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Fragmented Sleep Enhances Postoperative Neuroinflammation but Not Cognitive Dysfunction

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BACKGROUND: Sleep is integral to biologic function, and sleep disruption can result in both physiological and psychologic dysfunction including cognitive decline. Surgery activates the innate immune system, inducing neuroinflammatory changes that interfere with cognition. Because surgical patients with sleep disorders have an increased likelihood of exhibiting postoperative delirium, an acute form of cognitive decline, we investigated the contribution of perioperative sleep fragmentation (SF) to the neuroinflammatory and cognitive responses of surgery.
METHODS: The effects of 24-hour SF and surgery were explored in adult C57BL/6J male mice. The SF procedure started at 7 AM with cages being placed on a large platform orbital shaker that cycled every 120 seconds (30 seconds on/90 seconds off) for 24 hours. In separate cohorts, stabilized tibial fracture was performed either before or after the 24-hour SF procedure and assessed for systemic and hippocampal inflammation and cognition.
RESULTS: SF-induced nonhippocampal memory dysfunction (mean ± standard deviation [SD] of the difference in time spent between novel and familiar object for control was 4.7 ± 1.4 seconds, n = 8 versus SF −0.5 ± 0.2 seconds, n = 11, yielding an estimated treatment effect of 5.2 seconds [95% confidence interval {CI}, 2.6–7.7]; $P < .001$) and increased systemic interleukin-6 (median [25%–75% quartile] for control 0.0 [0.0–2.4] pg/mL versus 9.7 [6.3–12.9] pg/mL, n = 8/group, yielding an estimated treatment effect of 9.7 pg/mL [95% CI, 5.8–11.8]; $P < .0001$). SF reduced freezing time in hippocampal-dependent memory test (mean ± SD for control 49.3% ± 5.8% versus for SF 32.9% ± 5.8%, n = 10/group, estimated treatment effect = 16.4% [95% CI, 11.0–21.8]; $P < .0001$). Although surgery also reduced freezing time (mean ± SD for control 49.3% ± 5.8% versus for surgery 30.3% ± 3.3%, n = 10/group, estimated treatment effect = 19.0% [95% CI, 14.6–23.4]; $P < .0001$), memory impairment was not further exacerbated by combining SF with surgery. One day after SF, there was an increase in hippocampal messenger RNA expression of tumor necrosis factor-α (relative quantitation [RQ] 5.12-fold, n = 5/group [95% CI, 1.64–15.97]; $P < .01$), and 1 day after surgery, there was an increase in messenger RNA interleukin-6 (RQ 4.64-fold, n = 5 [95% CI, 1.48–14.56]; $P < .05$) and tumor necrosis factor-α (RQ 5.54-fold, n = 5 [95% CI, 2.92–10.51]; $P < .01$). These increments were more pronounced when either pre- or postoperative SF was combined with surgery.
CONCLUSIONS: Although SF and surgery can independently produce significant memory impairment, perioperative SF significantly increased hippocampal inflammation without further cognitive impairment. The dissociation between neuroinflammation and cognitive decline may relate to the use of a sole memory paradigm that does not capture other aspects of cognition, especially learning. (Anesth Analg 2016;XXX:00–00)

Sleep restores and repairs several mechanisms that are pivotal to learning and memory.[1] Slow-wave sleep weakens the synaptic strengthening that occurs during wakefulness and restores the brain to a state that is capable of appropriately processing new sensory input in subsequent periods of wakefulness.[2,3]

Unlike sleep deprivation, sleep fragmentation (SF) does not necessarily affect total sleep time but reduces the total amount of time spent in the deeper levels of sleep. Furthermore, the brain's capacity to successfully respond to cognitive challenges through compensatory recruitment becomes overwhelmed if the patient is not presented with appropriate and continual sleep. Optogenetic activation of orexinergic neurons, which play a key role in arousal processes, demonstrated that a minimal amount of uninterrupted sleep is crucial for memory consolidation.[4]

Interrupted, fragmented, and/or restricted sleep is a consequence of many diseases, including obstructive sleep apnea (OSA); this sleep disorder can result in adverse consequences including heart failure, stroke, coronary heart disease, and cognitive impairment.[5–8] The cognitive and structural deficits in patients with OSA may be secondary to SF and repetitive nocturnal intermittent hypoxemia.[9] Furthermore, OSA is an independent risk factor for the development of postoperative delirium, a form of acute cognitive dysfunction.[10]

