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Original Article

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Advantage conferred by overnight sleep on schema-related memory may last only a day

Hosein Aghayan Golkashani, Shohreh Ghorbani, Ruth L.F. Leong, Ju Lynn Ong, Michael W.L. Chee*

Centre for Sleep and Cognition, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

*Corresponding author. Michael W.L. Chee, Centre for Sleep and Cognition, Yong Loo Lin School of Medicine, MD1 Level 13 Rm 05B, National University of Singapore, 117549, Singapore. E-mail: michael.chee@nus.edu.sg.

Abstract

Study Objectives: Sleep contributes to declarative memory consolidation. Independently, schemas benefit memory. Here we investigated how sleep compared with active wake benefits schema consolidation 12 and 24 hours after initial learning.

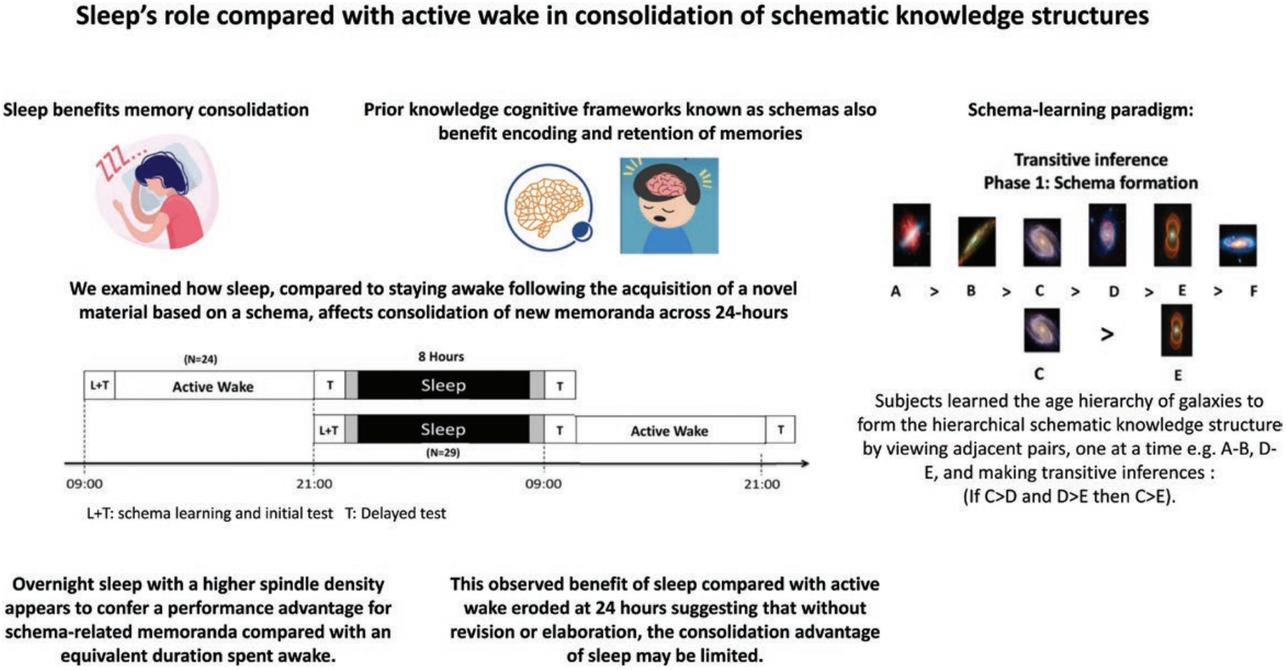
Methods: Fifty-three adolescents (age: 15–19 years) randomly assigned into sleep and active wake groups participated in a schema-learning protocol based on transitive inference (i.e. If B > C and C > D then B > D). Participants were tested immediately after learning and following 12-, and 24-hour intervals of wake or sleep for both the adjacent (e.g. B–C, C–D; relational memory) and inference pairs: (e.g.: B–D, B–E, and C–E). Memory performance following the respective 12- and 24-hour intervals were analyzed using a mixed ANOVA with schema (schema, no-schema) as the within-participant factor, and condition (sleep, wake) as the between-participant factor.

Results: Twelve hours after learning, there were significant main effects of condition (sleep, wake) and schema, as well as a significant interaction, whereby schema-related memory was significantly better in the sleep condition compared to wake. Higher sleep spindle density was most consistently associated with greater overnight schema-related memory benefit. After 24 hours, the memory advantage of initial sleep was diminished.

Conclusions: Overnight sleep preferentially benefits schema-related memory consolidation following initial learning compared with active wake, but this advantage may be eroded after a subsequent night of sleep. This is possibly due to delayed consolidation that might occur during subsequent sleep opportunities in the wake group.

Clinical Trial Information: Name: Investigating Preferred Nap Schedules for Adolescents (NFS5) URL: https://clinicaltrials.gov/ct2/show/NCT04044885. Registration: NCT04044885

Graphical Abstract



Sleep's role compared with active wake in consolidation of schematic knowledge structures

Sleep benefits memory consolidation

Prior knowledge cognitive frameworks known as schemas also benefit encoding and retention of memories

Schema-learning paradigm:

Transitive inference
Phase 1: Schema formation

We examined how sleep, compared to staying awake following the acquisition of a novel material based on a schema, affects consolidation of new memoranda across 24-hours

Subjects learned the age hierarchy of galaxies to form the hierarchical schematic knowledge structure by viewing adjacent pairs, one at a time e.g. A-B, D-E, and making transitive inferences : (If C>D and D>E then C>E).

Overnight sleep with a higher spindle density appears to confer a performance advantage for schema-related memoranda compared with an equivalent duration spent awake.

This observed benefit of sleep compared with active wake eroded at 24 hours suggesting that without revision or elaboration, the consolidation advantage of sleep may be limited.

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Participants learned the age hierarchy of galaxies by viewing adjacent pairs, one at a time e.g. A-B, D-E, and making transitive inferences : (If C>D and D>E then C>E).

Once this schema was learned to criterion, participants learned two new sets of galaxies: one set comprised galaxies from the schema and new, intercalated galaxies; the other contained unfamiliar galaxies (schema and no-schema conditions).

Key words: sleep; memory consolidation; schema; spindles

Statement of Significance

By comparing two groups of participants who were tasked with learning the order of a novel picture sequence as a schematic knowledge structure, we found that overnight sleep, particularly if it had higher spindle density, was associated with superior memory consolidation 12 hours after learning compared with a group who remained awake for an equivalent duration. With or without overnight sleep, we found that having a prior framework (schema) to assist the retention of new memoranda benefited performance. Sleep conferred a larger benefit to memoranda acquired with a schema. However, at 24 hours post-learning, the sleep advantage diminished, suggesting that over time memory consolidation may be less dependent on immediate post-learning sleep.

