JNeurosci
THE JOURNAL OF NEUROSCIENCE

Research Articles: Behavioral/Cognitive

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https://doi.org/10.1523/JNEUROSCI.0790-22.2023

Cite as: J. Neurosci 2023; 10.1523/JNEUROSCI.0790-22.2023

Received: 14 April 2022
Revised: 13 January 2023
Accepted: 18 January 2023

TITLE

Total sleep deprivation increases brain age prediction reversibly in multi-site samples of young healthy adults

ABBREVIATED TITLE

Sleep deprivation reversibly increases brain age

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NUMBER OF PAGES: 27

NUMBER OF TABLES: 2

NUMBER OF FIGURES: 5

WORDS: abstract (244), introduction (649), discussion (1466)

CONFLICTS OF INTEREST

The author declares no competing financial interests.

ACKNOWLEDGEMENTS

The authors gratefully thank their colleagues from the DLR division of Sleep and Human Factors Research and from Forschungszentrum Jülich (INM-2), especially for excellent support in the conductance of the study and data processing. The authors would like to gratefully acknowledge the financial support and endorsement from the DLR Management Board Young Research Group Leader Program and the Executive Board Member for Space Research and Technology (E.E.). This work was supported by the Institute for Scientific Information on Coffee (ISIC), the Swiss National Science Foundation (grant No. 320030_163439), the Clinical Research Priority Program Sleep & Health of the University of Zurich, and the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant agreement No. 798131 (S.C.H). The authors (C.C. & D.E.) thank the '2019 Helmholtz – OCPC – Program for the involvement of postdocs in bilateral collaboration projects' for their financial support that enabled this important study. The authors are grateful to the contribution

52 from the participants of all datasets and to Dr. Gustav Nilsonne for introducing the data of the Stockholm
53 Sleepy Brain project.

Abstract

Sleep loss pervasively affects the human brain at multiple levels. Age-related changes in several sleep characteristics indicate that reduced sleep quality is a frequent characteristic of aging. Conversely, sleep disruption may accelerate the aging process, yet it is not known what will happen to the age status of the brain if we can manipulate the sleep conditions. To tackle this question, we employed an approach of brain age to investigate whether sleep loss would cause age-related changes in the brain. We included MRI data of 134 healthy volunteers (mean chronological age of 25.3, between the age of 19 and 39, 42 females/92 males) from five datasets with different sleep conditions. Across three datasets with the condition of total sleep deprivation (> 24 hours of prolonged wakefulness), we consistently observed that total sleep deprivation increased brain age by 1-2 years regarding the group mean difference with the baseline. Interestingly, after one night of recovery sleep, brain age was not different from baseline. We also demonstrated the associations between the change in brain age after total sleep deprivation and the sleep variables measured during the recovery night. By contrast, brain age was not significantly changed by either acute (3 hours' time-in-bed for 1 night) or chronic partial sleep restriction (5 hours' time-in-bed for 5 continuous nights). Taken together, the convergent findings indicate that acute total sleep loss changes brain morphology in an aging-like direction in young participants and that these changes are reversible by recovery sleep.

Significance Statement

Sleep is fundamental for humans to maintain normal physical and psychological functions. Experimental sleep deprivation is a variable-controlling approach to engaging the brain among different sleep conditions for investigating the brain's responses to sleep loss. Here, we quantified the brain's response to sleep deprivation by using the change of brain age predictable with brain morphological features. In three independent datasets, we consistently found increased brain age after total sleep deprivation, which was associated with the change in sleep variables. Moreover, no significant change in brain age was found after partial sleep deprivation in another two datasets. Our study provided new evidence to explain the brain-wide effect of sleep loss in an aging-like direction.

Introduction

Sleep is essential for humans to maintain physical health (Reid et al., 2006; Grandner et al., 2012) and mental health (Freeman et al., 2017; Joao et al., 2018). Sleep-brain interactions have been demonstrated at multiple scales from molecules to whole-brain networks (Cirelli, 2009; Abel et al., 2013; Fultz et al., 2019; Winer et al., 2019). Experimental sleep deprivation (SD) provides a variable-controlling approach to manipulating sleep conditions for investigating sleep behaviors and the brain's responses to inadequate sleep (Van Dongen et al., 2003; Durmer and Dinges, 2005; Elmenhorst et al., 2017; Elmenhorst et al., 2018). Accompanied by the change of sleep behavior after SD, such as increased sleepiness (Hefti et al., 2013) and changed sleep quality (Elmenhorst et al., 2008), sleep loss leads to widespread effects on brain anatomy, including decreased volume of grey matter across various brain regions (Liu et al., 2014; Akerstedt et al., 2020; Long et al., 2020; Sun et al., 2020), broad alterations in cortical microstructure (Voldsbekk et al., 2022), extensive alterations in white matter microstructure (Elvsashagen et al., 2015; Voldsbekk et al., 2021), and augmented expansion rate of ventricles (Lo et al., 2014). These prior efforts highlight that the effect of SD is not particularly situated in specific brain tissues or regions, but widespread over the brain. Therefore, it would be critical to seek an approach to integrating the widespread effect of SD for establishing a more consistent view of the neuroanatomical effect caused by SD.