Cognitive dysfunction, including that seen in delirium, is prevalent in surgical and intensive care unit (ICU) patients and is associated with higher mortality rates.[11] Surgery activates the innate immune system, inducing neuroinflammatory changes that cause subsequent decline in cognitive function.[12] When surgical trauma-induced activation of the innate immune response fails to resolve, it may lead to

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persistent cognitive decline.[12,13] SF by itself can also induce activation of inflammatory mechanisms, more specifically tumor necrosis factor (TNF)-α-dependent pathways, which propagate the engagement of the innate immune system.[14,15] Polysomnographic studies have revealed profound sleep disruption in ICU patients with decreases in total sleep time, altered sleep architecture, and severe SF.[16,17] We posited that the combination of SF and surgery would enhance the neuroinflammatory response produced either alone or that the combination results in exacerbated cognitive impairment. Therefore, the aims of the study were to determine the effects of SF, either pre- or postoperatively, on surgery-induced neuroinflammation and cognitive decline.

METHODS

Experimental Procedures

Animals. All the experiments were conducted under a protocol approved by the Institutional Animal Care and Use Committee of the University of California, San Francisco, and conformed to the National Institutes of Health guidelines. Experiments were performed using 12- to 14-week-old male C57BL/6J mice (Jackson Laboratory, Bar Harbor, ME) under a 12:12-hour light-dark cycle in a constant temperature- and humidity-controlled environment with free access to food and water. Animals were tagged and randomly allocated to each group before any treatment or procedure (Figure 1). Researchers, who were blinded to the group assignment, performed all neurobehavioral tests. For those animals in which behavior was assessed, no blood harvesting or tissue sampling was performed to obviate possible confounding effects of fear conditioning testing on the analytes of interest.[18] Body weight was measured before any procedure and daily after that. The procedures did not influence body weight, and there was no unexpected lethality in this study.

Sleep Fragmentation

Sleep was interrupted for 30 seconds every 2 minutes as previously described.[19] Briefly, animals were kept in their home cage and placed on an analog orbital shaker (OS-500; VWR, Champaign, IL) at 7 AM. Repetitive on/off cycling of the shaker (30 seconds on/90 seconds off), set at 100 rpm, was controlled by a timer (traceable controller; Fisher Scientific, Pittsburgh, PA). A metal cage cardholder was suspended from the top of the cage, creating an additional audible stimulus when the holder knocked against the side of the cage. Standard laboratory chow was supplemented with aqueous gel. SF procedure lasted for 24 hours.

Surgical Trauma

Under aseptic conditions, groups of mice was subjected to a tibia fracture as previously described.[20–22] Mice were anesthetized with 2% isoflurane, and analgesia was achieved with 0.1 mg/kg buprenorphine subcutaneously immediately after anesthetic induction and before skin incision. Warming pads and temperature-controlled lights were used to maintain body temperature at 37°C ± 0.5°C. The entire procedure from induction of anesthesia to the end of surgery lasted 10 ± 3 minutes.

Nonhippocampal Learning and Memory: Novel Object Recognition

Novel object recognition (NOR) is based on the spontaneous tendency of rodents to spend more time exploring a novel object than a familiar one. For our study, we used a previously validated protocol.[23] Briefly, animals were familiarized for 2 days to the testing environment that differed from the home cage. At the end of the SF procedure, animals were presented with the to-be familiarized object in the testing environment (10 minutes). After the sample-object exposure, animals were

