UWL REPOSITORY

repository.uwl.ac.uk

Effects of propofol and sevoflurane on social and anxiety-related behaviours in sleep-deprived rats

Zhu, Jinpiao, Chen, Chang, Wu, Jinfeng and Manyande, Anne ORCID: https://orcid.org/0000-0002-8257-0722 (2023) Effects of propofol and sevoflurane on social and anxiety-related behaviours in sleep-deprived rats. British Journal of Anaesthesia, 131. pp. 531-541.

http://dx.doi.org/10.1016/j.bja.2023.05.025

This is the Published Version of the final output.

UWL repository link: https://repository.uwl.ac.uk/id/eprint/11433/

Alternative formats: If you require this document in an alternative format, please contact: open.research@uwl.ac.uk

Copyright: Creative Commons: Attribution-Noncommercial-No Derivative Works 4.0

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy: If you believe that this document breaches copyright, please contact us at open.research@uwl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

BJA

British Journal of Anaesthesia, 131 (3): 531–541 (2023)

doi: 10.1016/j.bja.2023.05.025
Advance Access Publication Date: 4 August 2023
Neuroscience and Neuroanaesthesia

Effects of propofol and sevoflurane on social and anxiety-related behaviours in sleep-deprived rats

Jinpiao Zhu[1,†], Chang Chen[1,†], Jinfeng Wu[2,3], Mengying He[1,2], Shuang Li[2], Yuanyuan Fang[1,2], Yan Zhou[4], Haibo Xu[5], Saeed Sadigh-Eteghad[6], Anne Manyande[7], Feng Zheng[1], Ting Chen[1], Fuqiang Xu[2,3], Daqing Ma[8,9], Jie Wang[2,3,*] and Zongze Zhang[1,*]

[1]Department of Anesthesiology, Zhongnan Hospital, Wuhan University, Wuhan, China, [2]Key Laboratory of Magnetic Resonance in Biological Systems, State Key Laboratory of Magnetic Resonance and Atomic and Molecular Physics, National Center for Magnetic Resonance in Wuhan, Wuhan Institute of Physics and Mathematics, Innovation Academy for Precision Measurement Science and Technology, Chinese Academy of Sciences-Wuhan National Laboratory for Optoelectronics, Wuhan, China, [3]University of Chinese Academy of Sciences, Beijing, China, [4]Frontier Science Center for Immunology and Metabolism, and Medical Research Institute at School of Medicine, Wuhan University, Wuhan, China, [5]Department of Radiology, Zhongnan Hospital, Wuhan University, Wuhan, China, [6]Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran, [7]School of Human and Social Sciences, University of West London, London, UK, [8]Division of Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, Chelsea and Westminster Hospital, London, UK and [9]Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China

*Corresponding authors. E-mails: jie.wang@apm.ac.cn, zhangzz@whu.edu.cn
[†]These authors contributed equally to this work.

Abstract

Background: Sleep disorders can profoundly affect neurological function. We investigated changes in social and anxiety-related brain functional connectivity induced by sleep deprivation, and the potential therapeutic effects of the general anaesthetics propofol and sevoflurane in rats.

Methods: Twelve-week-old male Sprague–Dawley rats were subjected to sleep deprivation for 20 h per day (from 14:00 to 10:00 the next day) for 4 consecutive weeks. They were free from sleep deprivation for the remaining 4 h during which they received propofol (40 mg kg^{-1} i.p.) or sevoflurane (2% for 2 h) per day or no treatment. These cohorts were instrumented for EEG/EMG recordings *on days 2, 14, and 28*. Different cohorts were used for open field and three-chambered social behavioural tests, functional MRI, nuclear magnetic resonance spectroscopy, and positron emission tomography imaging 48 h after 4 weeks of sleep deprivation.

Results: Propofol protected against sleep deprivation-induced anxiety behaviours with more time (44.7 [8.9] s *vs* 24.2 [4.1] s for the sleep-deprivation controls; P<0.001) spent in the central area of the open field test and improved social preference index by 30% (all P<0.01). Compared with the sleep-deprived rats, propofol treatment enhanced overall functional connectivity by 74% (P<0.05) and overall glucose metabolism by 30% (P<0.01), and improved glutamate kinetics by 20% (P<0.05). In contrast, these effects were not found after sevoflurane treatment.

Conclusions: Unlike sevoflurane, propofol reduced sleep deprivation-induced social and anxiety-related behaviours. Propofol might be superior to sevoflurane for patients with sleep disorders who receive anaesthesia, which should be studied in clinical studies.

Keywords: functional connectivity; propofol; REM sleep; sevoflurane; sleep deprivation; social behaviour

Received: 23 August 2022; **Accepted:** 16 May 2023

© 2023 The Authors. Published by Elsevier Ltd on behalf of British Journal of Anaesthesia. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
For Permissions, please email: permissions@elsevier.com

Editor's key points

- Sleep deprivation might contribute to adverse neurological events in the perioperative period.
- General anaesthetics might contribute to perioperative sleep disruption.
- Propofol protected against sleep-deprivation in contrast anxiety relative to sevoflurane.
- Propofol also increased postoperative functional connectivity and glucose metabolism in medial prefrontal cortex by brain imaging.

Brain health requires efficient glucose metabolism and regional (e.g. medial prefrontal cortex [mPFC]) functional integrity and connections,[1,2] and these are affected following sleep deprivation.[3] Sleep disorders are a public health problem globally,[4] and are also common in surgical patients.[5,6] Indeed, sleep disturbance has been found to be prevalent in postoperative patients, with an incidence up to 64.9%, which is caused by a variety of factors such as surgical trauma, pain, stress, and environmental noise.[6–10] Poor sleep quality is highly correlated with delayed recovery and cognitive function impairment as well as adverse cardiovascular events.[7] Therefore, reducing sleep disturbance, especially in patients before or following surgery, is urgently needed.

Previous studies have suggested that propofol anaesthesia facilitates recovery from rapid eye movement (REM) and non-REM (NREM) sleep deprivation[11]; however, this was not the case during or after sevoflurane anaesthesia.[12] Propofol was reported to increase glutamatergic excitatory synaptic transmission in the lateral habenula region and the spontaneous discharge rate of dopamine neurones in the ventral tegmental area, which potentially contributed to euphoric moods.[13,14] It is possible that propofol modulates emotion-related behaviours by improving both REM homeostasis and glutamatergic neuronal activity. Sleep deprivation considerably affected the functional connectivity in the mPFC.[15] The prelimbic cortex and the anterior cingulate cortex as mPFC subregions have long been thought to play a critical role in emotional and social processing. We hypothesised that enhancing REM sleep by propofol treatment during recovery from REM sleep deprivation is related to increased mPFC functional connectivity.

We carried out a series of studies, including analysing animal behaviours, EEG/EMG recordings, resting-state functional MRI (fMRI), and [^{18}F]-fluorodeoxyglucose positron emission tomography imaging (^{18}F-FDG-PET) to explore the effectiveness of anaesthetic (propofol *vs* sevoflurane) treatment on the restoration of neurological function after chronic sleep deprivation. Our aim was to understand the potential usefulness of propofol for improving sleep disorders of surgical patients whose sleep is commonly deprived. Our findings raise the possibility of using propofol to treat and facilitate recovery from chronic sleep disorders.

Methods

Animals

All animal procedures were approved by the Animal Ethics Committee of Wuhan University (WP2020-08075), and followed the ARRIVE (Animal Research: Reporting of *In Vivo* Experiments) guidelines. Twelve-week-old male Sprague–Dawley rats were purchased from Liaoning Changsheng Biotechnology Co. (Liaoning, China) (No: 110324200102912763). They were group-housed, five per cage, under controlled temperature (23°C [SD 1°C]), a 12-h light–dark cycle, and with free access to food and water. Rats that were exposed to vehicle or 60% O_2 served as the treatment controls; these treatments did not affect their sleep architecture (Supplementary Fig. S1). Therefore, these two control groups were omitted from further studies. Animals were randomly divided into four groups and used in the rest of the formal experiments, as follows: (1) naive control group (*ad libitum* sleep–wake, Con group); (2) 4 h of natural sleep after 20 h of continuous sleep deprivation (CSD+NS); (3) propofol treatment after 20 h of continuous sleep deprivation (CSD+Pro) and (4) sevoflurane exposure after 20 h of continuous sleep deprivation (CSD+Sev).

