral measures of memory consolidation.

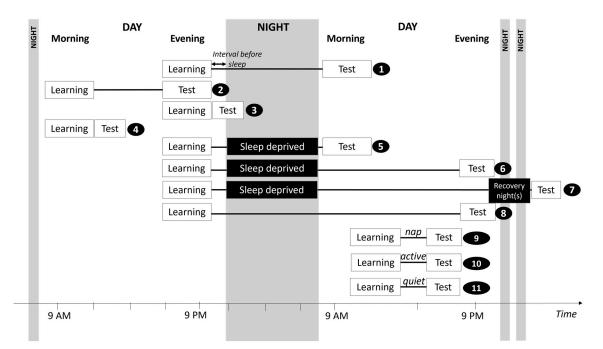
According to prominent empirical studies e.g., <sup>26,27</sup> and reviews on this topic <sup>18,28,29</sup>, in healthy adults declarative memory exhibits greater resistance to forgetting when encoding is followed by a period of sleep compared to a period of wakefulness. Additionally, non-declarative memory performance can even show improvement when sleep follows the training. The evidence supporting sleep-related memory consolidation is so compelling that it has been suggested that among putative functions of sleep, memory consolidation appears to be of paramount importance. In fact, it is widely acknowledged that active system consolidation (whereby memories are reactivated during sleep to be consolidated) may represent an evolutionarily conserved function of sleep <sup>3030,31</sup>. While such statements may be justified if based on converging evidence from a large body of heterogenous experimental approaches, we claim here that supporting evidence coming from individual experiments is not yet compelling, due to several experimental and methodological limitations. Indeed, the actual impact of sleep on memory consolidation is still under considerable debate, e.g., <sup>32–37</sup>.

Increasing evidence indicates that the effect of sleep on human memory consolidation is perhaps more multifaceted than initially thought e.g., <sup>28</sup>. In addition, the correlations observed between sleep electrophysiology (e.g., sleep spindles, stage 2 NREM sleep) and memory consolidation are often not replicated across studies <sup>32,33,35,38,39</sup>. Contradictory findings in the field are not an issue *per se* as they can highlight the complexity of the effect of sleep on memory consolidation – but the potential tendency to overlook them in favor of a more general view claiming that sleep is beneficial in every circumstance is nonetheless problematic. Thus, it is crucial to ensure that the contradictory effects observed in sleep and memory research are not attributable to methodological imprecision. Providing guidelines for future studies is crucial to maintaining progress in the field and would enable us to gain a clearer understanding of the role of sleep in memory and minimize the possibility of misleading or inaccurate findings.

In this Perspective, we present a guideline for researchers embarking on the design of new studies investigating the relationship between sleep and memory, with a specific focus on declarative and non-declarative memory consolidation. Such a comprehensive guideline is lacking so far (but see <sup>28</sup>), hindering progress toward a better understanding of the effect of sleep on memory in fields ranging from psychology to biology and neuroscience. We highlight three main methodological issues that could be responsible for some contradictory findings found in the literature. We then propose solutions for them to guide future research.

#### I. Experimental design

In this section, we identify four main areas that could benefit from improvements in the experimental designs and suggest solutions for each of them. Figure 1 illustrates the main study conditions that can be included in the experimental designs testing the effect of sleep on memory consolidation. It is important to note from the outset that it is difficult to address all of these methodological caveats in one parsimonious experimental design. Thus, several types of studies may be necessary to provide converging evidence to draw conclusions about the effect of sleep and memory <sup>40</sup>.



**Figure 1.** Illustration of 11 study conditions for testing the effect of sleep on memory consolidation, grouped in three main study designs. Conditions 1 and 2 depict the *evening-morning vs. morning-evening design*, including a 12-hour interval filled with sleep or wakefulness, respectively. Conditions 3 and 4 depict their respective control conditions, allowing them to rule out potential circadian effects during learning. Conditions 5-7 depict conditions of *sleep deprivation design*, with various retention intervals and optional recovery nights, while Condition 8 illustrates the sleep counterpart of Condition 6. Conditions 9-11 illustrate the conditions of *nap studies*. In the active condition (10), participants perform cognitive and/or physical activities, whereas activity is minimized in the quiet-rest condition (11). Using appropriate control conditions to test the effect of sleep on memory provides more validity to the results. For further details, see the main text.

The issues with non-optimal experimental designs fall into two main categories The first is related to the influence of the time of day during task performance. The second concerns whether the observed benefit of sleep over wake intervals is solely due to the reduced interference during sleep, raising the question of passive (through reduced interference) versus active (though sleep-specific neural processes) contributions of sleep to memory consolidation (for in-depth discussion see <sup>41</sup>). If sleep has only a passive role in this regard, then creating wake intervals with reduced external interferences during the post-learning interval may be sufficient to trigger a level of consolidation comparable to that of a sleep interval. The experimental designs we discuss below equally concern within-subjects and between-subjects designs, although the majority of examples in this text utilize the latter. Between-subjects designs eliminate confounding factors (such as the familiarity effect when a memory task is repeated within a study) but necessitate more careful control for potential variations between groups.

#### Time-of-day (circadian) effects

It has been shown that the time of day when the task is performed can impact learning and memory performance <sup>42,43</sup> (for negative results, see <sup>44</sup>). Time-of-day (circadian-related) effects can introduce confounding factors in sleep-related consolidation studies. Typically, these studies compare performance changes between a Sleep condition (i.e., learning in the evening and testing memory the next morning; Figure 1, condition 1) and a Wake condition (i.e., learning in the morning and testing memory the next evening; condition 2). Importantly, however, a greater off-line improvement in a Sleep condition compared to a Wake condition in such a design may be, at least partially, explained by two confounds: worse performance in the evening (i.e., when learning takes place in the Sleep condition) due to circadian effects, including a day-long buildup of fatigue 45; and/or better performance in the morning (i.e., when testing takes place in the Sleep condition) when participants are likely well rested. Probing circadian effects, one meta-analysis <sup>32</sup> of sleep-related motor memory consolidation revealed that performance is optimal when the test session occurs in the early afternoon. Notably, the issue of circadian effects can be even more pronounced across different stages of the human lifespan, particularly when comparing younger and older individuals with variations in chronotype and homeostatic sleep pressure <sup>46</sup>. In either case, the extent to which sleep itself contributes to improved performance compared to circadian factors remains unclear. However, when controlling for circadian effects during encoding and retrieval, sleep is still confounded with time-of-day as sleep usually occurs at night (although see <sup>47</sup> for an inverted 12-hour schedule with sleep occurring during daytime), potentially leading to more efficient consolidation for reasons unrelated to sleep itself.