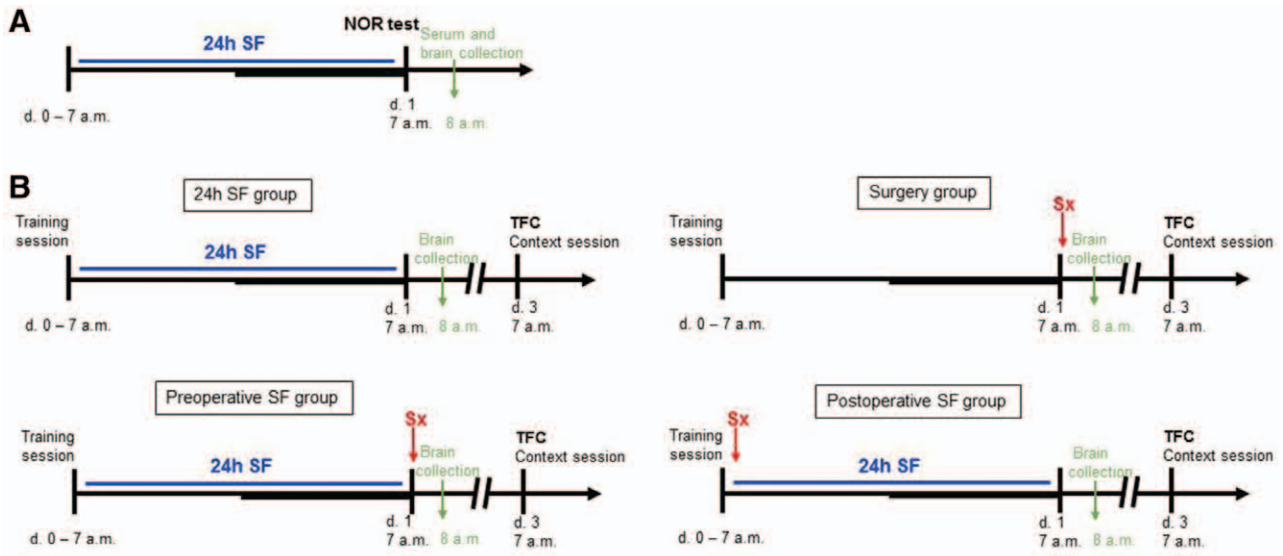

Figure 1. Study design. A, First experiment: mice were divided into 2 groups: control versus 24-hour sleep fragmentation (SF). The training session of the novel object recognition (NOR) memory test was performed immediately after cessation of the SF procedure (11 mice in the control group and 8 mice in the SF procedure group). A different cohort of animals was used to collect brain and serum samples (5 mice per group). B, Second experiment: mice were divided into 5 groups and tested according to the trace fear conditioning paradigm: control (no intervention); 24-hour SF; surgery; preoperative SF; postoperative SF. The training session of the memory test was performed right before any intervention, and the context session was performed 3 days later (10 mice per group). A different cohort of animals was used for inflammatory markers. Mice were euthanized 24 hours after the start of the intervention (5 mice per group). Sx indicates surgery; TFC, trace fear conditioning.

returned to the home cage for a retention period (1 hour). In the second phase, animals were returned to the environment and presented with 2 objects: the previously experienced sample object and a novel object (3–5 minutes). Object recognition was distinguished by the animal spending more time exploring the novel object. To score time of object interaction from video, a XNote Stopwatch (dnSoft Research Group) was used.[23]

Hippocampal-Dependent Learning and Memory: Trace Fear Conditioning

Fear conditioning is used to assess learning and memory in rodents, which are trained to associate a conditional stimulus such as a tone with an aversive, unconditional stimulus such as a foot-shock.[24] Freezing behavior is an indicator of aversive memory that is measured when subjects are re-exposed to the conditional stimulus. For this study, we used a previously published paradigm.[12,21,25,26] Briefly, the behavioral study was conducted using a conditioning chamber (Med Associates Inc, St. Albans, VT) and an unconditional stimulus (2 periods of 2-second foot-shock of 0.75 mAmp). Three days after the training session, mice were returned into the same chamber where training had occurred for a context test, during which no tones or foot-shocks were delivered. Freezing behavior in response to the context was recognized by the software as a total lack of movement excluding breathing but including movement of fur, vibrissae, and skeleton. The percentage of time spent freezing over the total time spent in the chamber to accomplish the test was used to score memory and learning abilities. A decrease in the percentage of time spent freezing indicated impairment of these abilities.

Systemic Inflammatory Response

After termination of both SF procedure and surgery (8 AM on day 1), blood was collected transcardially under terminal isoflurane anesthesia into heparin-coated syringes. Samples were centrifuged at 3400 rpm for 10 minutes, and plasma was collected and stored at −80°C until assaying. Blood samples taken from animals without intervention served as controls. Plasma interleukin-6 (IL-6) was measured using a commercially available enzyme-linked immunosorbent assay kit (Invitrogen, Grand Island, NY).