In parallel, it also remains unclear what would be the biological implication integrated from the widespread effect of SD on the human brain. Elicited by the associations between human aging and reduced sleep duration/increased sleep disruption (Lo et al., 2014; Mander et al., 2017; Boulos et al., 2019) and the relationships between brain aging and electroencephalographic activity during sleep (Panagiotou et al., 2017; Panagiotou et al., 2018; Sun et al., 2019), the age status of the human brain corresponds to the variation of sleep behaviors in part. Therefore, we hypothesized that the widespread effect of SD could be comprehensively represented by the brain-specific age status.

105 Following our hypothesis, we capitalized on the brain age model to capture the brain-specific age status
106 that is referred to as the predicted chronological age by combining well-trained machine-learning models
107 and brain-specific features (Franke et al., 2010; Cole and Franke, 2017). Given that the brain age models
108 are supposed to be trained on a large sample of healthy subjects for robustly capturing the relationship
109 between brain features and chronological age, the application of these models has shown not only high
110 test-retest reliability (Cole et al., 2017; Elliott et al., 2019; Richard et al., 2020; Beheshti et al., 2021) but
111 also effectiveness in a growing body of studies involved in brain maturation (Franke et al., 2012; Shi et al.,
112 2020; Truelove-Hill et al., 2020) and mental health (Cole et al., 2019b; Kaufmann et al., 2019; Sone et al.,
113 2021), in which the brain change is effectively represented by its specific age status. More importantly,
114 brain age can be derived by integrating the high-dimensional brain-wide neuroanatomical features into a
115 scalar index in a data-driven way, which is conceptually suitable for detecting the widespread effect of
116 SD in the brain.
117 Thus, we employed five datasets acquired from multiple sites with different extents of sleep restriction to
118 explore and verify the SD effect through brain-specific age status. By using the publicly available
119 brainageR model (Cole et al., 2018), we obtained the brain age of each participant among different sleep
120 conditions. Building on them, we investigated the change in brain age after total sleep deprivation (TSD),
121 partial sleep deprivation (PSD), and recovery sleep. To assess the behavioral implication of the changed
122 brain age, we further explored the association between the change in brain age and the sleep measures
123 derived from the polysomnographic data. To overview the study design, a workflow of our study was
124 shown in Figure 1.
125
126

Materials and Methods

Participants

To explore and confirm the effect of SD on brain age, we employed the data from four different previous studies as well as a public dataset. As the exploratory (or main) dataset, we used the 'Somnosafe' dataset which was designed to investigate the effects of SD on human behavioral performance (Hennecke et al., 2020). The participants were selected based on both questionnaires (covering general health status, substance abuse, sleep habits, and psychological screening) and a physical examination of blood and urine to exclude substance use and pregnancy. Only healthy and non-smoking volunteers were included (36 individuals, aged 20-39 years, 22 males/14 females). As the confirmation datasets, we first used another dataset, referred to as the "CSR" (Coffee and Sleep Restriction) dataset, which was designed to study the interactions between daily coffee intake and chronic sleep deprivation (Baur et al., 2020). Only the data of the control group of this study which received decaffeinated coffee was included in the current analyses, to avoid the potential effect of coffee intake (15 individuals, aged 22-37 years, 8 males/7 females). In addition to the inclusion criteria outlined above, only healthy carriers of homozygous C-allele of the ADORA2A single-nucleotide variant rs5751876 (Retey et al., 2007) were recruited. More information on participant recruitment is available in the original publication (Baur et al., 2020). Then, we used a third dataset (referred to as the 'NRU' dataset) in which each of the recruited healthy subjects had a baseline night followed by a night without sleep (20 individuals, aged 20-29 years, all males). Next, we used a fourth dataset (referred to as the 'UZH' dataset) which aimed at investigating the effects of age on molecular substrates of sleep-wake regulation (Weigend et al., 2019). Of the original dataset consisting of 9 men above 60 years old and 22 young men between 19 and 30 years old, only the young age group was included to match the age range of other datasets. Finally, we selected a public dataset from the Stockholm sleepy brain project ('Stockholm' dataset). More information about the dataset was available at https://openneuro.org/datasets/ds000201/versions/1.0.3. To match the age range of the previous datasets, we also only used the young group of the Stockholm datasets (41 individuals, aged 20-30 years,

20 males/21 females). All procedures of the Somnosafe and CSR datasets were approved by the Ethics Committee of the regional Medical Board (Ärztekammer Nordrhein). For the NRU dataset, the study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee for the capital region of Copenhagen. The UZH dataset was approved by the ethics committee of the Canton of Zürich for research on human participants. The Stockholm dataset was approved by the Regional Ethics Review Board of Stockholm for sharing the de-identified data. All participants of all studies gave written informed consent.