REM sleep deprivation

REM sleep deprivation was accomplished using the modified multiple platform technique.[16,17] The sleep deprivation tank (815×570×505 mm) consisted of 20 pedestals (OD 6 cm) arranged ~7 cm apart. The tank was filled with water up to ~1 cm below the top of the pedestals, which allowed movement of the rat between pedestals but decreased sleep (Fig. 1). The control cage consisted of a wire grid elevated over the water. Rats were placed in the sleep deprivation tank for 20 h per day (from 14:00 to 10:00 the following day) and allowed sleep recovery *ad libitum* for 4 h (from 10:00 to 14:00) of the rest of the day for 4 weeks, as reported previously.[17] The timeline of the experiment is shown in Figure 1.

Administration of anaesthetics

The rats in the CSD+Pro group were treated with a bolus injection of propofol (i.p. injection 40 mg kg^{-1}, AstraZeneca, Cambridge, UK) once a day for 4 continuous weeks following sleep deprivation, which induced loss of righting reflex (LORR) for about 1 h and sleep for another 1 h. The rats in the CSD+Sev group were exposed to sevoflurane (Maruishi Chemical Pharmaceutical Co., Ltd., Tsurumi-ku, Osaka, Japan) following sleep deprivation according to our previous study.[18] Briefly, they were exposed to ~2.0% sevoflurane (~1 inspired minimum alveolar concentration values[19]) mixed with 60% O_2 balanced with nitrogen in an anaesthesia chamber (30×30×20 cm) for 2 h, once/day, for 4 continuous weeks. The 'equi' potent dose of sevoflurane and propofol was noted with similar onset time (400–500 s) of LORR (Supplementary Fig. S2), and similar sedative duration
(2 h) and EEG delta/theta power ratio (Supplementary Fig. S3). Controlled body temperature (between 36.5°C and 37.5°C) was maintained by a heat pad. The physiological states of the rats were recorded using an animal monitoring system (PhysioSuite, Kent Scientific Co., Torrington, CT, USA). Their body temperature, heart rate, sevoflurane concentration, and oxygen saturation measured by pulse oximetry of the toe (SpO_2) were continuously monitored throughout anaesthetic-induced sedation (Supplementary Fig. S4).

EEG and EMG recording and analysis

Four stainless steel screws with wire leads and two Teflon-coated stainless steel wires were used as the electrodes for

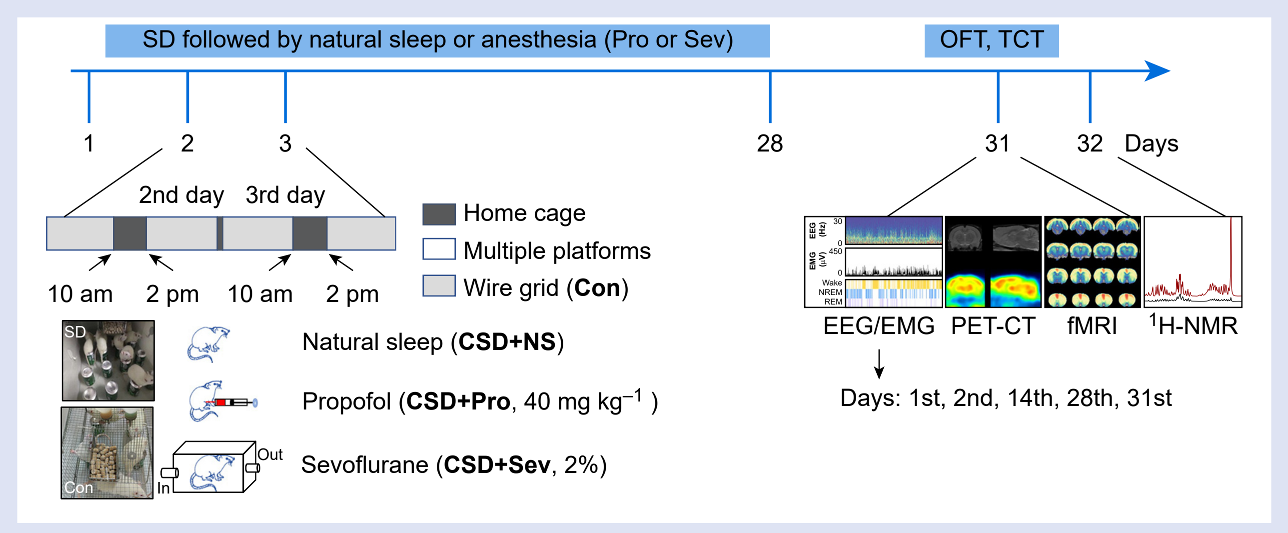

Fig 1. Illustration of the experimental design. Four different groups were involved: (1) naive control group (*ad libitum* sleep–wake, Con group); (2) 4 h of natural sleep after 20 h continuous sleep deprivation (CSD+NS); (3) propofol treatment after 20 h continuous sleep deprivation (CSD+Pro); and (4) sevoflurane exposure after 20 h continuous sleep deprivation (CSD+Sev). The model and treatment regimen continued for 28 days. Rat sleep states were investigated by EEG/EMG, the glucose metabolism by [^{18}F]-fluorodeoxyglucose positron emission tomography imaging (^{18}F-FDG-PET), the functional connectivity calculation in the whole brain by functional MRI (fMRI) and behavioural tests including open field test (OFT) and three-chamber social test (TCT) on day 31; and the metabolic kinetics study by ^{1}H-NMR on day 32. SD, sleep deprivation.

EEG and EMG recordings, respectively (see Supplementary material).

Animal behavioural studies

The rats received the open field test and three-chambered social test on day 31 (see the Supplementary material).

^{18}F-FDG PET scanning

After 48-h recovery from sleep deprivation, rats fasted for 12 h and were subjected to PET-CT scan (Raycan Technology Co., Ltd., Suzhou, China) (see Supplementary material).

fMRI data acquisition

Rats in all groups were scanned on a 7.0-T animal MRI scanner (Bruker Biospin GmbH, Germany) under 1.0–1.5% isoflurane light anaesthesia without cardiorespiratory depression. The detailed scanning procedure was described previously.[20] Detailed scanning protocol and data acquisition and processing are presented in the Supplementary material.

Proton nuclear magnetic resonance spectroscopy

The animals were used for the proton nuclear magnetic resonance spectroscopy (^{1}H-NMR) study to investigate the metabolic kinetics in the frontal, parietal, and temporal cortex, striatum, thalamus, occipital cortex, hippocampus, hypothalamus, midbrain, and pons. Brain sample preparation, NMR spectra acquisition, and data processing are presented in the Supplementary material.

Statistical analysis

The sample size was calculated based on our preliminary data, which showed that REM sleep deprivation caused hallmark symptoms of anxiety, as evidenced by decreased time spent in the central area of the open field test to 20 (4) s. If treatment improves anxiety by 40–45%, with a desired power of 80% and type I error set at 0.05,[21] then n=6–7/group was required. Therefore, n=6–8/group was used subsequently for experiments. For PET scanning, a minimum of n=3 is required as reported[22] and also confirmed in our study with G*Power analysis (see Supplementary Fig. S5). Data were tested for normality using the Shapiro–Wilk test and are presented as mean (SD) and dot plot to facilitate visual comparisons. Data were analysed with SPSS 20.0 (SPSS Inc., Armonk, NY, USA). One- or two-way analyses of variance were performed followed by Tukey's *post hoc* test and Bonferroni corrections for multiple comparisons where appropriate. A P-value less than 0.05 was considered to be of statistical significance.