Neuroinflammatory Response to Surgery

After termination of both SF procedure and surgery (8 AM on day 1), the hippocampus was rapidly extracted under a dissecting microscope and placed in RNAlater solution (Qiagen, Valencia, CA). Total RNA was extracted using RNeasy Lipid Tissue Kit (Qiagen). Extracted RNA was treated with recombinant DNase I using an RNase-Free DNase Set (Qiagen). Messenger RNA (mRNA) concentrations were determined with an ND-1000 spectrophotometer (NanoDrop Thermo Fisher Scientific, Wilmington, DE), and mRNA was reverse-transcribed to complementary DNA with a High-Capacity RNA-to-complementary DNA Kit (Applied Biosystems, Carlsbad, CA). TaqMan Fast Advanced Master Mix (Applied Biosystems) and specific gene expression assays were used for quantitative real-time polymerase chain reaction as follows: β-actin (ACTB) (NM_007393.1), IL-6 (Mm00446190_m1), TNF-α (Mm00443258_m1), and IL-1β (Mm01336189_m1). Quantitative polymerase chain reaction was performed using StepOnePlus (Applied Biosystems). Each sample was run in triplicate, and relative gene expression was calculated using the comparative threshold cycle ΔCt and normalized to ACTB. Results are expressed as fold-increase relative to controls.

Experimental Design

In specific aim 1, we determined the independent effect of SF ("treatment") on nonhippocampal-dependent cognitive function and inflammation in separate cohorts; treatment consisted of 24 hours of SF while control animals were submitted to the same handling but not placed on the orbital shaker (Figure 1A). After SF, groups were submitted to the NOR test. A different cohort of animals received either SF treatment or control conditions immediately after which serum and brain for assessment of inflammation were harvested.

In specific aim 2, we determined the perioperative (either pre- or postoperative) effects of SF on hippocampal-dependent memory (trace fear conditioning [TFC]) and inflammation after surgery. Five groups included a control (submitted to the same handling but not subjected to surgery or SF protocol), 24-hour SF with no surgery, surgery without SF, SF (preoperative) before surgery, and SF (postoperative) after surgery (Figure 1B). TFC training sessions were performed before any intervention and testing session at the end of procedures. To prevent possible confounding factors of behavioral testing on inflammatory markers, we used different cohorts of animals for the effect of perioperative SF on inflammation.

Statistical Analysis

Data are presented as mean ± standard deviation. Normality was tested with the Kolmogorov–Smirnov normality test. For data not normally distributed (plasma IL-6 control versus SF), results are presented as median (interquartile range, 25%–75%). Equality of variances was tested with the *F*-test. For 2-sample comparisons, *t* tests were used (using the Welch correction if necessary) and Mann-Whitney *U* test for data not normally distributed (plasma IL-6). On the basis of previous work,[22] we applied a log transformation (ln[X]) to the response of the blood cytokine expression before performing analysis to better adhere to the test model's assumptions of normally distributed residuals and homoscedasticity of residuals.

To test if perioperative SF increased hippocampal mRNA cytokine expression and induced hippocampal memory impairment, we performed comparisons of >2 groups (control versus SF + Sx and control versus Sx + SF). Means were compared using 1-way analysis of variance followed by *t* tests with a Bonferroni-corrected α level. We used Kruskal–Wallis test with the Dunn post test for nonparametric statistical analyses.

On the basis of previous freezing time data,[25] we estimated that a sample of 9 C57BL/6J surgical mice per group was necessary to demonstrate a 20% relative increase in percentage freezing time with 6% of standard deviation with 80% power at the 0.0125 α level (after adjusting for 4 comparisons) to reach a significant difference.

A 2-tailed P value <.05 was considered statistically significant for 2-group comparisons, and the significance threshold was adjusted for multiple comparisons with a Bonferroni correction. Prism 6 (GraphPad Software Inc, La Jolla, CA) was used to conduct the statistical analyses.