Introduction

Numerous animal and human studies support the proposition that sleep facilitates memory consolidation [1–4]. Additionally, sleep benefits the generalization of recently acquired memoranda, enabling the abstraction of commonalities among overlapping memory traces [5–7] to form gist-like representations [8–11]. This system consolidation goes beyond the passive protection against forgetting [12], and could bring about insights [13], promote structural generalization and analogical transfer in problem-solving [6], as well as enable one to draw inferences beyond what is directly learned [13–15]. It has been proposed that this process is driven by slow oscillations coupled with sleep spindles such that these enable memories to stabilize, reorganize, and in some cases, get boosted [3]. It is currently thought that these brain oscillations facilitate a gradual transformation of memories, moving them from the hippocampus to neocortical structures [16, 17].

Existing studies have established that the encoding, consolidation, and retrieval of newly acquired information is also impacted by its relationship to existing cognitive frameworks, or schemas [18–21]. Schema-driven memory benefits have been evaluated in several contexts, yet the role of sleep in formation and consolidation of schematic knowledge structures has been less explored with many outstanding questions. For example, how schematic memories are processed during sleep, and whether sleep preferentially facilitates consolidation of schema-related memoranda.

In an earlier study, a schema-learning protocol where participants learned facts found that higher sleep spindle density was linked to reduced decay of schema-related memories. This in turn was associated with increased disengagement of the hippocampus across a 24-hour retention interval implying neocortical transfer of the learned material [22]. In another study using a schema based on tones, schema-congruent memories were reported to be preferentially consolidated during rapid-eye movement (REM) sleep [23]. While a third study reported no preferential benefits of sleep to schema-conformant memories [24]. These discrepancies could have stemmed from use of different methodologies and experiments with small sample sizes. Importantly, lack of an active wake control, not examining the extent to which these observed benefits are specific to sleep, and uncertainty over the persistence of memory benefits, warrant further investigation. How sleep macrostructure and microstructure assist in the consolidation of schemas is also unclear [25].

Here we examined if there was an advantage of sleep over active–wake for schema-related memory integration and facilitation of inference. We used a schema-based learning paradigm based on transitive inference [26]. Adolescents were studied in view of the growing problem of inadequate sleep in this demographic, as well as the importance of learning and memory for their future success. Participants were randomly assigned to either sleep ($n = 29$) or active wake ($n = 24$) groups for 24 hours, and their memory performance was tested after 12- and 24-hour intervals. We hypothesized that sleep would preferentially benefit schema-driven memory integration and inference, and that gains would be correlated with the spindle density and amount of post-learning slow-wave sleep.

Methods

Participants

In this study, 57 healthy adolescents aged 15–19 years (29 males, $M = 16.43$, $SD = 1.03$ years) with no history of sleep disorders, meeting the eligibility criteria were included from an initial pool of 126 students recruited from various schools in Singapore. Participants were excluded if they had any known psychiatric conditions, a BMI ≥ 30, a history of smoking, or consumed over two cups of caffeinated beverages daily. Habitual short sleepers, as determined by actigraphy (time in bed less than 6 hours on weekdays and sleep extension less than 1 hour on weekends), were also excluded. Moreover, participants were prohibited from traveling across two time zones one month before the study. The complete study protocol is detailed elsewhere [27]. Four participants dropped out due to illness or personal reasons during the initial three nights before the main experiment, leaving a final sample of 53 who were randomly assigned to sleep ($n = 29$) and wake groups ($n = 24$). No significant differences were observed in the baseline demographic characteristics and regular sleep patterns between the two intervention groups (Table 1).

The National University of Singapore Institutional Review Board approved this study. Informed consent was obtained from all participants and legal guardians. The study was officially registered as a clinical trial (https://clinicaltrials.gov/ct2/show/NCT04044885)(https://clinicaltrials.gov/ct2/show/NCT04044885).

Study protocol

Participants were randomly allocated to either the sleep or active wake groups. Participants completed phase 1 to learn the schema

Table 1. Characteristics of Wake and Sleep Groups

	Sleep group		Wake group	
	Mean	**SD**	**Mean**	**SD**
N	29	—	24	—
Age (Years)	16.18	0.88	16.72	1.16
Gender (% Male)	48.28	—	45.83	—
Body Mass Index	20.49	3.08	20.17	3.13
Daily Caffeine Intake (Cups)	0.72	1.00	0.63	0.82
Morningness–Eveningness Questionnaire	49.45	6.18	48.83	6.80
Epworth Sleepiness Scale	7.66	3.04	7.42	3.09
Chronic Sleep Reduction Questionnaire	36.59	4.04	37.00	5.23
Pittsburgh Sleep Quality Index				
Weekday TIB (H)	7.59	1.38	7.36	1.16
Weekend TIB (H)	8.52	1.32	9.10	1.32
Weekday TST (H)	6.62	1.00	6.87	1.22
Weekend TST (H)	8.43	1.25	8.78	2.19
Nap TST (Min)	42.59	53.71	58.54	60.00
Global Score	4.48	1.70	4.22	1.24
Actigraphy				
Weekday TIB (H)	7.21	0.74	7.22	0.85
Weekend TIB (H)	8.36	1.04	8.40	1.17
Weekday TIB (H)	5.73	0.65	5.74	0.84
Weekend TIB (H)	6.65	0.94	6.74	1.26
Average TIB (H)	5.97	0.58	5.98	0.78
SE (%)	79.45	6.10	79.85	6.87

TIB = Time in bed; TST = total sleep time; SE = sleep efficiency. No significant differences observed contrasting the two groups using independent *t*-tests and Chi-squared tests.