Results

All animals went through the whole study, and no deaths occurred during the experiments.

Propofol reduced sleep deprivation-related social and anxiety behaviours

Example trace recordings during 5-min open field test on day 31 in a rat from each group show that Con and CSD+Pro rats spent more time in the centre zone compared with those in the CSD+NS or CSD+Sev rats (Fig. 2a). The time spent in the core area in the CSD+NS rats was 24.2 (4.1) s, and propofol treatment increased the time spent in the core area to 44.7

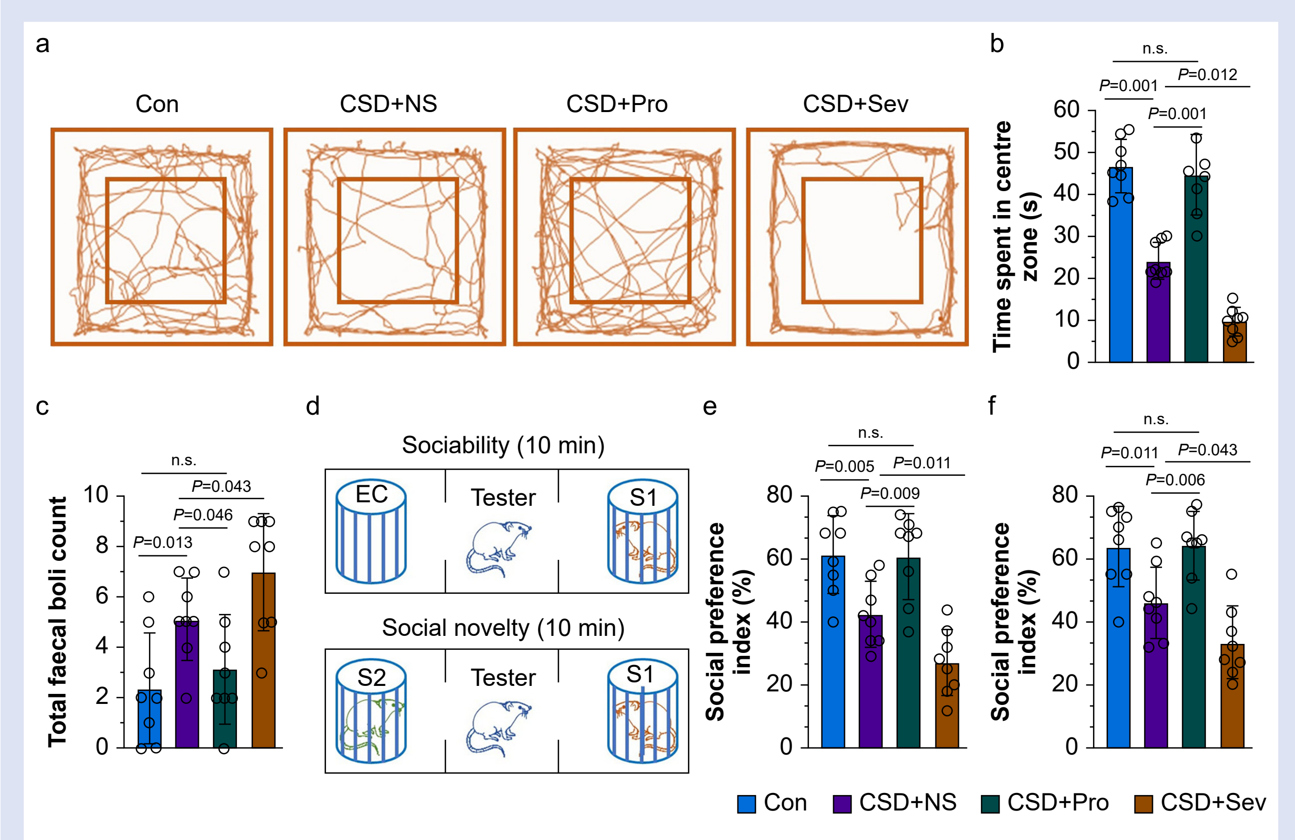

Fig 2. Propofol ameliorated sleep deprivation-related social and anxiety behaviours. (a) Representative trace of a rat in each group in the open field arena. (b) Quantification of time spent in the centre, and (c) faecal boli counts in the open field test. (d) Schematic diagrams of the three-chamber social test. (e) Quantification of time spent in the chamber with the empty wire cup (EC) and the chamber with the stranger 1 (S1) rat during the sociability test, and time spent in the chamber with the S1 rat and the chamber with the newly introduced stranger 2 (S2) rat during the social novelty test. Data are presented as mean (sd), n=8. Con, naive controls; CSD+NS, sleep deprivation controls; CSD+Pro, sleep-deprived rats treated with propofol; CSD+Sev, sleep-deprived rats exposed to sevoflurane, n.s., not significant. Data were compared using a two-way analysis of variance, and the p-values were adjusted using Bonferroni correction for multiple comparisons.

(8.9) s (P<0.05), whereas sevoflurane exposure significantly decreased this time to 9.7 (3.1) s (P<0.05) (Fig. 2b). Faecal boli counts showed that propofol significantly decreased faecal boli, whereas sevoflurane significantly increased faecal boli compared with CSD+NS (Fig. 2c). Data derived from the sociability and social novelty test (Fig. 2d) showed that CSD+Pro (60.6% [12.7%]) but not CSD+Sev (27.0% [9.8%]) treated rats spent more time with stranger 1 (Fig. 2e), compared with the CSD+NS group (42.4% [9.7%]). For the social novelty test, the CSD+Pro rats (64.1% [10.0%]), but not CSD+Sev (33.3% [10.7%]), had a preference for the newly introduced stranger 2 (Fig. 2f) in comparison with the CSD+NS group (46.0% [10.8%]).

Propofol promoted REM sleep after sleep deprivation

Sleep deprivation almost eliminated REM sleep (from 10.1% [2.4%] to 1.67% [0.12%]; P<0.001) (Fig. 3b). Representative EEG and EMG spectrograms in rats with or without propofol or sevoflurane treatment during sleep-deprived days 2, 14 and 28 were recorded and sleep structure pattern changes were noted (Fig. 3c–f). Further analyses showed that the percentage of REM sleep during the 4 h of recovery was significantly increased with propofol treatment (P<0.05, day 2, 21.1% [5.8%]; day 14, 23.0% [4.4%]; day 28, 23.9% [4.7%]) compared with those without any treatment (day 2, 14.8% [1.7%]; day 14, 16.2% [2.2%]; day 28, 14.4% [2.8%]) or treated with sevoflurane (day 2, 15.8% [5.0%]; day 14, 18.9% [2.3%]; day 28, 19.4% [3.5%]) throughout the study course (Fig. 3g–i). The REM and NREM sleep patterns were similar among the groups 48 h after recovery from treatments (Fig. 3j).