Hormones, such as growth hormone and cortisol, play a significant role in memory processes, and their release follows distinct circadian rhythms <sup>48</sup>. For instance, growth hormone peaks in the first half of the night, whereas its concentration is very low in the second half. By contrast, cortisol has its daily nadir in the first half of the night and its peak in the second half <sup>49</sup>. These hormonal fluctuations not only confound evening-morning vs. morning-evening (Figure 1, conditions 1 and 2, respectively) comparisons but also affect within-night comparisons that are permitted by the classical split-night paradigm, which compares the slow wave sleep (SWS)-rich first half of the night with the rapid-eye-movement (REM) sleep-rich second half <sup>50</sup>. Thus, the confounds of endocrine fluctuations across the circadian rhythm are difficult to avoid, rendering the split-night paradigm a challenge to interpret (among other reasons).

When examining the effects of nighttime sleep on memory consolidation, such as in an eveningmorning (Sleep) vs. morning-evening (Wake) design (Figure 1, conditions 1 and 2, respectively), it is essential to include additional control groups to separate should be tested to disentangle the circadian effects from the effect of sleep per se. Thus, a comprehensive design would include evening-morning (i.e., 12h Sleep; condition 1) and morning-evening (i.e., 12h Wake; condition 2) conditions, together with evening-alone (condition 3) and morning-alone (condition 4) conditions, the latter two conditions with immediate testing. A difference in *learning* performance (i.e., time taken to learn or overall performance during training) and/or in the immediate *retrieval* performance when learning/immediate testing takes place during the evening vs. in the morning would indicate potential circadian effects and preclude further interpretation about the effect of sleep on consolidation e.g., <sup>51–54</sup>. Note that there are studies that include circadian controls (control conditions 3 and 4) but find no effects of time of learning or testing 44. In such a design, a beneficial effect of sleep would be demonstrated only if: there is no difference in learning performance in the four conditions; there is no difference in retrieval performance between the morning-alone and the evening-alone conditions; and there is better retrieval in the evening-morning than in the morning-evening condition. Also, testing for interactions between delay (immediate vs. 12 hours) and encoding/test time (morning vs. evening) would be the most precise way to demonstrate sleep effects.

Another possible solution is to include sleep-deprived Wake control groups in evening-morning (12h Sleep-deprived) or evening-evening (24h Sleep-deprived) conditions (see Figure 1, conditions 5 and 6, respectively) and compare their performance with that of an evening-morning (12h Sleep; condition 1) group. In these sleep deprivation controls, learning takes place in the evening and testing takes place either in the morning or the next evening, with participants staying awake during the

night, or during both the night and the following day, respectively. In both cases, testing can take place either after sleep deprivation, with participants being acutely sleep deprived at testing, or testing can be delayed by another 24-48 hours to allow for one or two nights of recovery sleep (condition 7), with the sleep conditions likewise being tested after comparable delays.

The advantage of sleep deprivation control designs is that learning and testing take place at the same time of day in the 12h-Sleep and 12h Sleep-deprived groups, thus controlling for potential circadian differences that are an issue with the typical morning-evening (12h Wake; condition 2) controls. The same holds for the comparison of evening-evening groups, where one group could sleep (24h interval including a sleep period), while the other stayed awake (24h Sleep-deprived) in the delay period (see Figure 1 conditions 8 and 6, respectively). Including recovery sleep (condition 7) ensures that participants are not acutely sleep-deprived at testing, which reduces the (negative) impact of sleep deprivation on test performance. However, including recovery sleep comes at the price of extending the retention interval, which may likewise affect retrieval performance through processes of decay, forgetting, or memory restructuring. Moreover, recovery sleep may exert additional confounds related to potential compensatory effects on memory consolidation, and sleep rebound effects. That is, sleep during the recovery night(s) may compensate for the missed opportunity for sleep consolidation during the first night of sleep deprivation, thus masking the original effect on memory consolidation.

Only a few studies applied such sleep deprivation designs. One <sup>55</sup> examined the role of noradrenaline for sleep-dependent memory consolidation by pharmacologically blocking noradrenaline via clonidine administration in an evening-evening sleep vs. sleep deprivation design without recovery sleep (Figure 1 conditions 8 and 6, respectively). They observed impaired memory retention after clonidine administration in the Sleep group compared to placebo but no difference between clonidine and placebo in the Sleep-Deprived (wake) group, suggesting that noradrenaline supports memory consolidation specifically during sleep but not during wakefulness.

Another possible solution is to focus on the effect of daytime sleep (i.e., napping) on learning and memory performance, as in this case training and testing occur at the same time in the nap and awake groups (Figure 1 conditions 9 and 10, respectively) <sup>56</sup>. Note, however, that daytime and nighttime sleep are not identical (e.g., they differ in the neuromodulatory influence of cortisol and growth hormone, the secretion of which is seen only during nocturnal sleep) and might affect memory differently <sup>57</sup>. In addition, daytime naps might largely vary across participants with regards to the duration, depth, and composition of sleep (e.g., onset of REM stage in some, but not all participants), which should be taken into account during analysis and interpretation of these studies. Thus, employing conditions that include: 1) a wake consolidation interval, 2) a daytime nap consolidation interval (with similar time-of-day training and testing), and, 3) a night of sleep, would provide the opportunity to directly compare the relative contributions of wake, nap and night of sleep, with partial control over time-of-day.