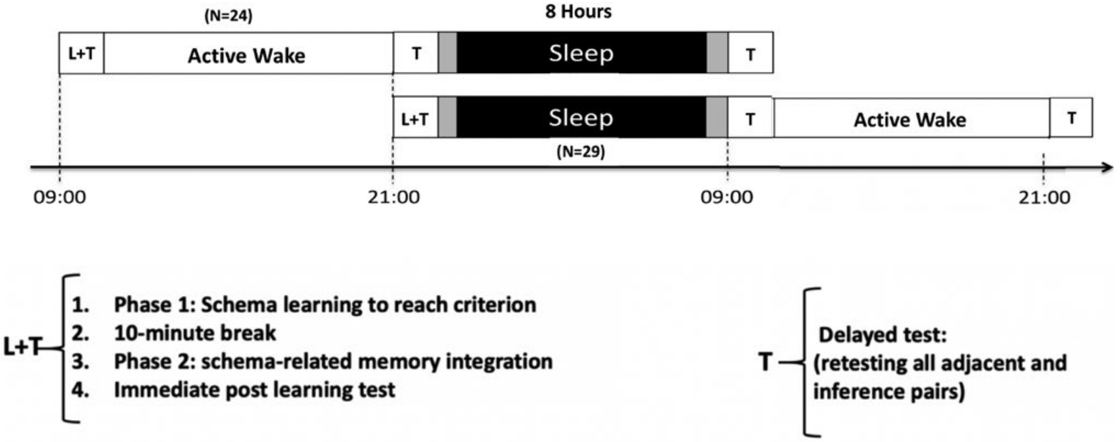

Figure 1. Schematic of the protocol: participants were randomly assigned to the sleep and active wake groups. Participants undertook phase 1 to learn the schema. Following a 10-minute break they were required to complete learning blocks associated with phase 2 where they learned a schema-related hierarchy (schema set) as well as a separate novel hierarchy (no-schema set). They were tested after a 12-hour (sleep–wake) interval, followed by a second test 24 hours after initial encoding session. Sleep was monitored using both actigraphy and polysomnography (PSG). L + T: schema learning and immediate test T: delayed test

then following a 10-minute break they completed learning blocks of phase 2 to learn the schema-related as well as the novel hierarchy. They were tested after a 12-hour (sleep–wake) interval, followed by a second test 24 hours after initial encoding session. Sleep was monitored using both polysomnography (PSG) and actigraphy (Figure 1).

Schema-learning paradigm

Despite decades of research and the recent renewed interest in the neuroscience community to study frameworks of organized information, there seems to be no consensus on what qualifies a schema. This has contributed to heterogeneity in the literature. It has been proposed that a working definition of schemas include “overlapping, organized knowledge representations” that have the following three features: benefiting memory performance; having a dynamic and adaptable nature when challenged by incongruent novel items, and facilitating novel inferences generalizing over what is directly learned [28]. A schema-based learning paradigm based on transitive inference was utilized in the current study [26] that included these essential features. This paradigm has been used in prior works [29–31].

The main paradigm consisted of two main phases as illustrated in Figure 2 and described in detail below. We included active feedback as explicit reinforcement across the learning blocks, as some studies have demonstrated that explicit reinforcement during learning is an essential factor in sleep-dependent benefits to transitive inference [15]. The main paradigm consisted of three main phases as shown in Figure 2 and explained in detail below.

Overview of the protocol

Initial schema formation consisted of two parts with a 10-minute break interval: (phase 1) to form the initial schema followed by (phase 2): schema-related memory integration and learning the no-schema condition. After finishing phase 2, participants underwent immediate and delayed test sessions following 12 hours containing sleep–active wake, and a final test 24 hours after the initial encoding (Figure 1).

Phase1: learning the schema to criterion

Participants were required to learn the correct order of items in a 7-item set related to an age hierarchy of galaxies. The learning process involved trial and error along with active feedback, alternating between learning and testing blocks, until participants achieved a criterion of over 85% accuracy. During the learning blocks, participants were shown two adjacent galaxies in the hierarchy (B–C, F–E, A–B, D–C, etc.) for 3 seconds and were asked: “Which galaxy is older?.” Participants were encouraged to actively engage in learning and provide responses. The correct answer was highlighted in green, irrespective of whether they responded or not. Non-adjacent pairs (B–D, C–E, B–E, etc.) were not presented during learning.

Every learning block was succeeded by a corresponding test block where participants were shown a pair of galaxies and indicated which item was older. They were shown learned adjacent pairs as well as non-adjacent items (inference pairs) that had not been encountered during learning (Figure 2A–B). No feedback was given. To correctly answer these questions, participants made transitive inferences (i.e. if $A > B$ and $B > C$ then $A > C$). This phase was concluded once 85% accuracy was reached. Based on pilot experiments and prior work we provisioned for a maximum of 20 learning and testing blocks to attain 85% accuracy. On average about 10 learning blocks were needed to reach the criterion ($M = 9.6$, $SD = 3.9$).

Phase 2: schema-related memory integration and learning the no-schema condition

This phase involved the learning of a novel hierarchy of galaxies that either leveraged on the acquired schema (schema condition) or contained items entirely not encountered before (no-schema condition). In the schema condition, participants were required to learn a new hierarchy that was intercalated with galaxies from phase 1 while maintaining the same ranking order. In the no-schema condition, participants were presented with a completely novel hierarchy. Tests on both schema and no-schema sets consisted of adjacent and inference pairs similar to phase 1. Critically, the inference test trials consisted of only novel galaxies for both hierarchies.

The procedures were identical to the previous phase and participants underwent six alternating learning and test blocks for both the schema and no-schema sets presented in an interleaved order. All of the items, right/left presentation on the screen, the interleaved order, and the order of presentation of pairs were randomized and counterbalanced in all phases (Figure 2A–B).

Hierarchy recall test as a measure to test free recall

Finally, participants were provided with two envelopes each containing the galaxy images of the schema/no-schema set mixed in a random arrangement and were tasked with reconstructing the accurate order of galaxies within each hierarchy from youngest to the eldest from left to right on the table. Similar to the computer tests hierarchy recall test was also counterbalanced with numbered envelopes and instructions on which to open first. The performance of participants was assessed based on the total number of errors made in reordering the galaxies, utilizing a method that penalizes the incorrect placement of an item relative to the deviation from its correct position [32].

Software and image source

Galaxy images were obtained from the HubbleSite galleries, which can be accessed at (https://hubblesite.org/images). The stimuli were created using E-Prime 2.0 software (Psychology Software Tools, Inc, Sharpsburg, PA).

PSG data acquisition and analyses

Electroencephalography (EEG) was conducted using a SOMNOtouch recorder (SOMNOmedics GmbH, Randersacker, Germany) on two central channels, C3 and C4, with reference to the contralateral mastoids (A1, A2), and Cz and Fpz as common reference and ground electrodes following the international 10–20 system. Electrooculography (EOG) and electromyography (EMG) of chin muscles were also recorded for sleep staging. The impedance was maintained below 5 kΩ prior to initiating the recording.