Study protocols

For the Somnosafe dataset, the subjects were randomly separated into either the control group (15 individuals, aged 21-39 years, 10 males/5 females) or the experimental group (21 individuals, aged 20-32 years, 12 males/9 females). All the subjects had one adaptation night followed by two baseline nights to accommodate the laboratory and the cognitive tests. Correspondingly, the subjects had 8-hour time in bed (TIB) for each night (23:00 – 07:00+1 or 24:00 – 08:00+1, '+1' indicated the next day). The subjects of the experimental group were exposed to chronic PSD as 5-hour TIB (02:00 – 07:00 or 03:00 – 08:00) for five sequential nights. The subjects of the control group still had 8-hour TIB for five sequential nights. Thereafter, all subjects had a recovery night (8-hour TIB, 23:00 – 07:00+1 or 24:00 – 08:00+1). After the recovery night, all the subjects went through TSD (07:00 – 21:00+1 or 08:00 – 22:00+1, 38 hours). Finally, the subjects had another 10-hour recovery night (21:00 – 07:00+1 or 22:00 – 08:00+1). MRI data were respectively acquired in the morning after the 5-nights PSD, the morning after the first recovery night, and the morning after the night of TSD. For each night, the polysomnographic data were recorded. More details about the experimental design could be found in our previous study (Hennecke et al., 2020). A schematic overview of the experimental design is available in Figure 2A.

For the CSR dataset, the experimental design was identical to the chronic PSD group of the Somnosafe dataset, except for no TSD. Briefly, one adaptation night of 8-hour TIB, two baseline nights of 8-hour TIB, five PSD nights of 5-hour TIB, and one recovery night of 8-hour TIB were sequentially conducted.

MRI data were acquired in the morning after the final baseline night, the 5-night PSD, and the recovery night, respectively. More information about the experimental design could be found in the original publication (Baur et al., 2020). A schematic overview of the experimental design is available in Figure 2B. For the NRU dataset, each subject had a baseline night with 8-hour TIB. Following the baseline night, each subject kept awake for 30 hours (no sleep for the corresponding night). After each night, the MRI data were acquired at around 6 p.m. to control for the circadian effect. A schematic overview of the experimental design is available in Figure 2C.

For the UZH dataset, all the subjects sequentially went through one adaption night (8-hour TIB, 23:00 – 07:00+1), one baseline night (8-hour TIB, 23:00 – 07:00+1), a 40-hour TSD, and a recovery night (10-hour TIB, 22:30 – 08:30+1). MRI scans were conducted after the baseline night, after the night of TSD, and after the recovery night, respectively. The start time of each scanning session was at roughly the same clock time (04:23 pm ± 23 mins). More details about the experimental design are available in the original report of that study (Weigend et al., 2019). A schematic overview of the experiment is available in Figure 2D.

The experimental design of the Stockholm dataset was based on acute PSD, where all the subjects were exposed to one night of PSD with 3-hour TIB. The subjects were randomly assigned into one of the two sessions (session 1: a full-sleep night followed by a PSD night; sleep session 2: a PSD night followed by a full-sleep night). The time interval between the full-sleep night and the PSD night was one month. MRI scanning was performed in the afternoon or the evening after the final night of each session. More details regarding the experimental design of the Stockholm dataset could be found in the previous publication (Nilsonne et al., 2017). A schematic overview of the experimental design is available in Figure 2E.

Polysomnographic data

Regarding the Somnosafe dataset, the polysomnographic data were acquired using electrodes attached according to the international 10–20 system (electroencephalogram: F4-A1, C4-A1, O2-A1, F3-A2, C3-A2, O1-A2; electrocardiography; electromyography; sampling rate: 256 Hz) (Hennecke et al., 2020).

Amplification with a time constant of 2.3 s and a low-pass filter (−6 dB at 70 Hz) were applied to the electroencephalogram signal. We further used the polysomnographic data of each night to correspondingly derive the sleep variables according to the American Academy of Sleep Medicine criteria (Berry et al., 2017). In detail, we included 13 summary measures of polysomnographic data in the current study. Regarding sleep period time, we calculated minutes spent in N1, N2, N3, rapid eye movement sleep, wake, the number of sleep stage changes, and the number of sleep stage changes per hour. Regarding sleep latency (unit: minutes), sleep onset latency, N3 sleep onset latency, and rapid eye movement (REM) onset latency were included. Regarding total sleep time, the number of arousals and the number of arousals per hour were included. Sleep efficiency was finally included.

MRI acquisition

For both the Somnosafe dataset and the CSR dataset, the T1-weighted (T1w) MRI data were acquired in the same scanner (3-Tesla Siemens Biograph mMR), using an MPRAGE sequence (176 sagittal slices, slice thickness 1 mm, field of view (FoV) = 256 × 256 mm^2, matrix size = 176 × 256 × 256; voxel size = 1 × 1 × 1 mm^3). For the NRU dataset, a 3-Tesla Siemens Prisma scanner was used to acquire the T1w dataset with an MPRAGE sequence (208 sagittal slices, slice thickness 1 mm, FoV = 256 × 256 mm^2, matrix size = 208 × 256 × 256; voxel size = 1 × 1 × 1 mm^3). For the UZH dataset, the T1w data were acquired using a combined 3-Tesla PET/MR scanner (SIGNA PET/MR; General Electric Healthcare) with an axial BRAVO sequence (176 axial slices, slice thickness 1 mm, FoV = 256 × 256 mm^2, matrix size = 256 × 256 × 176; voxel size = 1 × 1 × 1 mm^3). For the Stockholm dataset, the T1w data were acquired using a 3-Tesla MRI scanner (Discovery 750; General Electric Healthcare) with a sagittal BRAVO sequence (180 sagittal slices, slice thickness 1 mm, FoV = 240.03 × 240.03 mm^2, matrix size = 180 × 512 × 512; voxel size = 1 × 0.4688 × 0.4688 mm^3).