Besides controlling for circadian effects using additional groups/conditions, subjective sleepiness and objective vigilance before and after the encoding and testing sessions. These assessments offer valuable insight into participants' states and can be included as covariates in the analyses, or for participant exclusion based on extreme values. It is crucial to select reliable questionnaires/tasks, and a null effect with these assessments alone (i.e., without the inclusion of control groups/conditions discussed above) should not be used to dismiss an alternative explanation entirely, because null results could also be due to low statistical power (see below). Similarly, if there is no significant impact of the time of day on memory performance in control groups subjected to immediate tests, it may also be a result of insufficient statistical power. Therefore, the absence of a significant difference in performance between control groups tested in the morning and those tested in the evening does not conclusively prove the absence of circadian effects on performance, and every effort should be made to appropriately power the circadian control conditions as well as the Sleep/Wake conditions.

In conclusion, although none of the proposed solutions to address the potential caveat of circadian effects are ideal nor exhaustive, a combination of converging results across studies

employing additional control groups/conditions and questionnaires/tasks can accrue confidence in the conclusions regarding the effect of sleep on memory consolidation. At the same time, it is important to note that studies reporting null results when these control conditions/measurements are included should not take it as conclusive proof for the absence of circadian effects and dismiss alternative explanations (e.g., low statistical power).

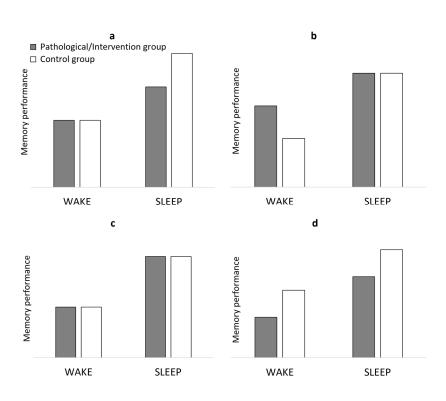
#### **Controls in sleep studies**

#### Controls in sleep pathology and intervention

Studies investigating the effect of sleep on memory consolidation sometimes compare experimental conditions across sleep intervals only. For example, studies in clinical populations with patients suffering from sleep disorders (e.g., primary insomnia, obstructive sleep apnea, sleep-disordered breathing) often compare a pathological group with a healthy control group and often use only an evening-morning sleep condition (Figure 1, condition 1) <sup>58,59</sup> (for reviews, see <sup>60,61</sup>). Importantly, however, if patients show a smaller benefit of the overnight period on performance compared to control participants, one cannot disentangle whether it is caused by the specific effect of that overnight sleep (i.e., state-dependent consolidation) or by a trait-dependent effect of sleep disturbances on memory processes (including encoding, retrieval, and consolidation), susceptibility to interference, or other aspects of cognition <sup>60,62-64</sup>. An additional issue is that pathologies can also influence circadian cycles <sup>65</sup>, thus, the time of peak performance may be shifted in such populations. Likewise, any of these issues need to be considered in aging populations, as aging impacts the prevalence of sleep disorders, cognitive performance, chronotype, and, in particular, memory functioning <sup>66,67</sup>.

Similarly, studies investigating sleep interventions (e.g., using pharmacological agents or electrical stimulation) typically only compare sleep conditions with vs. without intervention in an evening-morning design (Figure 1, condition 1). However, with this design, it cannot be ascertained whether any observed effects are sleep-specific or whether the intervention exerts general effects that are independent of sleep. To assess the specificity of sleep-related consolidation and sleep interventions, it is essential to include appropriate control groups/conditions in which participants stay awake for a comparable period and, in the case of intervention studies, also receive the same experimental manipulations as in the sleep groups/conditions. There are two main classes of wake controls in overnight studies: morning-evening (wake) controls (Figure 1, condition 2), and evening-morning (condition 1) or evening-evening (sleep deprived) controls (condition 6).

To demonstrate that a pathology (or an intervention) specifically affects sleep-related consolidation, a full Condition (Sleep vs. Wake) × Group (Pathology/Intervention vs. Control) design should be implemented, and the interaction should be significant (Figure 2, panels a and b). Instances of an incomplete design can be found in studies that do not include the Wake condition and only compare performance after sleep (among other examples). When no group difference is found in the Sleep condition, this can lead one to conclude that the groups do not differ with respect to sleep-related consolidation. This is the correct conclusion if the groups do not differ in the Wake conditions either (panel c). However, this conclusion is not supported if there is also a difference in the (unexamined) Wake condition (panel b). On the other hand, when a difference between the groups is found, an alternative interpretation can be that only the baseline performance is different in both groups (panel d), without any difference in the sleep-related consolidation (i.e., no interaction).



**Figure 2.** Schematic illustration of the necessity of the full Condition (Sleep vs. Wake) x Group (Pathology/Intervention vs. Control) design to show that a pathology (or intervention) affects sleep-related consolidation. The vertical axis represents memory performance during the testing/retrieval phase. Patterns depicted in panels a and b display cases where it can be concluded that the pathology or intervention specifically affects sleep-related memory consolidation (i.e., group-by-condition interaction), although the simple effect in the Sleep condition is different ins both panels. Patterns depicted in panels c and d display cases where it cannot be concluded that the pathology or intervention specifically affects sleep-related memory consolidation (i.e., no group-by-condition interaction) although again the simple effect in the Sleep condition is different in both panels. Note that in panels b and d, pathology, and intervention may have opposite effects (i.e., hindering or improving performance, respectively) compared to the control group, without changing the overall logic of the figure.