Propofol improved global brain glucose metabolism

Glucose metabolism, detected by [^{18}F]-FDG-PET scan, was decreased by 50% in most brain regions except in the pons (no changes), compared with those in Con after REM sleep deprivation (Supplementary Fig. S5 a and b; Supplementary Table S1). In CSD+Pro but not CSD+Sev rats, brain glucose metabolism improved by 80% in the mPFC compared with that in the Con group (4.3 [0.6] vs 5.3 [0.3]) (Supplementary Fig. S5a and b; see details in Supplementary Table S1). The areas under curves (AUCs) derived from Supplementary Fig. S5b further suggested that propofol treatment improved overall glucose metabolism by

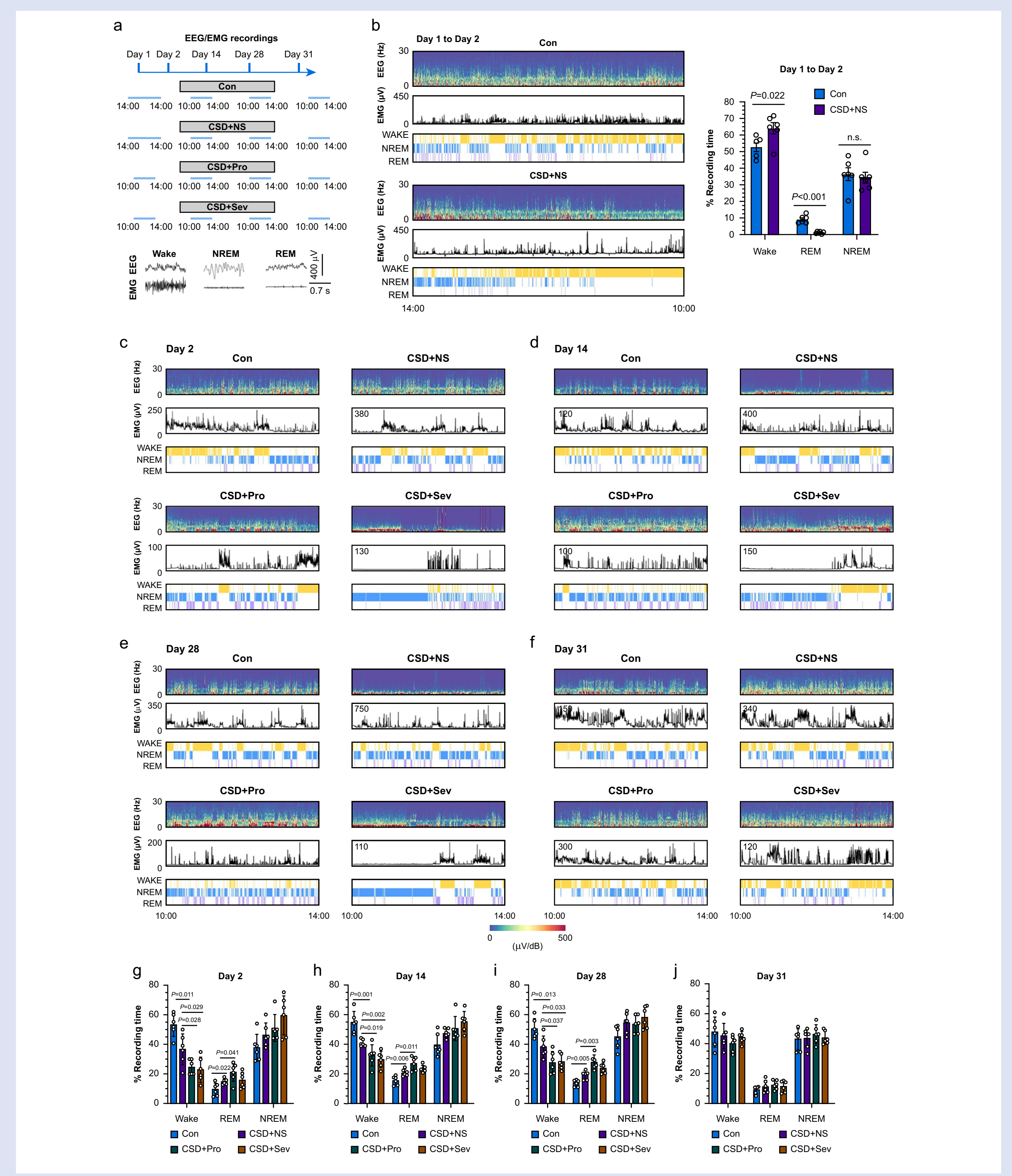

Fig 3. Propofol promoted REM sleep after sleep deprivation. (a) Schematic timeline of EEG and EMG recordings for four groups and representative signal profiles of EEG and EMG during wake, NREM, and REM state. (b) Representative spectrogram of EEG (top), EMG (middle), and brain states (bottom) annotated in the naive controls and sleep-deprived rats from 14:00 on day 1–10:00 on day 2 (left panel). Quantification of different sleep states (right histogram) in the naive and sleep-deprivation controls. The EMG data are presented as the RMS (y-axis). (c–f) Representative spectrogram of EEG (top), EMG (middle), and brain states (bottom) illustrated for four different groups for the period of 4 h (10:00 - 14:00) sleep recovery on day 2 (c), day 14 (d), day 28 (e), and day 31 (f). (g–j) Quantification of different sleep states for four different groups for the period of 4 h (10:00 - 14:00) sleep recovery on day 2 (g), day 14 (h), day 28 (i), and day 31 (j). Data are presented as mean (SD); n=6. Data were compared using a two-way analysis of variance, and the p-values were adjusted using Bonferroni correction for multiple comparisons. Con, naive controls; CSD+NS, sleep deprivation controls; CSD+Pro, sleep-deprived rats treated with propofol; CSD+Sev, sleep-deprived rats exposed to sevoflurane; NREM, non-REM; n.s., not significant; REM, rapid eye movement.

30% (P<0.05), whereas sevoflurane did not significantly affect glucose metabolism (P>0.05) (Supplementary Fig. S5c).

Propofol enhanced mPFC functional connectivity impaired by sleep deprivation

The prelimbic cortex is critical for complex behaviours such as sociability and emotion[23] a priori we selected prelimbic cortex a core area for brain functional connectivity analyses measured by fMRI (Fig. 4a). The CSD+NS rats exhibited an average 36.6% decrease in connectivity across all scanned brain regions, for example, hippocampal (Pearson's correlation coefficient (*r*)=0.26 ([0.15] *vs* 0.45 [0.11]) of the Con group] and auditory cortex (*r*=0.36 [0.10] *vs* 0.76 [0.10]) connectivity with the prelimbic cortex compared with the Con group (Fig. 4a). Overall functional connectivity between brain regions showed an improvement by 74% (P<0.05) in the CSD+Pro rats but not CSD+Sev compared with the CSD+NS group. Specifically, the functional connectivity between two regions were: prelimbic cortex–hippocampus (*r*=0.62 [0.13] *vs* 0.26 [0.15]), prelimbic–auditory cortex (*r*=0.55 [0.16] *vs* 0.36 [0.10]), cingulate–insular cortex (*r*=0.69 [0.15] *vs* 0.45 [0.13]), cingulate–striatum (*r*=0.67 [0.15] *vs* 0.31 [0.20]), cingulate–primary somatosensory motor (*r*=0.80 [0.10] *vs* 0.53 [0.27]), ventral thalamic–dorsal striatum (*r*=0.40 [0.16] *vs* 0.21 [0.12]), dorsal striatum–retrosplenial granular cortex (*r*=0.55 [0.15] *vs* 0.34 [0.17]), visual cortex–primary somatosensory (*r*=0.63 [0.17] *vs* 0.43 [0.11]), primary somatosensory motor–auditory (*r*=0.66 [0.15] *vs* 0.45 [0.16]), primary somatosensory–retrosplenial granular cortex (*r*=0.60 [0.16] *vs* 0.32 [0.27]) (Fig. 4b–d).