Brain age prediction

Before predicting the brain age, we conducted visual examinations of the T1w data avoiding the existence of excessive noise. Most of the included data showed high quality, except that two participants in the Somnosafe dataset and two participants in the UZH dataset were removed due to the existence of heavy noise for at least one T1w scan. So, the Somnosafe dataset finally included the T1w data of 34 participants (control group: 14 individuals, aged 21-39 years, 5 females; experimental group: 20 individuals, aged 20-32 years, 8 females). The UZH dataset finally included 20 participants (aged 19-30 years, all males). A summary table with the demographic characteristics of the participants of all datasets was shown in Table 1. Additionally, the bias field correction of all the T1w images was via ANTs' N4BiasFieldCorrection (Tustison et al., 2010).

A large sample was required for training a brain age model of high robustness and generalization ability, which was not feasible in our scenario. We alternatively used a publicly available model which had been well-trained. Specifically, we adopted the brainageR v2.1 model which was trained in 3,377 healthy individuals (mean age = 40.6 years, age range 18-92 years), and tested on 857 individuals (mean age = 40.1 years, age range 18-90 years) (Cole et al., 2015; Cole et al., 2017; Cole et al., 2018). The brainageR uses the voxel-wise volume of grey matter, white matter, and cerebrospinal fluid (CSF), which are segmented by SPM12 (https://www.fil.ion.ucl.ac.uk/spm), normalized to the MNI152 standard space by DARTEL (Ashburner, 2007), and smoothed with a 4 mm full-width-at-half-maximum (FWHM) smoothing kernel, as features integrated into the well-trained model of Gaussian processes regression to predict the brain age. More details about the brainageR model are available through GitHub (https://github.com/james-cole/brainageR).

Statistical analysis

Regarding the Somnosafe, CSR, and UZH datasets, we adopted a one-way repeated measures analysis of variance (ANOVA) to test the effect of SD over three conditions which were referred to as the within-subject factor. We further included gender (if applicable), group (either control or experimental group; only for the Somnosafe dataset), and chronological age as the between-subjects variables in the repeated

measures ANOVAs. Given that there were only two conditions (before/after SD) for both the NRU dataset and the Stockholm dataset, we used a paired sample t-test to determine the change in brain age between the two conditions for all datasets for consistency. We also conducted the post-hoc Tukey honestly significant difference test following the repeated measures ANOVA. All the analyses were conducted by using the Statistics and Machine Learning Toolbox in Matlab (Version 9.5.0, R2018b).

Additionally, in order to make a statement about the confidence into the null results, we selected the Bayesian repeated measures ANOVA to provide the corresponding Bayesian factor (BF) by rerunning the analysis with the same data used by the frequency-statistical ANOVA above. We specifically used JASP (Version 0.16.4) to conduct the analysis, which is an open-source software supported by the University of Amsterdam (https://jasp-stats.org/).

Results

Assessing the effect of sleep deprivation on brain age in the Somnosafe dataset

Regarding the Somnosafe dataset, we analyzed the variation of brain age that was derived from the T1w data acquired after each of the sequential sleep conditions including five baseline nights (or 5 chronic sleep restricted baseline nights for the experimental group), one night of recovery sleep, and one night of TSD (see Methods for details on the individual protocol).

Specifically, regarding the within-subject effect, we found an effect of sleep condition on brain age ($F(2, 58) = 7.49$, $p < 0.002$, $\eta^2 = 0.21$) via the repeated measures ANOVA where the sphericity assumption was not violated (Table 2). No interactions were found between the within-subject factor (sleep conditions) and the between-subjects variables including gender, group, and the interaction of both (Table 2). To illustrate the pair-wise comparisons clearly, the scatter plots of both the individual brain age under each of the sleep conditions and the corresponding change between any two conditions were shown in Figure 3A. Through the paired sample t-tests, we found that the brain age derived after the night of TSD increased compared to the brain age derived either after the baseline night ($t(33) = 3.38$, $p < 0.002$, mean difference = 0.94 years) or after the recovery night following the repeated PSD ($t(33) = 2.93$, $p < 0.01$, mean difference = 0.90 years). No significant difference was found between the recovery and baseline condition ($t(33) = 0.16$, $p = 0.88$, mean difference = 0.040 years). We also conducted the post-hoc Tukey test to confirm the above pair-wise comparison. We further broke down the effect of sleep deprivation into each group, i.e., the control group and the experimental group, by conducting another post-hoc Tukey test within each group. Similar patterns across sleep conditions were found within each group, although only the change in brain age between the conditions of baseline and TSD survived Tukey's multiple comparison corrections in the experimental group ($p = 0.015$ corrected by Tukey's honest significance test, mean difference = 1.09 years).

Regarding the between-subjects analysis, no significant effects were found in terms of gender, group, and the interaction of both on brain age (mean of the within-subject factor), while the chronological age

presented a significant between-subjects effect on the brain age, showing the significant correspondence between the chronological age and the predicted age ($F(1, 29) = 14.12$, $p < 0.001$, $\eta^2 = 0.33$).