Depending on the aims of the study, a full Condition (Sleep vs. Wake) x Group (Pathology/Intervention vs. Control) design may not always be feasible. This type of design has been used in only a handful of studies. One study <sup>68</sup> compared the effect of evening-morning (Sleep) vs. morning-evening (Wake) conditions (Figure 1, conditions 1 and 2) on consolidation of non-declarative/procedural and declarative memory in participants with insomnia and healthy control participants. For procedural memory, similar retention over the morning-evening (Wake) interval was observed in both groups (condition 2). However, the healthy control group showed better retention over the evening-morning (sleep) interval (condition 1) than did the insomnia group. This pattern of differences corresponds to Figure 2 panel a. The authors concluded that insomnia specifically impairs sleep-related consolidation in procedural memory. Since declarative memory retention did not differ significantly between the two groups, either in the Wake or in the Sleep condition (although it showed a trend towards the same overall pattern as in Figure 2 panel a), no conclusion about the effect of insomnia on sleep-related consolidation of declarative memory could be drawn in this case.

Finally, if we consider the potential benefits of sleep compared to wakefulness in two 12-hour conditions (morning-evening and evening-morning), it is possible to interpret the observed differences in two ways: either a sleep benefit or a wake cost. Including 24-hour conditions that involve nighttime sleep would help decide between the two hypotheses: if sleep merely acts as a passive mechanism to protect against interference, then wakefulness after sleep should have an

equally detrimental effect as wakefulness before sleep. Consequently, performance in the two 24hour conditions should be similar. On the other hand, if sleep actively contributes to more resilient cognitive representations, then wakefulness after sleep should be less detrimental compared to wakefulness before sleep. As a result, we would expect to observe superior performance in the evening-evening (24 hours) condition compared to the morning-morning (24 hours) condition <sup>41,69,70</sup>.

#### Control conditions in napping studies

Napping studies typically compare performance changes following an interval that includes daytime sleep with an interval that includes sustained wake at the same time of day (Figure 1, conditions 9 and 10). Therefore, they allow control over circadian effects. The duration of naps varies greatly across studies, ranging from 6 minutes <sup>71</sup> and 40-90 minutes <sup>57,72,73</sup> or even 3 hours <sup>74–76</sup>. The naps in most such studies take place around noon <sup>57,73,77</sup>, but sometimes in the early morning <sup>78</sup> or at night <sup>72</sup>. Split-night designs have also been applied, with 3-hour sleep periods either during the first (SWS-rich) or second (REM-rich) halves of the night <sup>75,79,80</sup>.

Importantly, as mentioned above, naps differ substantially with respect to the composition of sleep stages and hormonal concentrations, depending on the time of day and the duration of the nap. Moreover, including wake controls at the same time of the day and of the same duration does not rule out the possibility that other factors than sleep *per se* affect memory consolidation. For example, the general concern that reducing external interferences during the post-learning interval may be sufficient to aid off-line consolidation also pertains to nap studies e.g., <sup>21,81</sup>. The length of actual sleep during a nap is also critical. The nap condition may include a significant amount of quiet rest depending on sleep latency. If this is the case, the two conditions of quiet rest and nap may overlap significantly, making comparisons difficult <sup>82</sup>.

There are several potential methods to ensure that conclusions drawn from nap studies are valid. Appropriate control conditions can be specifically designed to control for factors such as the timing, duration, and reduced sensory input of daytime naps. Attending to variables such as their timing and during allows, for example, comparing naps with and without REM sleep e.g., <sup>56,83</sup>. Second, adding a quiet rest condition (Figure 1, condition 11) helps to distinguish whether sleep is a specific state that actively contributes to memory consolidation or a non-specific state that only passively protects memories from interference <sup>41</sup>. Studies using such a design have led to mixed findings, with some studies showing better consolidation in the nap condition than in the quiet rest condition 74.84,85 and others showing that quiet rest produced effects on memory consolidation similar to those observed in nap conditions <sup>86,87</sup>, suggesting that sleep *per se* may not be necessary for consolidation but rather only provides a favorable environment. Observations that memory reactivation occurs not only during sleep but also during quiet rest e.g., <sup>88</sup> using fMRI further highlight the need for such control conditions. Therefore, monitoring the wake (quiet rest) condition with polysomnography is essential to rule out any sleep-like brain activity during the quiet rest interval, as well as to examine whether polysomnographic indicators during wake (quiet rest) are specifically associated with memory consolidation <sup>82</sup>.

Note that a quiet rest condition would also serve as a supplementary control condition in a classic overnight design (Figure 1, condition 1) in addition to the usual control conditions, such as morning-evening (Wake) or evening-morning with Sleep-deprived condition (Figure 1 conditions 2 and 5, respectively). However, this solution is not feasible since it would be extremely difficult to stay in quiet wakefulness for 12 hours in the morning-evening (Wake) condition and it would be even more difficult (and stressful) to avoid falling asleep in a quiet environment in the evening-morning (Sleep-deprived) condition. Therefore, overnight studies typically use an *active* wake evening-morning (Sleep-deprived; condition 5) control condition to control for circadian effects in their design.

Finally, few studies have included both an overnight sleep (condition 1), a daytime nap (condition 9), and a quiet rest (wake; condition 11) condition in a single experimental design to understand the specific effect of sleep on consolidation <sup>89,90</sup>. While this approach introduces its own set of challenges (e.g., the architecture of a nap and overnight sleep is not comparable), it can be

advantageous as it allows: the direct comparison of the relative benefit of an overnight sleep vs. a nap; a better control for time-of-day effects; and the examination of specific benefits of napping.

#### Controlling the intervals between encoding and sleep

The time interval between the learning task and sleep onset (Figure 1 condition 1) may vary across experiments, conditions, and individuals, potentially hindering the assessment of the true effect of sleep on memory consolidation. Although consolidation of procedural memory appears rather insensitive to such effects <sup>28</sup>, in declarative memory, the more time that elapses between the end of the learning task and sleep onset, the smaller the sleep-related memory benefit <sup>26</sup>. A longer wake interval before sleep onset may hinder the manifestation of the beneficial effect of sleep due to the participant's involvement in activities that may interfere with recently learned information by reengaging the same cognitive processes and/or recruiting the same neural networks.

Experiments should control the duration of the interval between memory encoding and bedtime/sleep onset, as well as the participants' activities during this interval. To minimize interference during this interval, participants should go to bed as soon as possible after memory encoding. Such designs are more feasible when participants sleep in the lab during the experiment. If, however, participants sleep at home after the learning session, then mobile actigraphy or, as less-compelling substitutes, sleep diaries and post-experiment questionnaires, should be employed to assess the duration of this interval and the activities performed. This information then should be appropriately considered in data analysis.