Propofol increased glutamate metabolic kinetics

The ^{1}H-[^{13}C]-NMR spectra acquired from the frontal, parietal, and temporal cortex, striatum, thalamus, occipital cortex, hippocampus, hypothalamus, midbrain, and pons tissue were extracted at 30 min after [1–^{13}C]-glucose i.v. infusion (Fig. 5 and Supplementary Fig. S6). The top spectra represent the total enrichment ^{1}H-[^{12}C+^{13}C], whereas the bottom one depicts ^{13}C labelling of metabolites ^{1}H-[2*^{13}C] from [1–^{13}C]-glucose (Fig. 5a). Further analysis indicated that sleep deprivation reduced the ^{13}C enrichment level of glutamate-C4 (Glu4) in the frontal cortex (12.9% *vs* 15.0% of the Con group), parietal cortex (13.6% *vs* 16.4% of the Con group), striatum (12.4% *vs* 15.0% of the Con group) and thalamus (11.8% *vs* 14.8% of the Con group), whereas propofol but not sevoflurane improved overall the diminished Glu4 enrichment by 20% in these brain regions of the sleep-deprived rats (Fig. 5b). The enrichment of γ-aminobutyric acid-C2 (GABA2) was only decreased in the temporal cortex region in the sleep-deprived rats compared with that of the naive rats (13.8% *vs* 17.9%) (Fig. 5c), and there were no effects found after the treatment of propofol or sevoflurane compared with that of the sleep-deprived rats. The levels of both Glu-C3 and glutamine-C3 (Glx3) enrichment in the frontal, parietal, and temporal cortex, striatum and thalamus were also found to be lower in the sleep-deprived rats (Fig. 5d). Propofol increased Glx3 enrichment in the frontal cortex (6.4% *vs* 5.2%), parietal cortex (6.6% *vs* 5.7%), temporal cortex (5.8% *vs* 4.7%), striatum (5.9% *vs* 4.7%) and thalamus (6.5% *vs* 5.2%) relative to the sleep-deprived rats, but there was no statistical difference in Glx3 enrichment in these brain regions between the sleep-deprived rats with or without sevoflurane (Fig. 5d). However, there were no changes in the regions of occipital cortex, hippocampus, hypothalamus, midbrain, and pons after propofol treatment (Supplementary Fig. S6).

Discussion

We found that REM sleep deprivation induced anxiety and social behavioural deficits, decreased brain global glucose metabolism and glutamate kinetics in various brain regions, and impaired mPFC functional connectivity. Our data show that unlike sevoflurane, propofol provided protection against REM sleep deprivation-induced social and anxiety-related behaviours, which might be associated with REM sleep recovery, mPFC functional connectivity enhancement, and brain metabolism improvement (Fig. 6). The implications of our study are that propofol could be a potential treatment for chronic sleep disorders and might be superior to sevoflurane for patients with poor sleep quality who receive anaesthesia. Indeed, our study could explain why propofol improved sleep quality.[24,25]

Sleep deprivation for 4 weeks significantly reduced global glucose metabolism and functional connectivity in the vast majority of brain regions, which was prevented by propofol but not sevoflurane treatment. We also found that the excitatory and inhibitory neuronal function in the cortices and thalamus was decreased along with derangement in the homeostasis of Glu/Gln metabolism after sleep deprivation. Propofol selectively recovered glutamate metabolic kinetics in several brain regions, including the frontal, temporal and parietal cortex, striatum, and thalamus, which are responsible for anxiety and social behaviours. In contrast, sevoflurane did not alter whole brain glucose metabolism or GABAergic and glutamatergic neurotransmitter fluxes after sleep deprivation. Similarly, propofol anaesthesia was reported to be more effective in normalising extracellular Glu and GABA in the hippocampal CA1 region of rats subjected to 24-h sleep deprivation.[26] A precise balance between glutamatergic and GABAergic systems is critical for restoring optimal brain function.

After REM sleep deprivation, the normal regulation of the limbic system (hypothalamus, amygdala, cingulate cortex, hippocampus) failed, resulting in increased reactivity towards aversive emotional states.[3] The prelimbic and cingulate of mPFC send dense projections to cortical and subcortical regions, including the nucleus accumbens, hippocampus, insular cortex, and amygdala, which are crucial for normal emotion, social interaction, perception, and attention.[27] Along with the decrease in prefrontal activation during or after sleep deprivation, emotions were then deregulated. The anterior cingulate cortex and prelimbic cortex signals contribute to social behaviour and anxiety-like behaviour via modulating the nucleus accumbens, striatum, or amygdala function.[28] We found that propofol ameliorated sleep deprivation-induced anxiety-like behaviours and social deficits and these were likely related to the prelimbic cortex–ventral hippocampus, prelimbic cortex–auditory and cingulate–insular cortex, cingulate–striatum, and cingulate–primary somatosensory motor functional connectivity enhancement. In contrast, sevoflurane does not facilitate functional connectivity recovery. Indeed, sevoflurane was shown to block the episodic memory enhancement associated with emotional arousal at subanaesthetic concentrations, an effect associated with a reduction in connectivity between the amygdala and hippocampus.[29]

Preclinical studies reported that propofol anaesthesia appeared to maintain the homeostasis of both NREM and REM

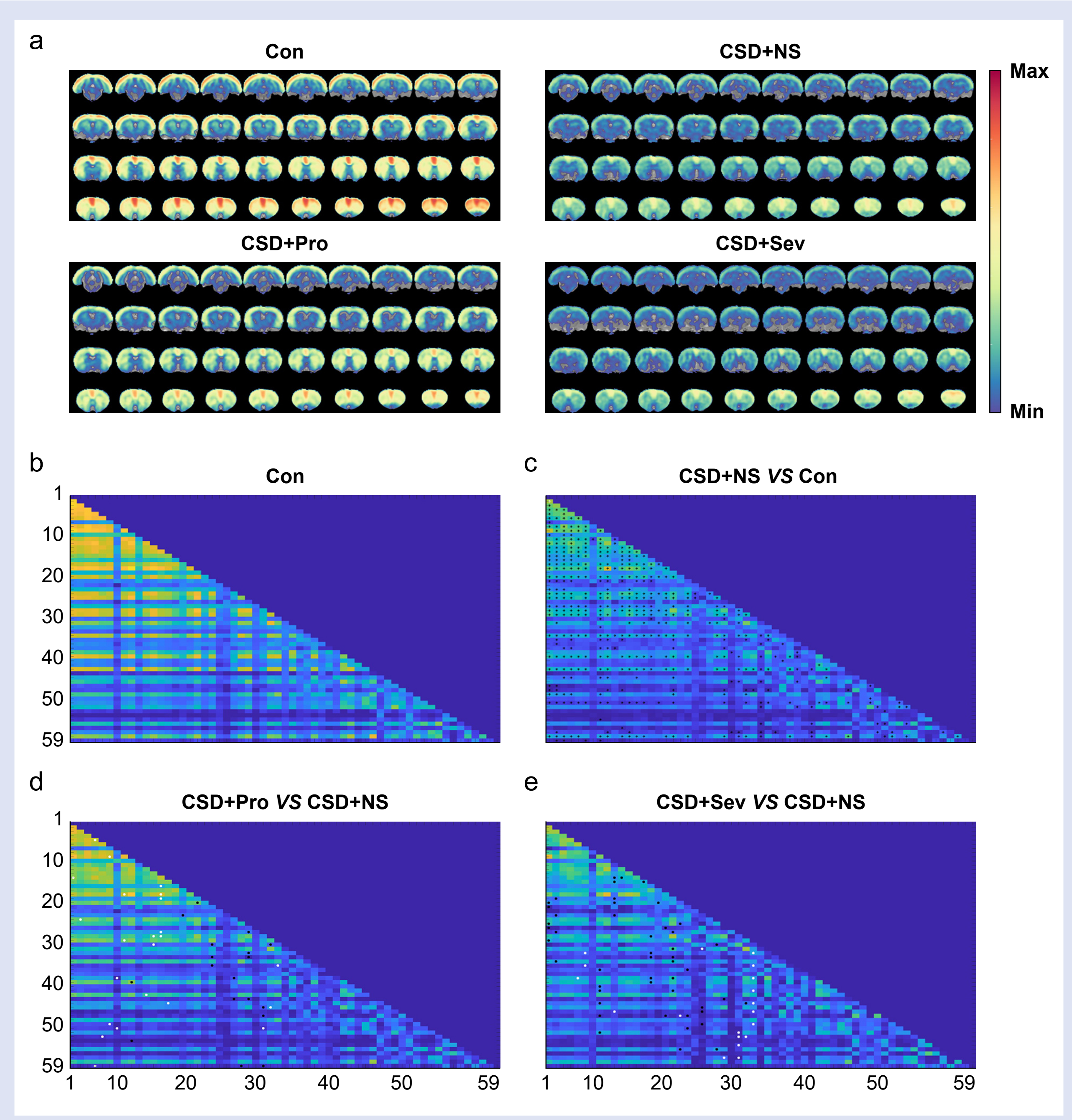

Fig 4. Propofol-enhanced mPFC functional connectivity impaired by sleep deprivation. (a) Representative images of whole brain functional connectivity for the prelimbic cortex in different groups. (b–e) Functional connectivity matrices in 59 brain regions for four groups (the names of the 59 brain regions are listed in Supplementary Table S2). Asterisks show suppressed functional connectivity values compared with the Con group, black dots show suppressed functional connectivity values compared with the CSD+NS group, and white dots show elevated functional connectivity values compared with the CSD+NS group. Data are presented as mean (sd); n=8. Con, naive controls; CSD+NS, sleep deprivation controls; CSD+Pro, sleep-deprived rats treated with propofol; CSD+Sev, sleep-deprived rats exposed to sevoflurane.