The PSG data were first visually examined and subsequently auto-scored using the Z3Score algorithm (https://z3score.com), which has been previously validated and demonstrated to be comparable to expert scorers. Additionally, the FASST EEG toolbox (http://www.montefiore.ulg.ac.be/~phillips/FASST.html) was utilized [33]. Sleep stages (N1, N2, N3, REM, and WASO) were scored based on 30-second epochs using the criteria outlined in the American Academy of Sleep Medicine Manual (AASM) [34]. Two records containing more than 10% artifacts were excluded from the final analyses. The reasons for exclusion included either premature termination of recordings by the device or inadequate data quality for sleep staging, for example, due to electrodes falling off during the night. Slow-wave activity (SWA), and slow-wave energy as integrated power in the delta band (0.5–4 Hz) were computed using methods previously published [35, 36].

Spindle detection

The Wonambi Python package, v5.24 (https://wonambi-python.github.io) was employed for automatic spindle detection using a validated algorithm [35]. Spindles were classified into slow (9–12 Hz), or fast (12–15 Hz) [35], and were detected for both N2 and

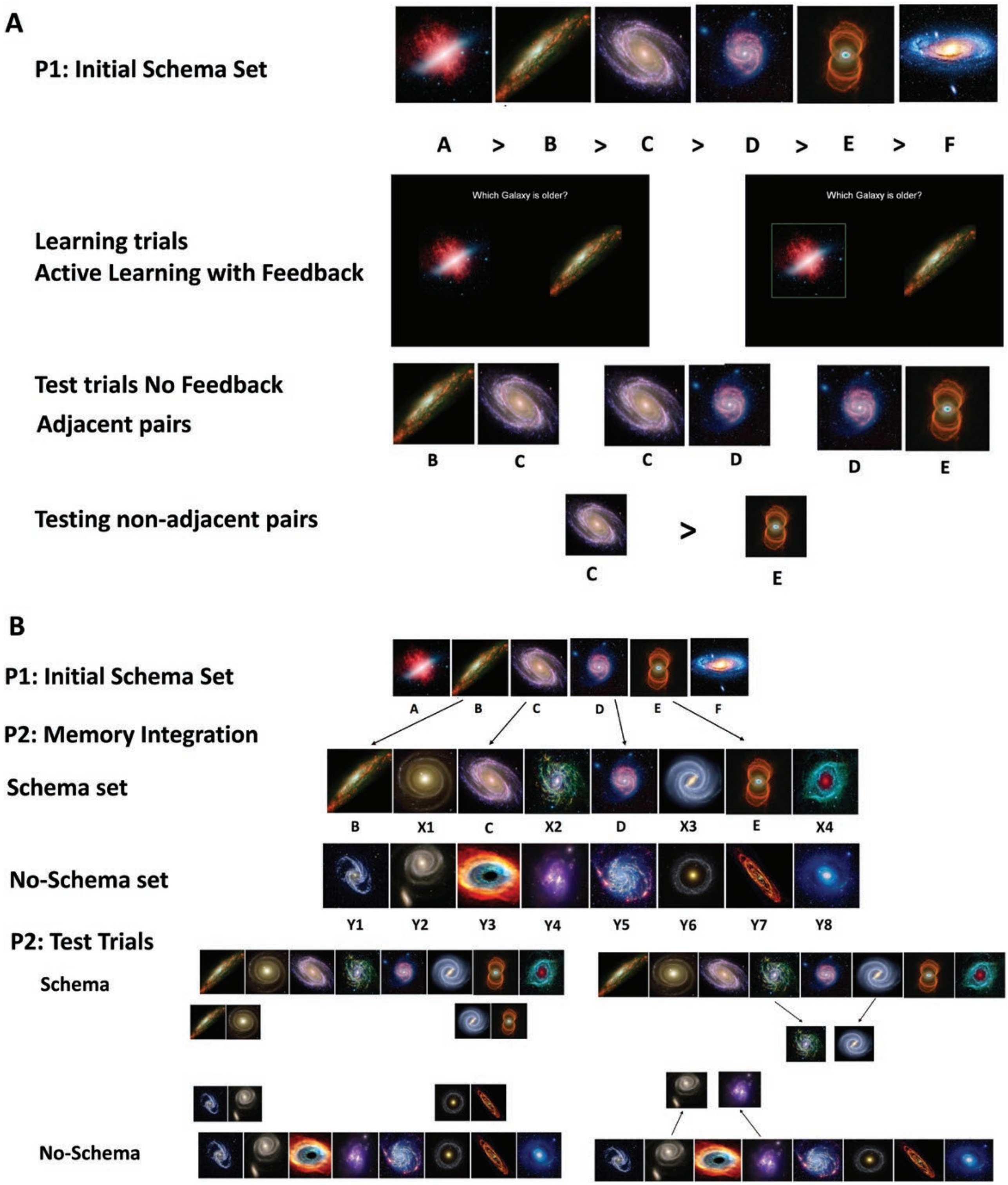

Figure 2. Brief overview of the experimental paradigm: (A) phase 1 (schema formation): Participants learned the age hierarchy of six galaxies (i.e. A > B > C > D > E > F) to criterion via feedback-based learning. In each trial, they were presented with two adjacent items (e.g. A–B i.e. adjacent pairs) and were asked: "Which galaxy is older?." Following each learning block, participants were tested (without feedback) on their memory for adjacent items as well as inference pairs (non-adjacent pairs, i.e. B–D, B–E, C–E). (B) Phase 2 (memory integration and schema updating): -participants learned two new hierarchies. The "schema" hierarchy contained four galaxies from the previously learned schema in phase 1 (i.e. B, C, D, and E) intercalated with four novel galaxies (i.e. X1–X4), while the "no schema" hierarchy comprised eight novel galaxies not encountered before (i.e. Y1–Y8). Learning and testing alternated between six schemas and six no-schema interleaved blocks. Importantly, in the schema set, learning trials always consisted of one galaxy from phase 1 and one new item, so that the acquired schema would serve as a scaffold to facilitate new learning (i.e. B–X1, X1–C, C–X2, X2–D, D–X3, X3–E, E–X4). Tests on both schema and no-schema sets consisted of adjacent and inference pairs similar to phase 1. The inference test trials consisted of only novel galaxies for both hierarchies (i.e. schema set: X1–X2, X1–X3, X2–X3; no-schema: Y2–Y4, Y2–Y6, Y4–Y6)

N3 sleep stages. Spindle count and spindle density (counts per minute) were used as the main spindle metrics [37]. We manually checked 10 participants' samples to verify the fidelity of automatic detection (for further details see Supplementary Materials).