#### II. Task characteristics and measurements

In this section, we will discuss various task characteristics and measurements that need to be taken into account when studying the impact of sleep on declarative and non-declarative memory (see also Box 1 detailing the issue of task complexity).

#### Box 1 | Addressing the issue of task complexity

A further challenge that affects sleep and memory research, as well as cognitive neuroscience and psychology in general, is that practically every task involves multiple cognitive processes e.g., <sup>146,147</sup>. Learning/memory scores used to assess behavioral performances reflect a mixture of these processes <sup>148</sup>. As learning progresses, these processes improve and contribute to performance variably. Consolidation affects task-related processes e.g., <sup>11,28,149,150</sup>, further complicated by individual differences.

Different types of learning and cognitive processes, as well as different retrieval processes, influence the effects of sleep on memory. Declarative memory paradigms assess recall (retrieval with or without a cue) and recognition (identifying prior stimulus encounters) <sup>18</sup>. Evidence suggests that sleep may enhance recall more than recognition by integrating new memories into existing knowledge networks, potentially increasing recall pathways. <sup>18</sup>. Procedural memory tasks also vary in their reliance on explicit (conscious) or implicit (unconscious) aspects of acquired knowledge e.g., <sup>151,152</sup>, leading to diverse findings and potentially obscuring the impact of sleep on different knowledge aspects.

Another important consideration is the interaction between different memory systems, such as declarative and procedural memory, during both learning and consolidation processes <sup>153</sup>. However, researchers sometimes include memory tasks that tap into different memory systems in a single experiment to optimize resource utilization. This practice may introduce interference in memory consolidation and potentially complicate the interpretation of post-learning sleep effects. For instance, studies have demonstrated that acquiring procedural memories immediately after a declarative memory task can be influenced by participants' memory performance in the preceding task, causing consolidation differences between wake and sleep conditions<sup>154</sup>.

We recommend using tasks and designs that disentangle the different cognitive processes in a task and assess their varying effects on sleep. For example, in declarative memory tasks, comparing

different retrieval aspects (free recall, cued recall, recognition) within the same design reveal potential variations in sleep effects. These effects may also vary depending on the type of information to be encoded, such as paired-associates learning <sup>76,155</sup>, word-list learning <sup>116,156</sup>, emotional picture learning <sup>57,157</sup> and object-location memory <sup>99,158</sup>, indicating partially distinct cognitive processes.

Contrasting the encoding (or /consolidation) of different information types within the same design is warranted. For procedural learning/memory, research has disentangled allocentric vs. egocentric representations <sup>159</sup>, perceptual vs. motor components of learning <sup>52</sup>, transition vs. ordinal representations <sup>160</sup>, and acquisition of statistical vs. sequential regularities <sup>87</sup>. Different sleep effects have been observed in some of these aspects <sup>148,160,161</sup>. To minimize confounding interactions between memory systems and identify sleep effects, administer tasks tapping into different memory systems using a between-participant design. Alternatively, in a within-participant design, counterbalance task administration order and treat it as a separate factor in data analysis.

#### Baseline measures and feedback

When designing a declarative memory paradigm, a critical question is what procedure to use to ensure that participants are exposed to a sufficient number of items for a later reliable and valid test of retrieval performance. In most sleep-related declarative memory studies that use cued or free recall, a certain learning criterion is defined, for instance, 60% of recall success. (Other methods involve restrictions of study time e.g., <sup>71</sup>, or a fixed number of trials e.g., <sup>91</sup>). If the learning criterion is not met after the first run of trials, a common strategy is to repeat the whole run, until the learning criterion is met e.g., <sup>92,93</sup>. Most researchers investigating sleep-related consolidation of declarative memory choose a learning criterion between 40% and 80% e.g., <sup>94,95</sup>, with a 60%-criterion often used for word-pair learning or visuospatial learning tasks e.g., <sup>69,92,93,96-99</sup>. Overall, based on these studies, the 60% learning criterion seems to be a reasonable choice to account for possible floor and ceiling effects.

An advantage of this procedure is that all participants encode a sufficient number of items for later retrieval testing. However, participants who needed several repetitions to meet the criterion are exposed to all items multiple times compared to those who met the criterion after the first presentation. These differences in repetitions could impact retrieval performance <sup>100–102</sup>. This effect deserves even more consideration in studies comparing different populations (e.g., healthy participants vs. patients, or children vs. adults) that presumably learn at a different pace.

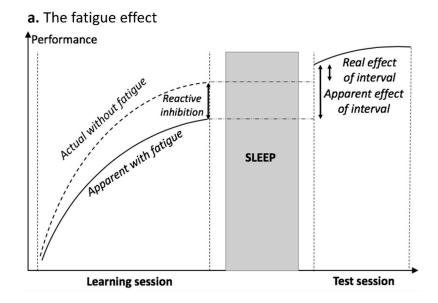
Another issue that arises in declarative memory paradigms is that the performance level observed during the last run of the learning phase (i.e., just when the learning criterion is met) is frequently used as a baseline measurement to evaluate recall performance after the retention interval. However, learning phase trials are often designed to give direct feedback, often in the form of providing the correct answer after each item, potentially resulting in further, unmeasured encoding. Therefore, the baseline measurement may not accurately reflect the exact memory state at the end of the learning phase, but rather probably underestimates it in such cases <sup>103–106</sup>.

An option to circumvent the use of a predefined learning criterion is the so-called selective reminding procedure <sup>107</sup>. All items are presented to the participant during a first study cycle. Subsequently, a first test run (with or without feedback) is conducted where all items are tested. In a second study cycle, only those items that were not recalled correctly during the first test cycle are presented. These runs continue until all items are recalled correctly once. This procedure enables all participants to encode the same number of items while no item is 'over-learned' for example, see <sup>108–110</sup>. This procedure could be used to reach 100% for the baseline level in all participants. However, one limitation of this 100% learning criterion approach is, that it is only suitable for those memory studies where a loss in declarative memory is expected over the retention interval. In other cases, using the selective reminding procedure with a lower predefined learning criterion (e.g., 60%) could ensure that there are no over-learned items while avoiding potential floor and ceiling effects.