RESULTS

Twenty-four Hours of SF Induces Memory Dysfunction and Increases Systemic and Neuroinflammatory Mediators

NOR test was assessed after 24 hours of SF. Sleep-fragmented animals were unable to differentiate between the familiar and the novel object as opposed to the control group that spent significantly more time at the novel object relative to the familiar (difference in time spent between novel and familiar object for control was 4.7 ± 1.4 seconds, n = 8 versus SF difference in time spent of −0.5 ± 0.2 seconds, n = 11; the mean estimated treatment effect size was 5.2 seconds [95% confidence interval {CI}, 2.6–7.7], P < .001; Figure 2). SF insult also produced a hippocampal-dependent memory dysfunction as evidenced by a significant decline in freezing time at day 3 on TFC (49.3% ± 5.8% versus 32.9 ± 5.8, n = 10, estimated treatment effect = 16.4 [95% CI, 11.0–21.8], P < .0001; Figure 3A).

SF produced an increase in systemic IL-6 that went from 0.0 (0.0–2.4) pg/mL in control versus 9.7 (6.3–12.9) pg/mL after SF, yielding an estimated treatment effect of 9.7 pg/mL (95% CI, 5.8–11.8), n = 8/group that was highly statistically significant (P < .0001; Figure 4) and a significant increase in hippocampal mRNA expression of TNF-α (relative quantitation [RQ] 5.12-fold difference [95% CI, 1.64–15.97], n = 5, P < .05; Figure 5A). Neither hippocampal mRNA expression of IL-6 (RQ 2.45-fold difference, n = 5, P = .09; Figure 6A) nor IL-1β (RQ 1.04-fold difference, n = 5, P = .46; Figure 7A) was significantly changed by SF.

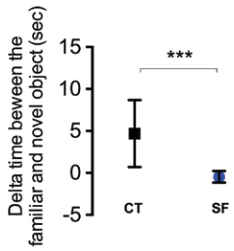

Figure 2. Effect of 24 hours of sleep fragmentation (SF) on nonhippocampal memory function assessed by using novel object recognition test (n = 11 control [CT], n = 8 SF; ***P < .001).

Surgery Induces Memory Dysfunction and Increases Neuroinflammatory Mediators

Surgery significantly decreased the percentage of freezing time (30.3% ± 3.3%, n = 10) when compared with the control group (49.3% ± 5.8%, n = 10); surgical estimated treatment effect was 19.0% (95% CI, 14.6–23.4) (P < .0001; Figure 3B). Twenty-four hours after surgery, we observed a significant increase in hippocampal mRNA expression of IL-6 (RQ 4.64-fold difference [95% CI, 1.48–14.56], n = 5, P < .05; Figure 6B) and TNF-α (RQ 5.54-fold difference [95% CI, 2.92–10.51], n = 5, P < .01; Figure 5B). Hippocampal mRNA expression of IL-1β was not different (RQ 1.57-fold difference, n = 5, P = .32; Figure 7B).

Perioperative SF Enhanced the Neuroinflammatory Response to Surgery but Did Not Exacerbate Surgery-Induced Memory Impairment

When SF was performed either preoperatively (SF + Sx) or postoperatively (Sx + SF), there was a significant increase in hippocampal mRNA expression of IL-6 (RQ 9.52-fold difference for SF + Sx [95% CI, 2.57–35.33], n = 5, P < .01 and RQ 4.61-fold difference for Sx + SF [95% CI, 1.59–13.31], n = 5, P < .05; Figure 6C), TNF-α (RQ 15.00-fold difference for SF + Sx [95% CI, 3.90–57.64], n = 5, P < .01, and RQ 7.60-fold difference for SX + SF [95% CI, 3.63–15.91], n = 5, P < .01; Figure 5C) but not for IL-1β (RQ 3.69-fold difference for SF + Sx [95% CI, 1.25–10.90]; n = 5, P = .07 and RQ 1.14-fold difference for Sx + SF [95% CI, 0.30–4.23], n = 5, P = .86; Figure 7C).

Memory impairment was not further exacerbated when SF is applied either preoperatively (49.3% ± 5.8% versus 43.9% ± 13.1% [95% CI, −6.2 to 17.0], n = 10, P = .56) or postoperatively (49.3% ± 5.8% versus 38.5% ± 12.3% [95% CI, −0.7 to 22.41], n = 10, P = .07; Figure 3C).