Statistical analyses

Memory performance was assessed both via the computer test by an item-by-item measure (% correct), as well as the number of recall errors in the hierarchy recall test. For each phase in both groups, we assessed memory performance using a mixed ANOVA to investigate consolidation of memories with schema learning (schema, no-schema), and test sessions (immediate, delayed: 12 hours/24 hours) as the within-participants factors, and consolidation condition (sleep, wake) as the between-participants factor. Change in memory following a 12-hour interval of (sleep–wake) was also examined using a mixed ANOVA with the within-participant factors of schema (schema, no-schema) and pair type (adjacent, inference) and between-participants factor of consolidation (sleep–wake). The immediate and delayed 12-hour/24-hour test results were compared with post hoc independent samples and paired *t*-tests. We examined associations of sleep stages and spindle measures with the memory performance, size of the schema-driven memory benefit (Schema—No-schema), and the change in recall errors in tests following nocturnal sessions using Spearman's correlation analyses. *P*-values of less than 0.05 were considered statistically significant. Data preprocessing and statistical analyses were conducted using MATLAB version R2017b (The MathWorks, Inc., Natick, MA) and SPSS 25.0 (IBM Corp., Armonk, New York).

Results

Initial schema learning at phase 1, and performance in phase 2 for sleep and wake groups

Initial learning of the schema, at phase 1 was comparable between sleep and wake groups. Independent sample *t*-tests revealed no significant differences in the number of trials required to reach the criterion in phase 1 in the sleep ($M = 9.3$, $SD = 4.7$), compared to the wake group ($M = 9.9$, $SD = 3.1$), $t(51) = 1.42$, $p = 0.158$. There was no significant difference in the performance for non-inference and inference pairs in phase 1 ($t \le 1.59$, $p \ge 0.12$). For performance across test blocks in phase 2, a repeated measures ANOVA with schema learning (schema, no-schema), and block (six levels) as within-participants factors, and consolidation condition (sleep, wake) as the between-participants factor found significant main effects of schema, $F(1,51) = 50.66$, $p < 0.001$, $\eta_p^2 = 0.49$, and block, $F(5,255) = 14.03$, $p < 0.001$, $\eta_p^2 = 0.21$, but no significant effect of consolidation condition, $F(1,51) = 0.27$, $p = 0.60$; indicating enhanced performance in the schema condition and improvements across the learning blocks for both sleep and wake groups. Critically, the initial learning of the schema, and no-schema sets at phase 2 were comparable between sleep and wake groups, with comparable performance in both schemas sets across blocks in Phase 2, $F(1,51) = 0.27$, $p = 0.60$, as well as the final block, $t(51) \le 0.67$, $p \ge 0.51$. Similarly, both groups performed comparably at the subsequent immediate test, $t(51) = 1.207$, $p = 0.233$. For additional information on the learning trajectory during phase 2 and block-level performance in both groups, please refer to Supplementary Figure 4.

Behavioral results (12-hour post-learning)

Sleep benefited the retrieval of schema-related items over no-schema items (Figures 3–5). A mixed ANOVA with schema learning (schema, no-schema), test session (immediate, delayed 12 hours), as the within-participant factor, and consolidation condition (sleep, wake) as the between-participant factor, revealed a significant interaction, whereby sleep benefited memory for the schema and not for the no-schema learning after 12 hours, $F_{(1,51)} = 4.503$, $p = 0.039$, $\eta_p^2 = 0.081$. Post hoc *t*-tests showed significantly improved performance in the sleep group for the schema-related memoranda, $t(28) = 3.65$, $p = 0.001$, compared with significant decay in the active–wake group, $t(23) = 2.83$, $p = 0.008$ (Figure 3). There was a significant main effect of sleep, wherein better memory performance was observed following sleep compared with active–wake, $F_{(1,51)} = 5.96$, $p = 0.018$, $\eta_p^2 = 0.105$. As expected, we also observed a significant main effect of schema regardless of sleep condition, $F_{(1,51)} = 34.53$, $p < .001$ $\eta_p^2 = 0.404$.

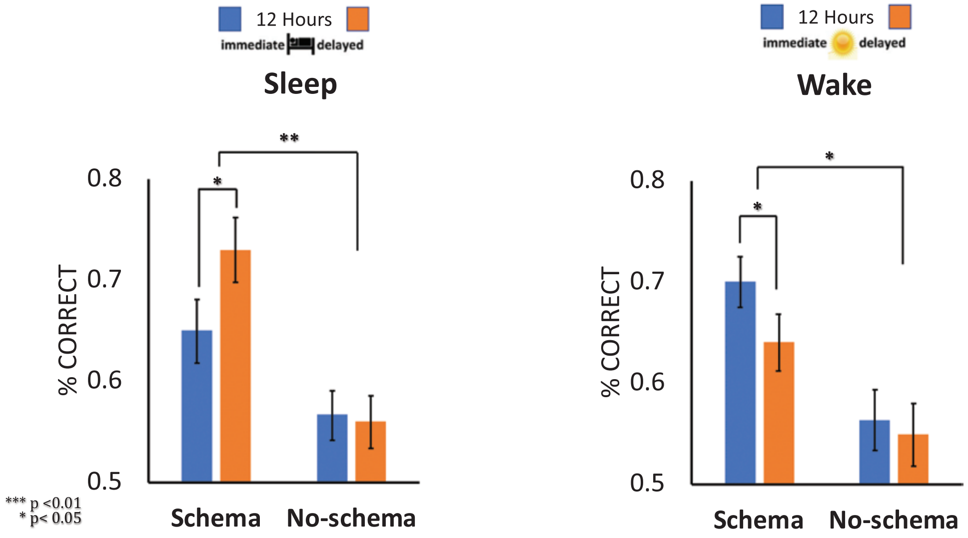

Figure 3. Schema-related memory was better preserved in the sleep group. Sleep preferentially boosted schema-related memory consolidation compared with active wake. The latter was associated with significant decay of these memory traces $^{**}p < 0.01$, $^{*}p < 0.05$