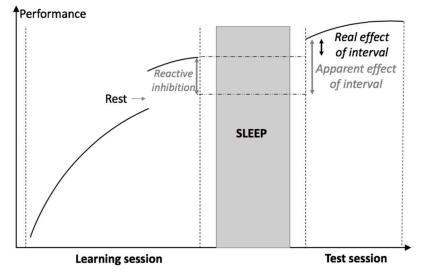
#### Fatigue effects in repetitive tasks

Some learning and memory paradigms involve continuous practice with a series of repetitions of the same action, such as pressing keys <sup>111</sup>. Learning is measured as the improvement in accuracy or in reaction times as the task progresses. Usually, the performance at the end of the training session serves as a baseline to measure improvement at the test session that takes place after an interval involving sleep or wakefulness. Yet, after a certain amount of time spent performing the task, the participant's observed improvement is less marked, which can be interpreted as a reactive inhibition effect that reflects the build-up of fatigue over the trials e.g., <sup>32,112</sup>. This effect often results in smaller improvement or even a decrease in performance as the task progresses. Thus, the measured performance after longer/extended practice is not representative of the level of expertise gained in the task and, therefore, comparing the performance at the test session with that of the end of the training session may lead to illusory sleep-related improvement and may also bias the quantification of the sleep benefit.

Figure 3 panel illustrates this issue, which can be even further exacerbated by averaging performance measures across multiple trials, instead of using trial-by-trial analysis. In several cases, after eliminating the reactive inhibition effect by releasing the presumed fatigue, the sleep-related off-line improvement was no longer observed e.g., <sup>113,114</sup>. Rather than an actual performance improvement, after the elimination of the reactive inhibition effect, the benefit of sleep was expressed as a stabilization of performance <sup>113,115</sup>. Although this issue is primarily relevant in procedural learning studies, reactive inhibition might also affect performance in declarative memory studies, particularly if they include repetitive presentations of the same items or a long period of memorization <sup>116</sup>.



**b.** The short-rest solution to the fatigue effect



c. The spaced-practice solution to the fatigue effect

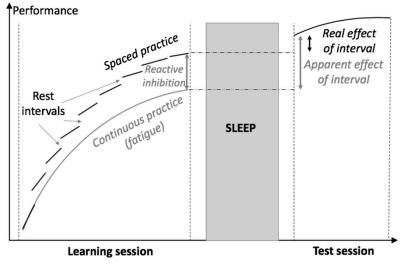


Figure 3. The fatigue effect may lead to overestimating interval-related (offline) improvement (panel a) and two solutions for this problem (panel b and c). Performance at the end of the learning session is often compared to that at the beginning of the test session to quantify sleep-related benefits for

consolidation. Panel a. illustrates that performance during learning may be hindered by fatigue (reactive inhibition leads to slower reaction times) and therefore does not accurately reflect actual learning. Panel b illustrates how a short rest interval introduced before the end of the learning session could restore learning performance. Panel c illustrates how introducing rest intervals during learning (i.e., spaced practice) could also help measure performance more accurately.

Resting for a few minutes after the training session appears to be sufficient to 'wash out' the effect of reactive inhibition on performance. Measuring performance after a break is therefore a more appropriate baseline to assess subsequent off-line consolidation e.g., <sup>87,112</sup>. Figure 3 panel b illustrates this solution. Moreover, the use of short (e.g., 10 s) performance intervals between longer (e.g., 30 s) rest intervals during the training session (often termed spaced practice) can also impede the accumulation of reactive inhibition compared to experimental designs that use massed practice in which there are longer task intervals e.g., <sup>112,113,117</sup>. Figure 3c illustrates this solution.

Other solutions to reactive inhibition involve the use of curve-fitting methods and computational modeling in data analysis. Here we highlight two curve-fitting methods. First, a function-based model (e.g., a power function for reaction time improvement) can be fitted to the training session data and used to predict future performance (under the null hypothesis that the delay between training and test sessions has no effect on performance). This method enables a comparison between the predicted (under H<sub>0</sub>) and the actual outcomes measured during the test session. This way, one avoids averaging over data points to compute a pre-post gain—a procedure that may yield illusory off-line performance gains if performance improves between the end of the training session and the beginning of the test session, wherein the data averaging is done <sup>32</sup>. As a second and more formal approach, a function can be fitted to the training and test session data and then a continuity test can be used to infer whether the performance is a simple continuation of that function from the training session to the test session, or whether there is an abrupt change between the sessions (see details on these approaches in <sup>32</sup>).

Using computational models on trial-by-trial data can also help overcome the issue of fatigue by directly including reactive inhibition as a separate parameter in the model. For instance, in a probabilistic sequence learning task, one study <sup>118</sup> used such a model to enable the estimation of the actual magnitude of learning, independent of the effect of reactive inhibition. Such models can be used in a wide range of learning and memory tasks, including finger tapping and other sequence learning tasks.

#### **III.** Data analysis practices

Studies of sleep and memory encounter comparable challenges as the whole field of psychology and neuroscience, which has been discussed in recent years under the umbrella term of the 'replication crisis' <sup>119–121</sup>. Consequently, these studies could likewise gain from embracing the evolving practices that are currently being adopted within the scientific community at large (see e.g., <sup>122</sup> about publication bias in sleep and motor sequence learning literature). This ongoing reassessment of research practices seeks to address issues such as inadequate sample size and low statistical power, inadequate control for multiple comparisons that might result in exaggerating the importance of spurious correlations, and the lack of consideration for individual differences.