sleep.[11] Previous studies also show that propofol used in ICU settings also improved sleep architecture toward normal.[24,25] In contrast, a Cochrane review indicated that there was insufficient evidence to suggest that propofol improves the quality and quantity of sleep in the ICU.[30] However, we found that the REM but not NREM sleep was recovered with propofol treatment under the REM sleep-deprived condition. The discrepancy between these studies and our study is unknown but likely a result of the acute *vs* chronic experimental settings, the dosage of propofol,[31] and the health status of study subjects,[32] but this warrants further study. Furthermore, in line with previous studies using an REM sleep deprivation

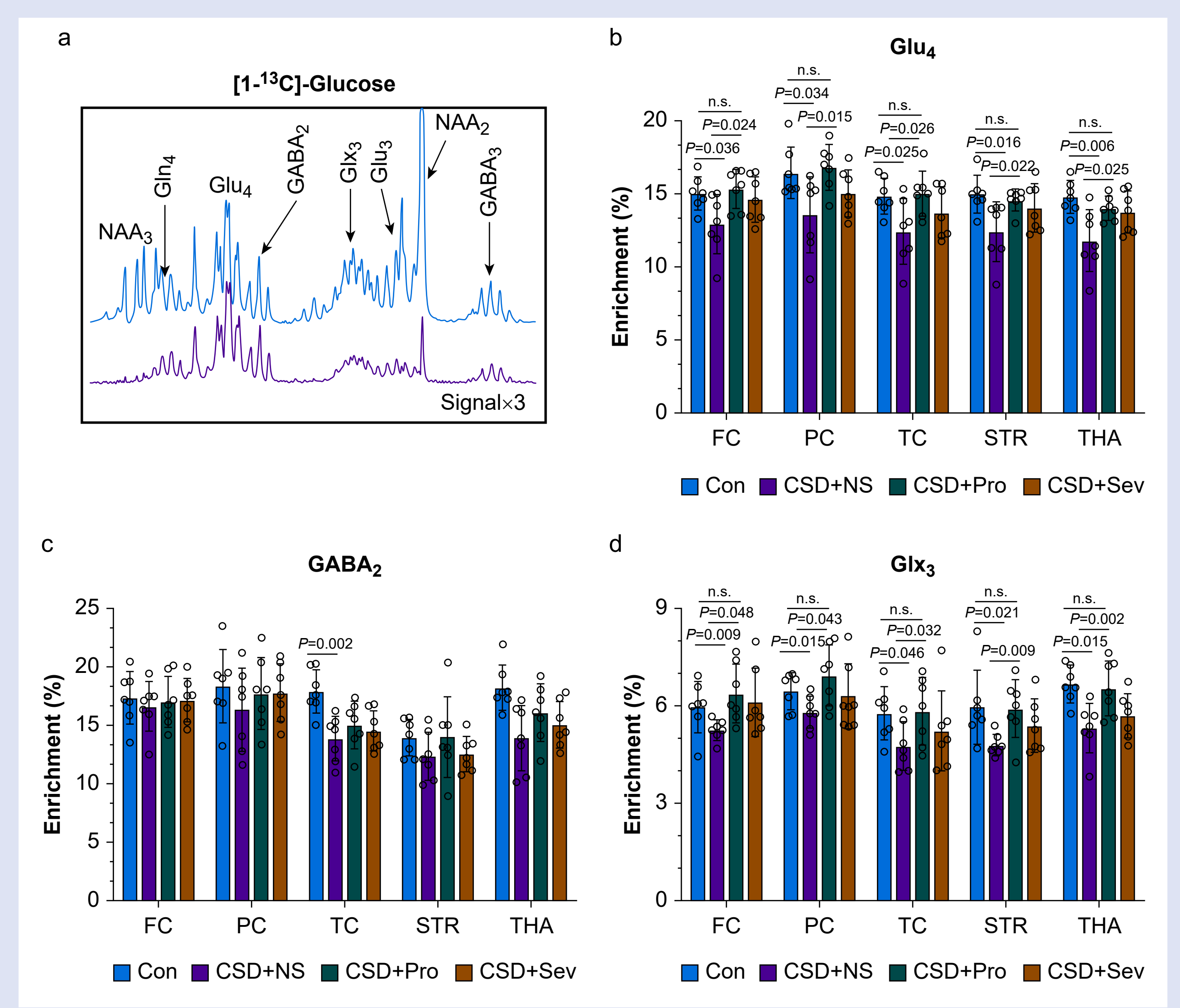

Fig 5. Propofol increased glutamate metabolic kinetics. (a) ^{1}H-[^{13}C]-NMR spectra obtained from the frontal cortex (FC), parietal cortex (PC), temporal cortex (TC), striatum (STR), and thalamus (THA) tissue extract at 30 min after [1−^{13}C]-glucose i.v. infusion. The top spectrum (black) represents the total enrichment of ^{1}H-[^{12}C+^{13}C], whereas the bottom spectrum (red) shows ^{13}C labelling of metabolites ^{1}H-[2*^{13}C] from [1−^{13}C]-glucose. (b) Quantification of enrichment levels of Glu4, GABA2 (c), and Glx3 (d) in different brain regions in the four groups. Data are presented as mean (sd), n=7. Con, naive controls; CSD+NS, sleep deprivation controls; CSD+Pro, sleep-deprived rats treated with propofol; CSD+Sev, sleep-deprived rats exposed to sevoflurane; GABA2, γ-aminobutyric acid-C2; GABA3, γ-aminobutyric acid-C3; Gln4, glutamine-C4; Glu3, glutamate-C3; Glu4, glutamate-C4; Glx3, glutamine-C3; NAA2, N-acetyl aspartate-C2; NAA3, N-acetyl aspartate-C3. Data were compared using a two-way analysis of variance, and the p-values were adjusted using Bonferroni correction for multiple comparisons.

model[33] and a total sleep deprivation model,[9] our data also suggested that unlike propofol, sevoflurane does not satisfy the homeostatic need for REM sleep. Interestingly, mice that were only exposed to inhalational agents without sleep deprivation showed very different REM sleep recovery.[34,35] Collectively, inhaled anaesthetics may disturb the REM sleep homeostasis in health and disease conditions *per se*.

Chronic sleep disorders before surgery, sleep disturbances after surgery, or both, frequently occur in surgical patients. Preoperative comorbidity, anaesthesia, surgical trauma, postoperative pain, and anxiety may all lead to the development of postoperative sleep disorders, which are common in postoperative surgical patients and also contribute to poor surgical outcomes.[7,36] Our previous study showed that compared with sevoflurane-based anaesthesia, propofol anaesthesia decreased the incidence of delayed neurocognitive recovery at 1 week after surgery,[37] which might partially be explained by the propofol-induced sleep improvement examined in our study. Taken together, our current work suggests that propofol could be a better anaesthetic choice for people with sleep disorders who receive anaesthesia, surgery, or both, in those who have a high risk to develop sleep disorders after anaesthesia and surgery.