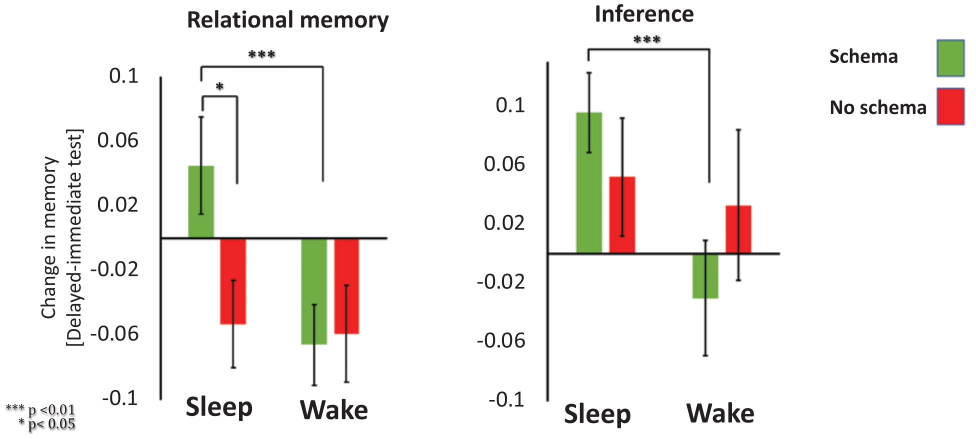

Figure 4. Schema-related memory was better preserved in the sleep group. The boost was particularly observed for the inference pairs in the schema condition. ***$p < 0.01$, *$p < 0.05$

Effects of sleep on schema-driven relational memory and inference (12-hour post-learning)

Memory performance results for relational memory (adjacent pairs) and inference (non-adjacent pairs) are displayed in Figure 4. A mixed ANOVA to investigate change in memory performance with schema learning (schema, no-schema), and pair type (adjacent, inference) as the within-participant factors, and consolidation condition (sleep, wake) as the between-participant factor, revealed significant main effects of sleep, $F_{(1,51)} = 7.38$, $p = .009$, $\eta_p^2 = 0.126$, as well as a significant consolidation condition by schema interaction, where schema-related memory was better preserved in the sleep group, $F_{(1,51)} = 4.95$, $p = 0.031$, $\eta_p^2 = 0.088$. Moreover, we found a significant main effect of pair type, suggesting greater memory benefits for the inference pairs after the sleep–wake interval, $F_{(1,51)} = 6.924$, $p = 0.011$, $\eta_p^2 = 0.120$. In particular, the greatest improvement was seen in the sleep group for the inference pairs embedded within the original schema, $t(51) = 2.737$, $p = 0.009$. See Supplementary Materials for exploratory analyses on potential proactive interference (Supplementary Figures 5 and 6).

Hierarchy recall test

There was a significant condition (sleep, wake) by schema learning (schema, no-schema) interaction, $F_{(1,51)} = 6.248$, $p = 0.016$, $\eta_p^2 = 0.109$, indicating that sleep preferentially protected schema-related memories (Figure 5). Follow-up tests showed a significant reduction in the number of errors in the schema set in the sleep group compared with active wake, $t(51) = 4.181$, $p < 0.001$. There was also a significant decrease in the number of errors in the schema compared with the no-schema set that was only observed in the sleep group, $t(28) = 2.460$, $p = 0.020$.

Comparing behavioral results at 24-hour and 12-hour post learning

A mixed ANOVA to investigate change in memory performance across all the sessions with schema learning (schema, no-schema), and test session (12 and 24 hours) as the within-participant factors, and consolidation condition (sleep, wake) as the between-participant factor, showed a trend for the better performance in the sleep group, $F_{(1,51)} = 3.424$, $p > 0.070$, $\eta_p^2 = 0.063$, and a trend for schema by sleep interaction, $F_{(1,51)} = 3.559$, $p > 0.065$, $\eta_p^2 < 0.065$, with no other significant main effects or interactions (Figure 6A). The same mixed ANOVA analyses to investigate recall errors yielded similar results with no significant main effects of sleep condition and no significant schema by sleep interaction across 24 hours, $F_{(1,51)} < 1.878$, $p > 0177$, $\eta_p^2 < 0.070$ (Figure 6B).

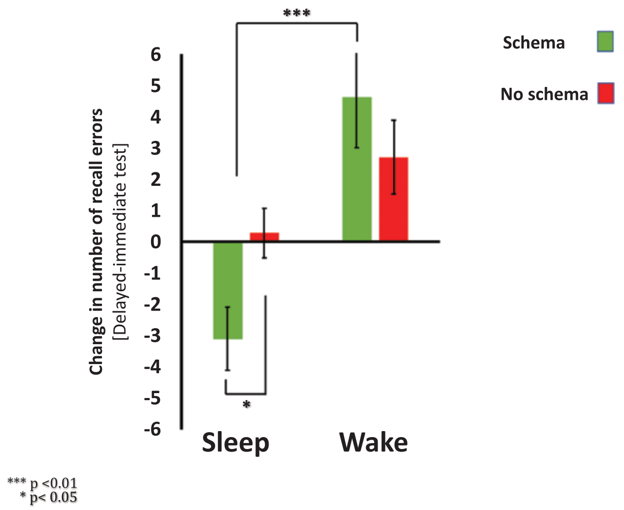

Figure 5. Accuracy of the recall performance improved for the schema-related set in the sleep group. Following a 12-hour interval containing sleep participants committed significantly less recall errors in the schema-related set compared with active wake. ***$p < 0.01$, *$p < 0.05$

Behavioral associations with sleep macro and microstructure

Higher schema-related memory benefit was associated with increased fast spindle density, particularly during N2, $r(26) = 0.489$, $p = 0.011$. Moreover, higher spindle density in N2 was significantly associated with decreased number of errors in the hierarchy recall test, $r(26) = -.540$, $p = 0.006$ (Figure 7).

Overnight gain in schema benefits on the small number of inference pairs was associated with the amount of SWS sleep obtained, $r(26) = 0.478$, $p = 0.013$, and the magnitude of SWA/SWE, $r(26) \geq 0.537$, $p \leq 0.005$. Other than this specific correlation, no significant correlations with overall schema-driven memory benefits and relational memory were found with slow-wave sleep measures. Likewise, no significant associations with other sleep stages were found, $r(26) \leq 0.375$, $p \geq 0.131$. Sleep architecture and spindle features measured with polysomnography are listed in Table 2.