#### Statistical power

Studies of sleep-related consolidation have typically used samples with 12-20 participants per group e.g., <sup>26,122,123</sup>, or in some cases even smaller samples e.g., <sup>124</sup>. This may be due to complicated or demanding study designs, difficulties recruiting clinical populations, and/or drop-outs of participants (i.e., experimental attrition). Moreover, sample sizes have usually not been determined by *a priori* power analyses based on expected effect sizes. Importantly, small sample sizes could result in low statistical power, potentially increasing Type 2 errors (i.e., not detecting an existing effect), as well as non-replicable, spurious findings. For instance, a recent meta-analysis on the relationship

between sleep deprivation and memory reveals that studies conducted in this area suffer from a severe lack of statistical power<sup>125</sup>. On average, the statistical power in studies investigating the impact of sleep deprivation on learning prior to sleep has been found to be as low as 14%. Even in other experimental approaches, the power is very often below the optimal level of around 80% <sup>125,126</sup>. By contrast, a common but questionable practice of collecting additional data until a significant effect is reached could increase Type 1 errors (i.e., detecting an effect that does not exist), again, leading to non-replicable findings.

Another issue that arises from underpowered studies is the interpretation of non-significant findings or statistical trends. For example, non-significant effects could be observed in pre-sleep vs. post-sleep comparisons when consolidation results in stabilization of the acquired knowledge without forgetting or off-line performance improvement (i.e., no performance change). Drawing conclusions regarding whether sleep promotes the stabilization of acquired knowledge or has no effect on certain aspects of memory consolidation compared to wakefulness cannot be based solely on non-significant results obtained through classical statistical approaches (e.g., frequentist t-test, ANOVA, correlation, etc.). In order to make such determinations, it is imperative to assess whether our study possesses sufficient statistical power.

As is the case for any and all research using inferential statistics to test hypotheses, *a priori* power analyses before data collection are necessary, as well as Bayesian statistical approaches during and after data collection. It has long been recommended in guidelines (e.g., published by the American Psychological Association <sup>127</sup>) that experimenters should determine the sample size before starting the experiment by computing power analyses based on the expected effect size estimated or found in previous studies that observed similar effects.

For particularly costly experimental protocols, Bayesian statistical analyses <sup>128–131</sup> computed in the course of data collection can be used to determine whether there is enough evidence in favor of a given a priori defined effect so that one can stop data collection <sup>132,133</sup>; however, such analyses are rarely reported in the field of sleep-related memory consolidation (although see <sup>134</sup> for an exception) whereas they are increasingly reported in other areas of psychology and neuroscience. Additionally, effect sizes should be clearly reported to provide an estimate of the magnitude of the observed effect <sup>135</sup>. Hence, the utilization of a priori power analysis, Bayesian analyses, and the reporting of effect sizes enable a more nuanced and quantitative assessment of the impact of sleep on memory consolidation.

#### Spurious correlations

Beyond the comparison of groups or conditions, conclusions about the effect of sleep are often based on correlations between behavioral performance and sleep polysomnographic parameters e.g., <sup>87,136</sup> (see also the next subsection). However, inadequate statistical practices can lead to spurious correlations being identified e.g., 32,33,39,137. For instance, polysomnography provides a wealth of parameter combinations, including different spindle parameters (absolute/relative number, amplitude, length, activity) at different frequencies (slow/fast) at different scalp regions/electrodes during different sleep stages and different fractions of the night. This can result in an inflated 'researcher's degrees of freedom', as the multiplicative nature of these parameters can quickly result in hundreds of possible combinations. For example, consider that in studies utilizing polysomnography, a minimum of five correlation tests are typically conducted. These tests investigate the association between memory performance and each sleep stage, along with total sleep time. Unfortunately, these studies often fail to correct for multiple comparisons. With only five tests the probability of Type I error increases to 23% ((1-0.5)^5), and we must stress that many studies perform even more comparisons without necessarily reporting all of them. Thus, investigators need to be parsimonious in their approach, both in terms of the number of statistical tests they need to employ to test their research hypotheses, but, also to ensure that they are either following a welljustified and systematic exploratory approach or have made strong apriori hypotheses in these cases.

When dealing with small sample sizes, it is crucial to recognize that effect size estimates tend to be less precise. Consequently, correlations that were previously reported may fail to be replicated when larger sample sizes are employed due to the increased precision of the effect size measurements <sup>137</sup>. For example, between sleep parameters and episodic memory consolidation, one study <sup>138</sup> did not find any significant correlation in a large sample of 929 participants. The correlations to be computed should be planned *a priori* (see also Box 2) and corrected for multiple comparisons to avoid increases in Type 1 errors <sup>139</sup>. Non-significant planned correlations should also be systematically reported <sup>140</sup>. If no relationship is expected between certain sleep parameters and behavioral performance, Bayesian approaches should be used to draw conclusions in favor of the null hypothesis instead of (or in addition to) reporting non-significant p-values (see previous subsection).

#### **Box 2** | Open science practices

Other fields of cognitive neuroscience and psychology using techniques such as fMRI have engaged in open science initiatives by, for example, depositing raw data in open-access databases (e.g., OpenfMRI <sup>162</sup>), which have recently been extended to other neuroimaging and electrophysiological methods such as EEG (OpenNEURO <sup>163</sup>). However, sleep and memory research lags in adopting open science practices <sup>164</sup>, despite positive examples emerging <sup>165–167</sup>. Research transparency is further hindered by the lack of pre-registration of the studies on sleep and memory (but see <sup>168</sup> for an exception).

#### Data deposition

Publicly available data enables re-analysis using new techniques. For example, For example, recent studies identified two REM microstate types (tonic vs. phasic), each with different characteristics <sup>169,170</sup>. Access to previous sleep EEG datasets would enable testing the role of REM microstructure in memory consolidation. Open databases facilitate re-analysis and meta-analyses, addressing non-significant results and spurious findings. To maximize the benefits of previous research in the scientific community, sleep researchers should embrace open science <sup>171</sup> and make data publicly available. Platforms like Open Science Framework <sup>172</sup>, OpenNeuro.org <sup>163</sup>, Scientific Data, or sleepdata.org offer repositories. Developing a specific open database for sleep research with EEG, polysomnographic and behavioral data would further benefit this field.