The performance of the prediction of brain age was evaluated from two aspects. First, high Pearson correlation coefficients were found among the predicted age of different conditions (minimal Pearson correlation coefficient $r > 0.95$), which illustrated the reliability of the brain age model and the correspondence of subjects across the three conditions. Second, for each condition, the predicted age was also highly correlated with the chronological age, indicated by a high Pearson correlation coefficient (> 0.60) and a low mean absolute error (MAE < 3.95 years). The MAE was referred to as the average absolute difference between the predicted age and the chronological age.

Verifying the effect of total sleep deprivation on brain age

To confirm the effect of TSD found in the Somnosafe dataset, we analyzed another two independent datasets and compared the derived brain age between the conditions of baseline and TSD using a paired sample t-test. The brain age also increased after TSD in both the NRU dataset (TSD – baseline: $t(19) = 3.21$, $p < 0.005$, mean difference = 2.13 years; Figure 3B) and the UZH dataset (TSD – baseline: $t(19) = 2.37$, $p < 0.05$, mean difference = 1.07 years; Figure 3C).

In order to test whether the significant effect of TSD on brain structures could be detected by using univariate comparison, we further leveraged the paired t-test to respectively conduct the comparisons of grey matter and white matter between the state of TSD and the baseline state based on the grey matter volume and the white matter volume that were the same features used to predict the brain age. In the three datasets, we did not find significant clusters after the correction of multiple comparisons (false discovery rate (FDR) < 0.05) in either grey matter or white matter. We further demonstrated that the similarity between the statistic maps (the T maps) of the three datasets was quite low (Figure 3D).

Repeated partial sleep deprivation and acute partial sleep deprivation do not affect brain age

Regarding the findings in the Somnosafe dataset, there was no significant condition-by-group (i.e., experiment/control group) interaction effect on brain age, which suggested to further confirm the effect of partial sleep deprivation on the brain age. Therefore, we next assessed the effect of PSD by tracing the change in brain age from the baseline. Specifically, we compared the derived brain age between the conditions of baseline and PSD in the CSR dataset (5-nights repeated PSD; 5 hours in bed per night) and in the Stockholm dataset (1-night acute PSD; 3 hours in bed) respectively, via a paired sample t-test. No significant difference between PSD and baseline was found in both datasets (for the CSR dataset, $t(14) = 0.74$, $p = 0.47$; for the Stockholm dataset, $t(40) = -1.70$, $p = 0.098$; Figure 4A & 4B). We further provided the Bayesian factor (BF) to describe the confidence into the null result of the PSD effects (for the CSR dataset, $BF_{10} = 0.41$; for the Stockholm dataset, $BF_{10} = 0.76$), which indicated anecdotal evidence to reject the null hypothesis.

Brain age returns to the baseline level after recovery sleep

We examined the effect of recovery sleep on brain age following the baseline-SD-recovery sequence. Given that we had two types of SD, i.e., PSD and TSD, we separately assessed the effect of recovery sleep under different conditions of SD. In the PSD dataset (i.e., the CSR dataset), no significant change in brain age in the baseline-CSD-recovery sequence was found by conducting paired sample t-tests between each pair of conditions (Figure 4A). This was consistent with the analysis of repeated ANOVA in which no significant within-subject effect was found ($F(2, 24) = 0.52$, $p = 0.65$, $\eta^2 = 0.035$, $BF_{10} = 0.02$) and the sphericity assumption was not violated (the Mauchly's test for sphericity: $p = 0.17$, $DF = 2$). Here, chronological age and gender were included as the between-subjects variables. In the TSD dataset (i.e., the UZH dataset), brain age returned to the baseline level after 1-night recovery sleep (Figure 3C), revealing no significant difference between the baseline and the recovery conditions (recovery – baseline: $t(19) = -0.47$, $p = 0.64$, $BF_{10} = 0.33$). Similarly, a difference between the recovery and the TSD conditions was found (TSD – recovery: $t(19) = 2.24$, $p < 0.05$, mean difference = 0.95 years; Figure 3C).

Correspondingly, a significant within-subject effect was found via the repeated measures ANOVA ($F(2, 36) = 4.54$, $p < 0.05$ after Greenhouse-Geisser correction, $\eta^2 = 0.20$). As the sphericity assumption was slightly violated here ($p = 0.041$, $DF = 2$), we used the Greenhouse-Geisser approach to correct the p value of the within-subject effect. Additionally, the chronological age was included as the between-subjects variable.

Associations between the changes in sleep behavior and brain age

To gain more understanding of the increased brain age after TSD, we analyzed the associations between the change in brain age and sleep behaviors including the measure of sleepiness (Karolinska Sleepiness Scale [KSS], a 9-point scale spanning from extremely alert [= 1] to extremely sleepy [= 9]) (Akerstedt and Gillberg, 1990) and the measures derived from the polysomnographic data in the Somnosafe dataset (34 subjects). For the correlation analyses, the change in brain age (TSD – baseline or TSD – recovery) was normalized by dividing the corresponding chronological age. Here, the recovery sleep was referred to as the first recovery night after repeated PSD (R, Figure 2A).