Our study has several limitations. Firstly, young healthy rats were used; this is different from most clinical patients who may be older and have comorbidities, surgical conditions,

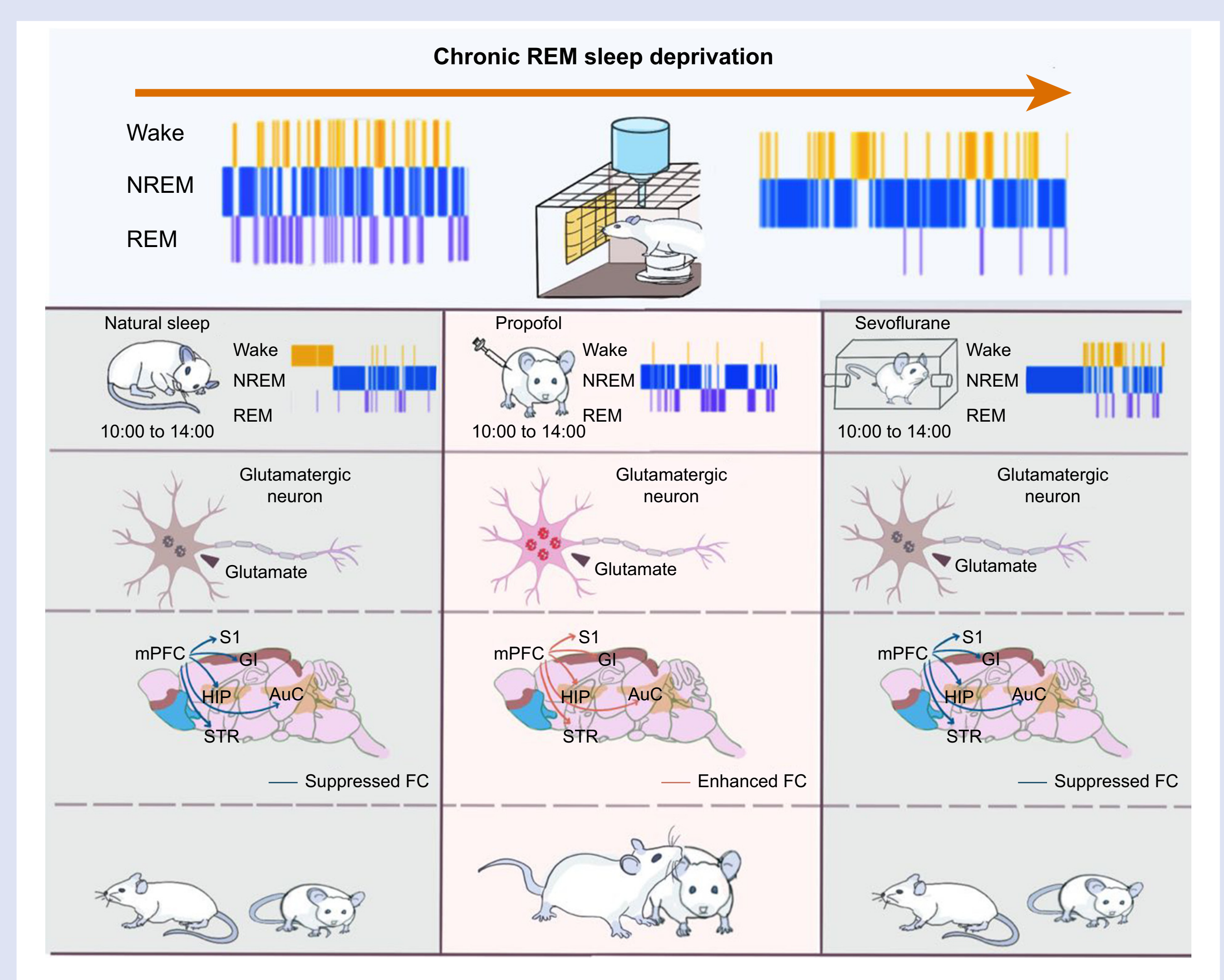

Fig 6. Illustration of underlying mechanisms. Rats were subjected to sleep deprivation for 4 weeks without any treatment (left panel), or with propofol (middle panel) or sevoflurane treatment (right panel). EEG and EMG were recorded (top panel). Propofol but not sevoflurane treatment ameliorates REM sleep deprivation-induced social and anxiety-related behaviours through enhancing REM sleep recovery, glutamate kinetics, and mPFC functional connectivity. FC, frontal cortex; HIP, hippocampus; mPFC, medial prefrontal cortex; AuC, auditory cortex; GI, granular insular cortex; S1, primary somatosensory cortex; NREM, non-REM; REM, rapid eye movement; STR, striatum.

or both. Therefore, our work should be treated as proof of concept, but its translational value is subject to further study. Secondly, keeping animal welfare in mind, the number of experimental animals was minimised in our experiments, which might affect our results. However, this is unlikely because randomisation strategies and power calculations were applied. Thirdly, due to anaesthetic-induced multiparameter changes, it is difficult to define the equipotent dose of sevoflurane and propofol. However, LORR and delta/theta ratio, both of which represent the unconscious state, are similar in both the groups and hence equivalent-doses of sevoflurane and propofol were likely used in our experiments. Finally, the disease model and treatment regimen might not closely relate to clinical situations. However, sleep disorders are complicated conditions and longer treatment time is often required.[38] Interestingly, the neurobiological mechanisms of sleep and anaesthesia have some overlap.[39] This implies that anaesthetics such as propofol might provide an option to treat sleep disorders. Indeed, continuous i.v. infusion of propofol for 2 h over 5 consecutive nights restored normal sleep for up to 6 months in patients with refractory chronic primary insomnia.[40] Furthermore, propofol-based anaesthesia was reported to be associated with a decrease in postoperative neurocognitive impairment in older people compared with sevoflurane-based anaesthesia.[37] All these findings suggest that propofol could provides certain benefits for patients with or without surgery *per se*, but require further study.

Conclusions

Propofol, but not sevoflurane, restored sleep quality after prolonged sleep deprivation in rats through promoting medial prefrontal cortex functional connectivity and brain glutamate and glucose metabolism dynamics. Thus, referring to our present study and previous studies in humans[24,25,40] and rodents,[11] propofol-induced sedation and sleep homeostasis, in particular REM sleep, could have benefits in patients with sleep disorders.

Authors' contributions

Study design/planning: JZ, CC, JW, ZZ
Study conduct: JZ, MH, YF, SL, CT
Data analysis: JZ, JW, JFW, SL, HX, YZ, FZ, FX
Writing of manuscript: JZ, CC, ZZ, SS, AM, DM
Revising of manuscript: CC, JW, DM

Declaration of interest

DM is the board member of *the British Journal of Anaesthesia* and the other authors declare no conflict of interest.

Funding

National Natural Science Foundation of China (NO. 81771160, 81671060, 31771193 and 81901109), and National Natural Science Foundation (NSF) of Hubei Province (No. 2020CFA059).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2023.05.025.