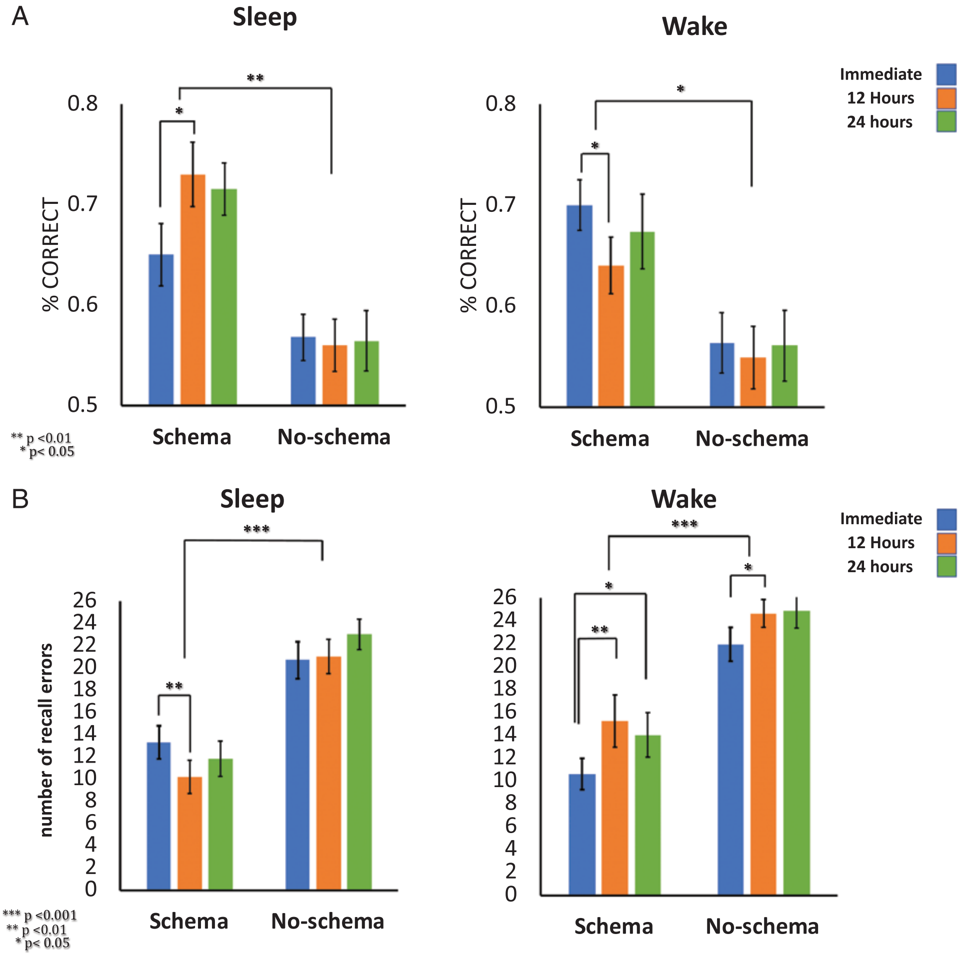

Figure 6. (A) Comparing memory performance across all test sessions between sleep and wake groups. We observed nonsignificant improvement for schema-related items in the wake group following the nocturnal sleep in the 24-hour delayed test session. Overall the difference between sleep and wake groups was less evident following delayed nocturnal sleep consolidation opportunity of the wake group. ***p < 0.01, *$p < 0.05$. (B) Comparing recall errors in hierarchy recall test performance across all test sessions between sleep and wake groups. Similarly, we observed nonsignificant improvement in the wake group for the schema-related set following the delayed nocturnal sleep consolidation opportunity, resulting in diminished differences between the sleep and wake groups after 24 hours. ***$p < 0.01$, *$p < 0.05$

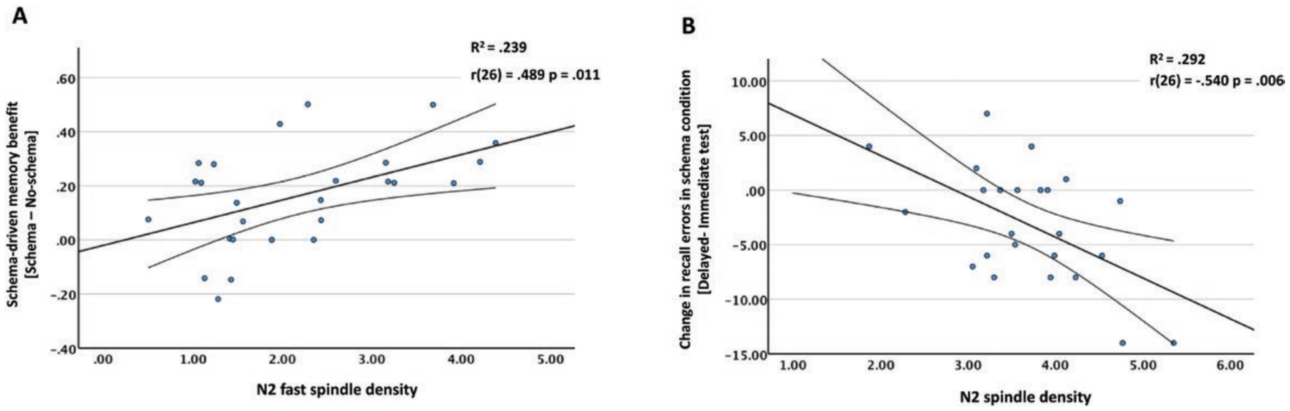

Figure 7. Schema Benefit and Spindle Correlations. (A) Higher fast spindle density in stage 2 sleep was associated with higher overnight schema-driven memory benefits. (B) Moreover, Higher spindle density in stage 2 sleep was associated with reduced recall errors in the schema schema-related set.

Discussion

Our findings suggest that sleep supports schema-related memory consolidation. Overnight, sleep was associated with outsized benefit on the consolidation of new schema-related memoranda relative to the active wake condition, particularly for non-adjacent inference pairs. Retrieving these memoranda requires access to non-explicit, hierarchically organized information. Higher sleep spindle density during post-learning sleep was associated

Table 2. Sleep Architecture (%) and Spindle Features Measured With Polysomnography

	Mean	SD
N1 %	1.42	0.82
N2 %	52.18	5.09
N3 %	25.45	4.81
REM %	20.95	4.13
TST (min)	449.86	27.20
Spindle count	1107.42	196.89
Spindle density	3.49	0.47
Fast spindle count	373.28	170.01
Fast spindle density	1.28	0.68

N1, Stage 1 Sleep; N2, Stage 2 Sleep; REM = Rapid-Eye Movement Sleep; TST = Total Sleep Time. Spindle Density, Spindles/Min.

with fewer errors in the hierarchy recall test, and fast spindle density predicted the enhanced overnight schema-driven memory benefits. Interestingly, the advantage of post-learning sleep on memory performance diminished 24 hours after the initial learning.