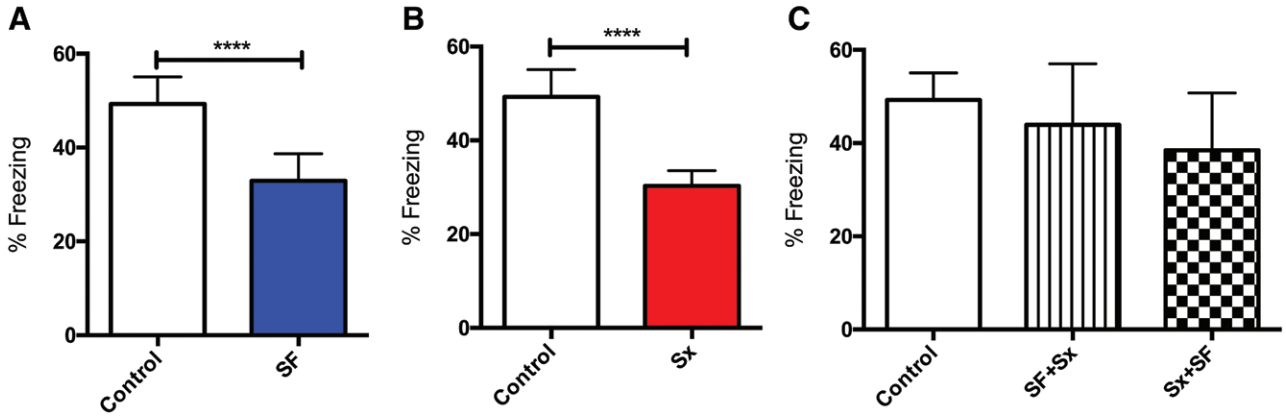

Figure 3. A–C, Effects of perioperative sleep fragmentation (SF) on cognitive decline. Contextual fear response reveals hippocampal-dependent memory impairment at day 3. Quantification of the freezing time percentage according to the 5 groups (n = 10; ***P < .001, ****P < .0001). Sx, tibia surgery.

DISCUSSION

Dissociation Between Neuroinflammation and Cognitive Test

SF disrupts memory in both a nonhippocampal- and a hippocampal-dependent manner. We show that although SF and surgery can independently produce significant memory impairment (Figures 2 and 3), perioperative SF significantly increased hippocampal inflammation (Figures 5 and 6) without further cognitive impairment (Figure 3C). This dissociation between neuroinflammation and cognitive decline may relate to our use of memory paradigms that do not capture all aspects of cognition or a preconditioning effect. Variations in behavior are thought to derive from lasting changes in synaptic strength and neuronal excitability. Plasticity is thought to play a key role in the physiological development of neural circuitries, and recent evidence shows that the impairment of mechanisms of neuroplasticity may underlie changes in memory.[27] During systemic or central nervous system inflammation, the modulation exerted by neuroinflammatory mediators on synaptic plasticity might negatively or positively influence brain neuronal networks functioning.[28] Activation of a cytokine network in the brain is a physiologic relevant phenomenon not only for long-term potentiation maintenance, but also for certain types of learning.[29] Interfering with cytokine signaling can either inhibit or support long-term potentiation maintenance.[29] The hippocampus is particularly prone to develop synaptic transmission and plasticity deficits during inflammatory processes.[30]

We chose an SF model that is characterized by a decrease in rapid eye movement (REM) and non-rapid eye movement (NREM) sleep.[19] This type of sleep disturbance closely resembles both patients with OSA and also the type of sleep disorder reported in acute care facilities.[31,32] During recovery, mice exhibit a rebound in REM sleep time and an increase in the depth of NREM sleep as measured by delta (1–4 Hz) power in the electroencephalogram.[19]

Although SF and surgery separately produced memory dysfunction, when combined, cognitive function reverted back to the control state. It may be possible that by day 3 the rebound REM and NREM sleep is enough to restore the brain to a state that is capable of appropriately processing sensory input. It has been shown that rebound sleep shortly after stroke onset may be causally associated with neuroprotection through an ischemic preconditioning mechanism.[33] The neuroprotective effects of acute sleep deprivation are in agreement with previous reports of neuroprotection and attenuation of microglial responses in rats subjected to global ischemia.[34]

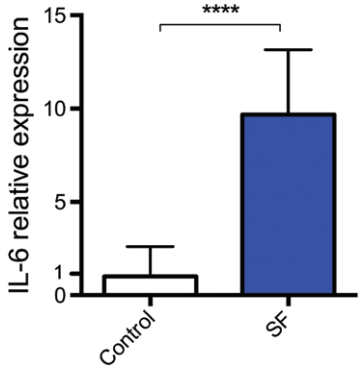

Figure 4. Effect of 24-hour sleep fragmentation (SF) on systemic interleukin-6 (IL-6) serum concentration. IL-6 expression data were normalized according to the mean value of the control group and received a log transformation (ln[X]) (n = 8; ***P < .001).