The change in KSS score (TSD – baseline) was positively associated with the corresponding change in brain age (TSD – baseline; Pearson correlation coefficient $r = 0.36$, $p < 0.05$; Figure 5A). We further included group and gender as covariates to conduct another partial correlation to find a similar effect ($r = 0.415$, $p < 0.05$). Moreover, no significant association was found between the change in KSS score (TSD – recovery) and the change in brain age (TSD – recovery; $r = 0.23$, $p = 0.20$).

Regarding the polysomnographic data, we included 13 summary measures (see Methods for details on these measures). We focused on the polysomnographic measures of the final recovery sleep following TSD (R2, Figure 2A), which was the reaction to the sleep debt after TSD. We normalized these measures of R2 using the same measures at baseline, i.e., R2 / baseline, to increase the comparability across participants. After conducting the FDR correction, we found two kinds of significant associations between normalized sleep measures and the change of brain age between the conditions of TSD and baseline. Specifically, the normalized wake time (WT) during sleep period time (SPT) positively

359 correlated with the change of brain age (TSD – baseline; $r = 0.55$, $p < 0.05$, FDR corrected; Figure 5B).
360 The normalized time spent in stage N1 sleep during SPT was negatively associated with the change of
361 brain age (TSD – baseline; $r = -0.51$, $p < 0.05$, FDR corrected; Figure 5C). Additionally, when adding
362 gender and group as covariates, we could still find the two kinds of associations after FDR correction.
363

Discussion

Along with the in-lab manipulation of sleep deprivation conditions, this study was built on a series of studies conceptualizing brain age as a brain-specific biomarker for aging and mental health (Cole et al., 2019a; Elliott et al., 2019; Franke and Gaser, 2019; Kaufmann et al., 2019; Bashyam et al., 2020). Large sample size would be beneficial to train the brain age model of high reliability, which was not applicable to our datasets. So, instead of training a new prediction model of brain age with the current datasets, we turned to use the brainageR model which had been trained on a large sample. This might be considered as a general way to estimate brain age in small samples as we did not fine-tune any parameter specific to our datasets, which was conceptually similar to external validation of the established machine learning model (Ho et al., 2020). One additional consideration to using brainageR in our study was that the model simultaneously adopted grey matter, white matter, and CSF as features, which fitted the previous findings of the widespread effects of SD on the human brain (Elvsashagen et al., 2017; Shokri-Kojori et al., 2018; Eide et al., 2021; Voldsbekk et al., 2021). More interestingly, the benefits and the uniqueness of using the approach of brain age in our analysis were highlighted by the inconsistent findings in the univariate comparisons of brain structures by using the same data from the prediction of brain age (Figure 3D). Finally, given the high test-retest reliability of brain age models (Richard et al., 2020; Beheshti et al., 2021), we focused on the change of brain age across experimental conditions during a short period for the same participant, which would be beneficial to reduce the systematic bias of prediction model.

The main findings of our study pointed out the increased brain age after acute TSD. In contrast, we did not find a significant change in brain age with the condition of either acute or repeated PSD, which might indicate minor brain morphological changes under these conditions. An alternative explanation might be that our statistical power was limited by the current sample size and not able to detect a comparatively weak effect. Importantly, although the MRI scanners and the corresponding sequences were not the same across our datasets, the effect of acute TSD on brain age was confirmed by two additional datasets, thus, making it unlikely an effect caused by random errors. More interestingly, we confirmed the effect of 10-

hour recovery sleep on brain age which returned to baseline level. The recovery effect was also found in previous studies regarding cognitive performances (Yamazaki et al., 2021) and brain functional connectivity as determined by fMRI (Chai et al., 2020).

Given the short time interval of about 24 hours between the MRI scans in our datasets, our findings demonstrated the sensitivity of brain age to the dynamic change of brain morphology in such a short period. Similarly, previous studies found a change in brain age over a longer period such as the menstrual cycle (Franke et al., 2015). Moreover, the long-term associations between neuroanatomy and sleep behavior (Lo et al., 2014; Tahmasian et al., 2020) might further contribute to explaining that the neuroanatomy-based brain age showed a response to SD. Especially, a recent study found a significant association between changes in brain age and lower scores on the Pittsburgh Sleep Quality Index in an elderly population and even claimed that it was related to a 2-year increase above the chronological age (Ramduny et al., 2022). This finding complemented our assessments and supported the relevance of the use of MRI-based brain age. Digging deeper into the biological factor underpinning the potential change of brain morphology induced by sleep deprivation, it may be related to the brain interstitial volume which was found to increase by 60% after natural sleep in live mice (Xie et al., 2013). Correspondingly, the flow of CSF into and out of the human brain was found to be affected by slow oscillatory neuronal activity during natural sleep (Fultz et al., 2019). More directly, the increased amount of CSF tracer was found in the cerebral cortex and white matter after 24-hour TSD, indicating impaired CSF tracer movement in the brain parenchyma (Eide et al., 2021). Therefore, acute TSD might partly disturb these biological processes to affect the inward/outward gradient of CSF which in turn would promote the dynamic change of brain morphology. Besides the flow of CSF, other neurobiological factors might also account for our results about the change in brain age that were predicted by using the features of grey matter and white matter. Specifically, sleep deprivation was found to affect neuroplasticity (Alkadhi et al., 2013; Krause et al., 2017), which might relate to the myelin dynamics of the brain (de Vivo and Bellesi, 2019). Interestingly, the myelination of the brain could be affected by the oligodendrocyte precursor cells that have faster proliferation during sleep (Bellesi et al., 2013; Grumbach et al., 2020). Therefore, prolonged

wakefulness especially caused by total sleep deprivation might affect myelination by impairing the oligodendrocyte functions (Bellesi, 2015), which could further be detected by MRI signals.