#### **Pre-registration**

Another way of increasing transparency of research is to pre-register studies before data collection <sup>173,174</sup>. Pre-registration includes the specification of the research question, experimental design, participant population, sample size and planned analysis methods. Pre-registration is already the gold standard in many fields of research, including for clinical trials in medical research <sup>175,176</sup>. The neuroscience and psychology fields increasingly recognize the importance of pre-registration as well. Yet, this option has been largely neglected in sleep and memory research so far.

Studies can be pre-registered in different ways. One option is pre-registration in independent online registries like the Open Science Framework or ClinicalTrials.gov. In these registries, researchers provide a detailed description of their planned study that can be accessed by other researchers as well as journal editors and reviewers to determine whether the pre-specified plan was followed adequately. Another option is to write a registered report, which is a novel publication type offered by an increasing number of journals (e.g., Plos Biology, eLife, eNeuro, Nature Human Behaviour, Cortex). A registered report usually undergoes two stages of peer review, first before data collection to determine the appropriateness of the research plan and methodology, and then after data collection covering the full research report including the results. If the first round of peer review is successful, the authors are typically offered 'in principle acceptance' by the journal, allowing the results to be published irrespective of the actual findings.

Both procedures, pre-registration in online registries and registered reports, increase the quality of research by reducing inappropriate data analysis practices, including p-hacking, HARKing

(hypothesizing after the results are known), and the application of unplanned statistical tests <sup>175–177</sup>. Additionally, registered reports could also reduce the file-drawer problem because the study, irrespective of finding significant or non-significant results, could be published in the target journal.

#### Controlling for individual differences in general cognitive abilities

Certain features of sleep (e.g., sleep spindles) appear to be highly correlated with trait-like individual differences in cognitive abilities. Particularly strong relationships have been identified for cognitive abilities related to reasoning, problem-solving, the ability to identify complex patterns and relationships, and the use of logic (i.e., 'fluid intelligence') <sup>141–145</sup>. Since these cognitive abilities are associated with certain features of sleep and with memory functions, they may confound the associations revealed between sleep and memory consolidation. Therefore, when the specific effect of sleep on memory consolidation is tested, associations between sleep (e.g., spindles) and these cognitive abilities (e.g., intelligence) should be controlled for.

The problem of disentangling individual differences in the associations between sleep and general cognitive abilities from the associations between sleep and memory can be addressed by at least two ways. First, one can employ neurocognitive assessments (e.g., intelligence testing) and include these scores as covariates to statistically control for possible confounding effects when testing the specific associations between sleep and memory consolidation. Second, a comparable baseline night of sleep together with an appropriate control task can be included in the study design. This control task should be comparable to the experimental task without engaging the specific targeted processes that are the focus of sleep-related memory consolidation. Comparing the two experimental conditions can reveal the specific effect of sleep on the memory process of interest.

#### Conclusion

In this article, we have highlighted three sets of critical methodological issues that impede research in the field of sleep and memory, and offered solutions to avoid or address them (Table 1). It is important to note that all scientific disciplines may suffer from similar issues. Research on the relationship between sleep and memory is still quite fortunate in this respect, as the field benefits from a large number of studies contributing to replication efforts and converging evidence for any particular research question. However, there is still a need to refine aspects of the methodology to ensure that appropriate controls, measurements, and data analysis practices are employed for probing the specific effect of sleep on memory. We believe that implementing the solutions presented here will lead to results with higher validity and reliability, and significantly advance our understanding of the complex relationship between sleep and memory research but also in other fields of psychology and neuroscience, applying these solutions where appropriate could benefit the broader scientific community as well. Implementing these solutions is undoubtedly challenging: it can increase the duration and cost of research. Adopting the practices above will help advance the field in the long term.

Table 1. Summar	y of issues in slee	p-memory research	n and prop	oosed solutions.

Wider issues	Specific issues	Solutions
Non-optimal experimental	Time-of-day (circadian)	Using multiple control conditions in
designs may lead to	effects	addition to the morning-evening vs.
inaccurate conclusions due to		evening-morning design. These
confounding variables		could include morning alone,
		evening alone, evening-morning
		and evening-evening with sleep-
		deprived (with and without
		recovery sleep) control conditions.

17	

		Napping conditions. Assessing sleepiness and vigilance.
	Controls in sleep (pathology and intervention studies)	Including a morning-evening condition and/or an evening- morning sleep deprivation condition. Including a control group.
	Controls in napping studies	Considering time of day and duration of nap. Including a quiet-wake control condition. Monitoring the nap with polysomnography.
	Controlling the interval between memory encoding and sleep onset	Controlling for duration of and participant's activity during the interval between end of task and sleep. Monitoring the activities during the interval with actigraphy and/or questionnaires.
Task characteristics and measurements	Baseline measurements and feedback effects (declarative memory)	Using a selective reminding procedure, possibly combined with a predefined learning criterion.
	Fatigue effect in repetitive non- declarative memory tasks may lead to a spurious beneficial effect of sleep by negatively affecting performance after a longer practice	Using appropriate experimental designs, e.g., including post-rest performance at the end of the training session as a baseline, and promoting learning through spaced rather than massed practice. Using appropriate data analysis methods, such as curve fitting and computational modeling.
Inappropriate data analysis practices, including use of small sample sizes and inappropriate analyses/reporting, may lead to spurious correlations and incorrect conclusions.	Small sample size and low statistical power	Determining the required sample size a priori. Using Bayesian analyses to decide when to stop data collection. Reporting Bayes Factors and effect sizes.
	Spurious correlations between sleep parameters and memory consolidation	Planning correlation analyses of interest in advance, correcting for multiple comparisons, and reporting non-significant planned comparisons.
	Not controlling for individual differences in general cognitive abilities in correlational studies of sleep and memory	Including neurocognitive assessments of general cognitive abilities as covariates. Including a baseline night of sleep with an appropriate control task.

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