Limitations

One of the caveats of our study is that sleep deprivation/SF methods can induce stress responses, which may affect memory,[35–38] whereas some studies have shown that SF methods only modestly elevate plasma corticosterone.[39] It could be argued that stress is a confounding factor, producing immobility and thus influencing the amount and extent of freezing in fear conditioning. Our study's design attempts to address this concern by delaying the context session in the trace fear paradigm test by 3 days after surgery and/or SF; we also chose an SF method in which animals are kept in their original environmentally enriched home cages, thus mitigating the amount of stress. From our previous work, we have demonstrated that the surgical memory dysfunction phenotype is still present at day 3 while inflammatory markers are back to normal levels. Stress corticosteroids may underlie some of the deficits identified in both sleep-fragmented humans and animals in our model. Even if our model does have a stress response associated, it is also a normal response to sleep deprivation in humans and not a potential cofounder.[40]

Cytokines were determined at different time points than the behavioral measurements. Although we used

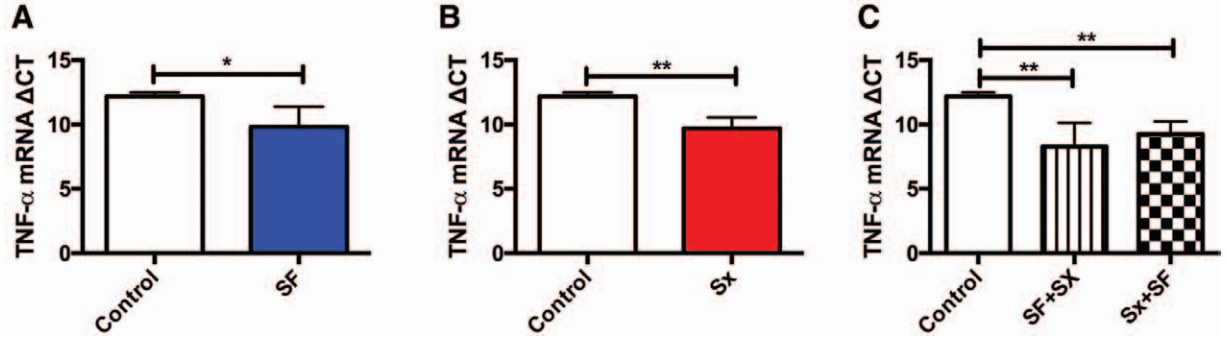

Figure 5. A–C, Effects of perioperative sleep fragmentation (SF) on hippocampal transcription of tumor necrosis factor (TNF)-α (ΔCT) 24 hours after tibia surgery (n = 5; *P < .05; **P < .01; ***P < .001; for each panel we used the same control). Sx indicates tibia surgery.