We measured the sleep behavior using two types of measures including a subjective one (KSS score) and an objective one (polysomnographic data) in the Somnosafe dataset. We found a positive association between the change in KSS score and the change in brain age, where an increased brain age indicated increased sleepiness after TSD. However, we should notice that the different or nonsynchronous effects of recovery sleep after repeated PSD might exist on brain age and subjective sleepiness. For example, compared to the baseline, we did not find that PSD significantly affected the brain age after the recovery sleep following PSD. In contrast, the fast recovery of KSS outcomes during the recovery sleep after PSD was found in previous studies (Banks et al., 2010).

Regarding the polysomnographic data, we focused on the data of the recovery night, which represented the reaction of sleep behavior to prolonged wakefulness. We considered the changed brain age as a representative response of brain morphology to TSD. Specifically, the wake time in the recovery night following TSD showed a positive association with increased brain age. Correspondingly, the sleep efficiency in the recovery night following TSD was negatively correlated with the change in brain age, although it didn't survive the FDR correction for multiple comparisons. Noticeably, sleep efficiency in the recovery night following TSD increased in all subjects compared to baseline, suggesting an increase in sleep pressure after the TSD. This was further supported by our finding of the negative relationship between the changed brain age and the changed N1 sleep period, which indicated that the participants having increased brain age after total sleep deprivation tended to show a quicker transition from being awake to falling asleep. More interestingly, in a recent large meta-analysis, wake time and sleep efficiency were found as two prominent polysomnographic parameters respectively showing a significant increase or decrease with normative aging (Boulos et al., 2019). Therefore, these results indicated the aging-like sleep quality accompanied by increased brain age after TSD, which was consistent with previous studies showing the aging-like effect of SD on cognitive performance (Harrison et al., 2000) and brain network characteristics (Zhou et al., 2017) in young cohorts.

Several limitations and corresponding future directions are worth mentioning. First, because we used brain age to index the features of the whole brain, which was based on a non-linear prediction model, it's not straightforward to demonstrate whether there would be specific brain regions affected by SD to drive the increase in brain age. Second, although the complexity of in-lab sleep experiments may restrict the number of subjects, larger studies are desirable to confirm the effects of sleep deprivation, especially for chronic or partial sleep deprivation which may have weak effects compared to TSD. Third, although there was no significant interaction between the sex variable and the conditions of sleep deprivation in our ANOVA results, we should not neglect the effect of sex differences on sleep. Therefore, further comparative studies separately conducted in each gender may still be required when having enough samples. The limitations notwithstanding, we provided new evidence that acute sleep deprivation drove the brain morphology and the corresponding sleep behavior in an aging-like direction, emphasizing the relevance of sleep for aging. Brain age also provided a data-driven approach to identify the individualized vulnerability/resistance to sleep deprivation. Especially, total sleep deprivation for one whole night was demonstrated to be an efficient therapeutic tool again depression (Giedke and Schwarzler, 2002), although its effect might not be highly sustainable (Ioannou et al., 2021). Our findings indexed the individualized brain structural response to sleep deprivation by using brain age, which may be further combined with wake therapy of depression to interpret or even predict the sustainability of the therapeutic effect.

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Figure/Table Legends

Figures:

Figure 1

Figure 1. A schematic diagram showing the analytic steps.

Figure 2

Figure 2. The schematic demonstration of the study protocol for each dataset. (A) The experimental protocol for the Somnosafe dataset. TIB is for the time in bed. 'A' is for the adaption day. B1 and B2 are for the two baseline days. E1-5 are for the 5-night chronic sleep deprivation (the experimental group received 5-h TIB per night, the control group had 8-h TIB per night). R is for the first recovery night. TSD is for the total sleep deprivation of the whole night. R2 is for the second recovery night following TSD. (B) The experimental protocol for the CSR dataset. All the abbreviations have the same meaning as the Somnosafe dataset. (C) The experimental protocol for the NRU dataset. 'B' is for the baseline day. (D) The experimental protocol for the UZH dataset. Here, R is for the recovery night following TSD. (E) The experimental protocol for the Stockholm dataset. PSD is for partial sleep deprivation of one night (3-h TIB).