Consistent with prior studies, we found enhanced schema-related memories over a night of sleep compared to a day of active wakefulness [22, 23, 38–44]. We also observed a trend towards improvement in schema-related memories in the 24-hour delayed test following the nocturnal sleep in the wake group, suggesting that additional consolidation might have occurred during second night of post-learning sleep. This finding concurs with the recent findings that the benefits of post-learning sleep diminished across 24 hours [24, 45]. Furthermore, this observation is consistent with a study by Schönauer and colleagues, suggesting that hippocampus could serve as a temporary buffer for encoded information acquired during prolonged periods of wakefulness, and that system consolidation may still occur during subsequent sleep opportunities [46]. This could explain why the initially observed memory performance advantage subsided in the sleep compared with the wake group as participants in the wake group had a nocturnal sleep opportunity after 24 hours.

On the surface, the present finding appears to contradict our earlier study that found that the benefits of post-learning sleep on schema-related memories could be extended for at least two weeks [40]. However, a key difference between these studies is that in the former one, multiple retrievals and restudy phases, as well as repeated testing could have reinforced neural representations of the memoranda. In particular, the power of retrieval practice and testing effect in consolidating memories has been highlighted by a series of studies as a potent learning method [47, 48], especially when free recall is used similar to our paradigm [49].

Another recent study may be at odds with the present findings. Ashton and colleagues found that sleep bolstered schematically *incongruent* rather than congruent memories [24]. However, the “schema-learning paradigm” used in that study lacks essential features such as an overlapping associative network structure, adaptability, development across multiple episodes, and in particular facilitation of inference [18, 28, 50]. Moreover, *recognition-based* tasks have been reported to favor the no-schema condition due to novelty effects while *recall-based* tasks like the one used here tend to bring out the benefits of schema [18, 19] Finally, schema-incongruent stimuli that are highly incongruent could induce benefit by virtue of their novelty [51].

We found that higher fast spindle density in particular was predictive of better performance in the schema-related set. In line with these findings, prior knowledge has been reported as an essential prerequisite of successful memory reactivation, and sleep spindles have been shown to play an active role in this process [44]. Increased spindle activity has been associated with higher memory reactivation and better memory integration into prior knowledge structures, as well as accelerated disengagement of memories from hippocampal networks [22].

Our ability to make inferences is particularly facilitated by schemas. Employing their overlapping memory traces and activated structures of background knowledge, schemas start to enrich the ongoing experience with logical inferences. Contrary to our expectations, we found limited support for the role of slow-wave sleep in schema-related memory consolidation. SWS measures were only significantly associated with the overnight gains in inferential performance, and did not predict the overall performance, and relational memory in both the computer test and the hierarchy recall test. While these exploratory findings provide speculative evidence that SWS could facilitate inference, it is important to note that these effects might only be replicated under specific boundary conditions. This finding concurs with a recent publication by March et al. that highlighted the potential role of sleep spindles rather than SWS in schema-related memory integration [52]. Recent work has also called into question the robustness of memory benefits of SWS measures, suggesting that the reported associations of SWS and memory performance may be overstated [53, 54], and might not be replicable in relatively small sample size studies with low statistical power [55]. Related to this and with respect to these associations with inference, Werchan & Gomez showed that earlier findings on the improved overnight performance in transitive inference could only be replicated when participants underwent reinforcement learning, and not with other learning conditions [15]. Nonetheless, inferential reasoning within the context of transforming schemas might benefit from additional synergistic effects related to slow-wave sleep, as well as successful replay of overlapping memory traces [56, 57]. Additional research is needed to clearly determine the precise function of sleep and the putative neurocognitive processes involved in transitive inference and flexible transformation of schematic knowledge structures.

We did not find any significant correlations between schema-related memory performance and other sleep stages. The role of REM sleep in schema-related inferences and memory consolidation remains mixed as some report that extraction of hidden regularities benefits from SWS rather than REM sleep [58–60], while others found otherwise [23]. These observed discrepancies could be partly explained by the diverse nature of schematic knowledge and the major differences in the schema-based learning paradigms. In particular, contrary to our paradigm, Durrant et al.’s task focused on the tonality schema that is less generalizable and did not incorporate aspects of inference and dynamic adaptability [28, 56]. This could also be the case for other inconsistent findings by studies that employed different schema-learning paradigms that did not incorporate essential schema features as discussed earlier.

Limitations and future directions

First, despite reported sleep-dependent benefits to schema-based learning in children [61], and young adults [22, 42]; caution must be taken before generalizing our findings in adolescents to adults. Sleep and brain structure–function during adolescence appear to be interconnected [62]. It has been documented that cortical gray matter and sleep slow-wave activity (SWA) decrease during adolescence along with maturation of cognition [63, 64]. Of note, age-adjusted analyses in the current study yielded the same results, as most of these neurodevelopmental changes occur before the age of 15 and we did not have a wide age range in our sample.

Second, while we have shown that sleep spindles might play a role in consolidation and transformation of recently acquired schemas [40], many open questions remain. For example, what is the exact process by which existing knowledge in the cortex is modified or revised, and how do sleep spindles enable this flexible schema-updating process? [65] Furthermore, as recently shown replay-associated phenomena could be present during periods of resting wakefulness that might confer similar benefits to consolidation and transformation of memories [66, 67]. In this regard, the effects of multiple cycles of nocturnal sleep and wakefulness in transformation of schematic knowledge structures remain to be fully investigated. Especially, the underlying neuronal mechanisms in dynamic transformation of schemas during offline periods of sleep or resting wake is an interesting research question to be probed in future studies [68].

Finally, only central electrodes were used, which may have restricted our capability to detect slow spindles that are mainly present in the frontal regions, while being sensitive to detect fast spindles that are predominantly distributed in the centroparietal regions [69, 70]. Despite this limitation, our findings are aligned with prior works investigating spindle characteristics in adolescents using C3 and C4 electrodes [31, 71, 72].

Conclusions

Overnight sleep with a higher spindle density appears to confer a performance advantage for schema-related memoranda compared with an equivalent duration spent awake. However, this advantage in performance in the sleep group diminished over 24 hours, possibly due to delayed consolidation from subsequent nocturnal sleep in the wake group.

Supplementary Material

Supplementary material is available at *SLEEP Advances* online.

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Author Contribution

Hosein Aghayan Golkashani (Conceptualization, Methodology, Formal analysis, Visualization, Writing - Original draft preparation), Shohreh Ghorbani (Data Curation, Formal analysis, Visualization, Software, Writing - Review & Editing), Ruth L.F. Leong (Methodology, Writing - Review & Editing), Ju Lynn Ong (Formal analysis, Writing - Review & Editing), Michael W.L. Chee (Supervision, Methodology, Writing - Review & Editing, Funding acquisition).

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Data Availability

The data and analytic scripts utilized in this publication are accessible upon reasonable request.

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