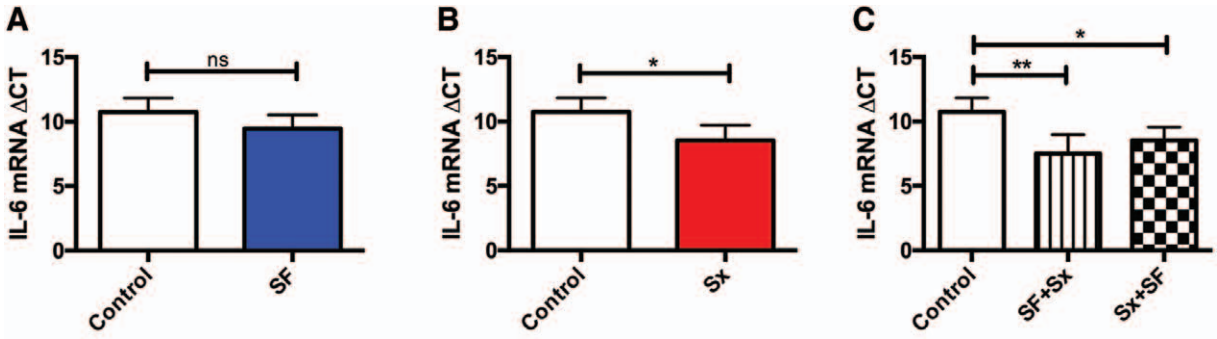

Figure 6. A–C, Effects of perioperative sleep fragmentation (SF) on hippocampal transcription of interleukin-6 (IL-6) (ΔCT) 24 hours after tibia surgery (n = 5; *P < .05; **P < .01; for each panel we used the same control). Sx indicates tibia surgery.

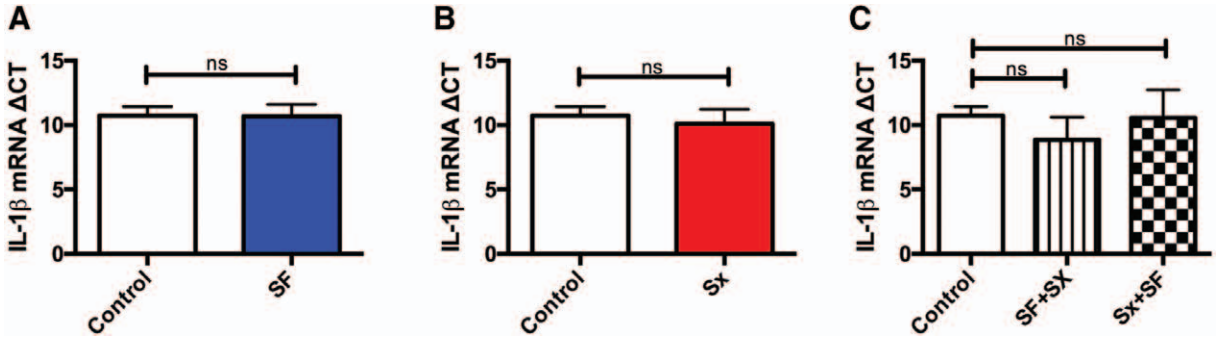

Figure 7. A–C, Effects of perioperative sleep fragmentation (SF) on hippocampal transcription of interleukin-1β (IL-1β) (ΔCT) 24 hours after tibia surgery (n = 5; ns; for each panel we used the same control). Sx indicates tibia surgery; ns, not significant.

our previous experience in cytokine profile,[41,42] we cannot assure that harvesting samples and measuring behavior at the same times would have yielded different results.

Another limitation of our work with several experiments is that we did not adjust the P value for multiple tests, which makes our results more exploratory and hypothesis-generating.

These data support the need to adopt interventions that can provide patients with appropriate rest to mitigate neuroinflammation. Although we recognize that the etiology of cognitive dysfunction in surgical/ICU patients may be multifactorial, if the restorative and reparative benefits of sleep mitigate the development of inflammation, this may result in shorter ICU or postoperative lengths of stay. Subsequent studies are warranted to both understand the mechanisms involved in the reversion of memory function after SF and also improve our knowledge of postoperative cognitive dysfunction and ameliorate its adverse effects.

DISCLOSURES

Name: Susana Vacas, MD, PhD.
Contribution: This author helped design the study, conduct the study, collect the data, analyze the data, and prepare the manuscript.
Conflicts of Interest: None.
Name: Vincent Degos, MD, PhD.
Contribution: This author helped analyze the data and prepare the manuscript.
Conflicts of Interest: None.
Name: Mervyn Maze, MB, ChB.
Contribution: This author helped design the study, analyze the data, and prepare the manuscript.
Conflicts of Interest: Mervyn Maze is the coinventor of the use of dexmedetomidine for sedation; dexmedetomidine is being investigated as a nondelirium-producing sedative. Dr Maze does not and will not receive royalties on the sales of dexmedetomidine for its sedative and putative delirium-reducing indications. Dr Maze is also the coinventor of the use of xenon for neuroprotection and cofounder of NeuroproteXeon that is pursuing the commercial use of xenon for neuroprotection that may include delirium reduction.
This manuscript was handled by: David Hillman, MD.

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