Figure 3

Figure 3. The effect of total sleep deprivation on the brain age. The predicted brain age of each participant is labeled as a blue diamond. The change in brain age between a pair of experimental conditions, corresponding to the x-axis, is labeled as a red diamond. The label of x-axis (left side, each panel) is corresponding to the experimental sequence. B is for the baseline condition. R is for the recovery sleep condition. TSD is for the total sleep deprivation condition. Green circles represent the means. Grey bars represent 95% CI. * indicates a statistically significant effect at $p < 0.05$ (n.s.: $p >= 0.05$) via the paired sample t-test. 0 is enclosed by a red box, which indicates no change between any two conditions. (A) Left: the predicted brain age across three experimental conditions in the Somnosafe dataset. Right: the pair-wise comparison of brain age change (TSD – B: $t(33) = 3.3847$, $p = 0.0019$, mean difference = 0.9361 years; TSD – R: $t(33) = 2.9255$, $p = 0.0062$, mean difference = 0.8959 years; R – B: $t(33) = 0.1580$, $p = 0.8754$, mean difference = 0.0402 years). (B) Left: the predicted brain age across two experimental conditions in the NRU dataset. Right: the pair-wise comparison of brain age change (TSD – B: $t(19) = 3.2133$, $p = 0.0046$, mean difference = 2.1255 years). (C) Left: the predicted brain age across three experimental conditions in the UZH dataset. Right: the pair-wise comparison of brain age change (TSD – B: $t(19) = 2.3645$, $p = 0.0289$, mean difference = 1.0739 years; TSD – R: $t(19) = 2.2394$, $p = 0.0373$, mean difference = 0.9497 years; R – B: $t(19) = 0.4715$, $p = 0.6426$, mean difference = 0.1241 years;). (D) The similarity between the T statistic maps derived from the paired t-test between the data collected after the night of total sleep deprivation and the data collected after the baseline night. Left: The results were based on the comparison of grey matter

volume in the three datasets. The similarity was assessed by using the Pearson correlation coefficient r as shown in each cell. The exemplar slices of the T statistic maps were shown below for each dataset. Right: The results were based on the comparison of white matter volume.

Figure 4

Figure 4. The effect of partial sleep deprivation on the brain. (A) Left: the predicted brain age across three experimental conditions in the CSR dataset. Right: the pair-wise comparison of brain age change. No significant effect was detected (PSD – B: $t(14) = 0.7444$, $p = 0.4689$, mean difference = 0.2546 years; PSD – R: $t(14) = 0.9675$, $p = 0.3497$, mean difference = 0.2176 years; R – B: $t(14) = 0.1497$, $p = 0.8831$, mean difference = 0.0370 years). (B) Left: the predicted brain age across two experimental conditions in the Stockholm dataset. Right: the pair-wise comparison of brain age change. No significant effect was detected (PSD – B: $t(40) = -1.6969$, $p = 0.0975$, mean difference = -0.4773 years).

Figure 5

Fig. 5. The associations between the change of brain age and sleep behavior in the Somnosafe dataset. Δbrainage refers to the change of brain age (TSD – baseline), which is normalized by the corresponding chronological age. The horizontal red (blue) arrow points to the increased (decreased) brain age after TSD. Pearson correlation coefficient (r) and p value (p) are shown. The least-squares reference line (dashed and red) is used to show the linear tendency for the correlation. (A) The association between the KSS change (ΔKSS, TSD – baseline) and Δbrainage. The results after adding covariates are shown in Figure 4-1. (B) The association between the normalized wake time (WT, TSD / baseline) in the recovery night following TSD and Δbrainage. 1 is enclosed by a red box, which indicates equal WT between two conditions. (C) The association between the normalized N1 in the recovery night following TSD and Δbrainage. N1 refers to the time spent in stage N1 sleep during sleep period time.

Tables:

Table 1

Demographic information of the participants of five datasets after quality control.

Table 2

The repeated measures ANOVA results of brain age in the Somnosafe dataset. C refers to the within-subject effect corresponding to different sleep conditions. ** indicates $p < 0.005$. SumSq: Type III Sum of Squares. DF: degree of freedom. η^2: partial eta squared. Mauchly's test for sphericity: $p = 0.396$.

Table 1

Demographic information of the participants of five datasets after quality control

Datasets		***Age (mean ± std)***	***Gender (female/male)***	***Number of MRI scans***	***Having TSD (yes or no)***	***Having PSD (yes or no)***
Somnosafe	*Control group*	27.71 ± 6.02	5/9	3	yes	no
	Experimental group	25.60 ± 3.44	8/12	3	yes	yes (5 nights)
CSR		28.25 ± 5.39	7/8	3	no	yes (5 nights)
NRU		24.05 ± 2.76	0/20	2	yes	no
UZH		25.06 ± 3.23	0/20	3	yes	no
Stockholm		23.85 ± 2.58	21/20	2	no	yes (1 night)

Table 2

The repeated measures ANOVA results of brain age in the Somnosafe dataset. C refers to the within-subject effect corresponding to different sleep conditions. ** indicates $p < 0.005$. SumSq: Type III Sum of Squares. DF: degree of freedom. η^2: partial eta squared. Mauchly's test for sphericity: $p = 0.396$.

Source	*SumSq*	*DF*	*F*	*PValue*	η^2
C	20.189	2	7.486	**0.00128****	0.205
Age × C	3.819	2	1.416	0.251	0.0466
Gender × C	4.490	2	1.665	0.198	0.0543
Group × C	0.0337	2	0.0125	0.988	0.0004
Group × Gender × C	2.799	2	1.038	0.361	0.0346
Error	78.214	58