References

1. van Praag H, Fleshner M, Schwartz MW, Mattson MP. Exercise, energy intake, glucose homeostasis, and the brain. *J Neurosci* 2014; **34**: 15139–49
2. Hodkinson DJ, O'Daly O, Zunszain PA, et al. Circadian and homeostatic modulation of functional connectivity and regional cerebral blood flow in humans under normal entrained conditions. *J Cereb Blood Flow Metab* 2014; **34**: 1493–9
3. Krause AJ, Simon EB, Mander BA, et al. The sleep-deprived human brain. *Nat Rev Neurosci* 2017; **18**: 404–18
4. Institute of Medicine (US). In: Colton HH, Altevogt BM, editors. *Committee on sleep medicine and Research. Sleep Disorders and sleep deprivation: an unmet public health problem*. Washington, DC: The National Academies Press; 2006
5. Halle IH, Westgaard TK, Wahba A, Oksholm T, Rustoen T, Gjeilo KH. Trajectory of sleep disturbances in patients undergoing lung cancer surgery: a prospective study. *Interact Cardiovasc Thorac Surg* 2017; **25**: 285–91
6. Seid Tegegne S, Fenta Alemnew E. Postoperative poor sleep quality and its associated factors among adult patients: a multicenter cross-sectional study. *Ann Med Surg (Lond)* 2022; **74**, 103273
7. Rampes S, Ma K, Divecha YA, Alam A, Ma D. Postoperative sleep disorders and their potential impacts on surgical outcomes. *J Biomed Res* 2019; **34**: 271–80
8. Rosenberg-Adamsen S, Kehlet H, Dodds C, Rosenberg J. Postoperative sleep disturbances: mechanisms and clinical implications. *Br J Anaesth* 1996; **76**: 552–9
9. Liao WC, Huang CY, Huang TY, Hwang SL. A systematic review of sleep patterns and factors that disturb sleep after heart surgery. *J Nurs Res* 2011; **19**: 275–88
10. Chung F, Liao P, Yegneswaran B, Shapiro CM, Kang W. Postoperative changes in sleep-disordered breathing and sleep architecture in patients with obstructive sleep apnea. *Anesthesiology* 2014; **120**: 287–98
11. Tung A, Bergmann BM, Herrera S, Cao D, Mendelson WB. Recovery from sleep deprivation occurs during propofol anesthesia. *Anesthesiology* 2004; **100**: 1419–26
12. Pal D, Lipinski WJ, Walker AJ, Turner AM, Mashour GA. State-specific effects of sevoflurane anesthesia on sleep homeostasis: selective recovery of slow wave but not rapid eye movement sleep. *Anesthesiology* 2011; **114**: 302–10
13. Gelegen C, Miracca G, Ran MZ, et al. Excitatory pathways from the lateral habenula enable propofol-induced sedation. *Curr Biol* 2018; **28**: 580–587.e5
14. Li K-Y, Xiao C, Xiong M, Delphin E, Ye J-H. Nanomolar propofol stimulates glutamate transmission to dopamine neurons: a possible mechanism of abuse potential? *J Pharmacol Exp Ther* 2008; **325**: 165–74
15. Verweij IM, Romeijn N, Smit DJ, Piantoni G, Van Someren EJ, van der Werf YD. Sleep deprivation leads to a loss of functional connectivity in frontal brain regions. *BMC Neurosci* 2014; **15**: 88
16. Machado RB, Hipolide DC, Benedito-Silva AA, Tufik S. Sleep deprivation induced by the modified multiple platform technique: quantification of sleep loss and recovery. *Brain Res* 2004; **1004**: 45–51
17. Holth JK, Fritschi SK, Wang C, et al. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science* 2019; **363**: 880–4
18. Zhu J, Zhang Z, Jia J, et al. Sevoflurane induces learning and memory impairment in young mice through a reduction in neuronal glucose transporter 3. *Cell Mol Neurobiol* 2020; **40**: 879–95
19. Orliaguet G, Vivien B, Langeron O, Bouhemad B, Coriat P, Riou B. Minimum alveolar concentration of volatile anesthetics in rats during postnatal maturation. *Anesthesiology* 2001; **95**: 734–9
20. Chen L, Li S, Zhou Y, et al. Neuronal mechanisms of adenosine A2A receptors in the loss of consciousness induced by propofol general anesthesia with functional magnetic resonance imaging. *J Neurochem* 2021; **156**: 1020–32
21. Faul F, Erdfelder E, Lang AG, Buchner AG. *Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007; **39**: 175–91
22. Shingaki T, Katayama Y, Nakaoka T, et al. Visualization of drug translocation in the nasal cavity and pharmacokinetic analysis on nasal drug absorption using positron emission tomography in the rat. *Eur J Pharm Biopharm* 2016; **99**: 45–53
23. He ZX, Young L, Ma XM, et al. Increased anxiety and decreased sociability induced by paternal deprivation involve the PVN-PrL OTergic pathway. *Elife* 2019; **8**, e44026
24. Georgopoulos D, Kondili E, Alexopoulou C, Younes M. Effects of sedatives on sleep architecture measured with odds ratio product in critically ill patients. *Crit Care Explor* 2021; **3**, e0503
25. Engelmann C, Wallenborn J, Olthoff D, Kaisers UX, Ruffert H. Propofol versus flunitrazepam for inducing and maintaining sleep in postoperative ICU patients. *Indian J Crit Care Med* 2014; **18**: 212–9
26. Xie F, Li X, Bao M, et al. Anesthetic propofol normalized the increased release of glutamate and gamma-amino butyric acid in hippocampus after paradoxical sleep deprivation in rats. *Neurol Res* 2015; **37**: 1102–7

27. Hughes BL, Beer JS. Orbitofrontal cortex and anterior cingulate cortex are modulated by motivated social cognition. *Cereb Cortex* 2012; **22**: 1372–81
28. Gellner AK, Voelter J, Schmidt U, et al. Molecular and neurocircuitry mechanisms of social avoidance. *Cell Mol Life Sci* 2021; **78**: 1163–89
29. Alkire MT, Gruver R, Miller J, McReynolds JR, Hahn EL, Cahill L. Neuroimaging analysis of an anesthetic gas that blocks human emotional memory. *Proc Natl Acad Sci U S A* 2008; **105**: 1722–7
30. Lewis SR, Schofield-Robinson OJ, Alderson P, Smith AF. Propofol for the promotion of sleep in adults in the intensive care unit. *Cochrane Database Syst Rev* 2018; **1**: CD012454
31. Yue X-F, Wang A-Z, Hou Y-P, Fan K. Effects of propofol on sleep architecture and sleep–wake systems in rats. *Behav Brain Res* 2021; **411**, 113380
32. Zhang H, Yin J, Jia L, et al. Effects of dopamine transporter in the ventral tegmental area on sleep recovery after propofol anesthesia in sleep-deprived rats. *Sleep Med* 2022; **100**: 269–79
33. Mashour GA, Lipinski WJ, Matlen LB, et al. Isoflurane anesthesia does not satisfy the homeostatic need for rapid eye movement sleep. *Anesth Analg* 2010; **110**: 1283–9
34. Pick J, Chen Y, Moore Jason T, et al. Rapid eye movement sleep debt accrues in mice exposed to volatile anesthetics. *Anesthesiology* 2011; **115**: 702–12
35. Zhang H, Wheat H, Wang P, et al. RGS proteins and $G\alpha_{i2}$ modulate sleep, wakefulness, and disruption of sleep/wake states after isoflurane and sevoflurane anesthesia. *Sleep* 2016; **39**: 393–404
36. Krenk L, Jennum P, Kehlet H. Sleep disturbances after fast-track hip and knee arthroplasty. *Br J Anaesth* 2012; **109**: 769–75
37. Zhang Y, Shan GJ, Zhang YX, et al. Propofol compared with sevoflurane general anaesthesia is associated with decreased delayed neurocognitive recovery in older adults. *Br J Anaesth* 2018; **121**: 595–604
38. Morin AK, Jarvis CI, Lynch AM. Therapeutic options for sleep-maintenance and sleep-onset insomnia. *Pharmacotherapy* 2007; **27**: 89–110
39. Nelson LE, Franks NP, Maze M. Rested and refreshed after anesthesia? Overlapping neurobiologic mechanisms of sleep and anesthesia. *Anesthesiology* 2004; **100**: 1341–2
40. Xu Z, Jiang X, Li W, Gao D, Li X, Liu J. Propofol-induced sleep: efficacy and safety in patients with refractory chronic primary insomnia. *Cell Biochem Biophys* 2011; **60**: 161–6

Handling editor: Robert Sanders