



Occupational circadian disruption and brain structure: evidence from normative developmental brain lifespan trajectories

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Abstract

Shift work disrupts circadian rhythms and is associated with adverse health outcomes. However, its effects on structural differences in the brain remain unclear. We applied the normative brain lifespan chart methodology to evaluate whether shift workers exhibit neuroanatomical deviations from age- and sex-specific reference trajectories. We analyzed structural brain magnetic resonance imaging (MRI) data from 111 healthcare workers comprising 33 shift workers and 78 nonshift workers recruited from a tertiary hospital in South Korea. Six global brain metrics, namely ventricular volume, gray matter volume, white matter volume, subcortical gray matter volume, cortical surface area, and cortical thickness, were extracted using FreeSurfer 7.4. The brain structures of the participants were benchmarked against the normative reference distributions derived from 123,984 MRI scans. Group differences were examined using multiple linear regression models, adjusted for age and intracranial volume. Sex-stratified and regional analyses were conducted to identify the potential occupational neuroplasticity patterns. Global brain metrics showed no significant differences between shift and nonshift workers after adjusting for covariates. However, sex-stratified analyses revealed that female shift workers exhibited nominally lower gray matter volumes ($p=0.002$) and higher cortical surface areas ($p=0.008$) than did nonshift workers in unadjusted analyses. These associations were attenuated after adjusting for age and the intracranial volume. Regional analyses that did not survive multiple comparison correction suggested sex-specific spatial patterns. Male shift workers showed elevated prefrontal and parietal volumes compatible with executive function demands, whereas female shift workers displayed reduced limbic and occipital volumes, suggesting altered emotional processing. This study represents the application of normative brain lifespan charts in occupational neuroscience. Although global structural measures showed null findings, sex-specific patterns suggested that occupational neuroplasticity may manifest through functional reorganization rather than macrostructural brain deviation. Future multimodal investigations that integrate functional neuroimaging, circadian biomarkers, and neurocognitive assessments are warranted.

Keywords Shift work · Circadian disruption · Brain lifespan charts · MRI · Neuroplasticity · Neuroimaging · Brain aging

Introduction

Recent advances in neuroimaging have facilitated the construction of brain reference charts across the human lifespan, similar to growth charts in pediatric medicine; these charts were created by aggregating large-scale magnetic resonance imaging (MRI) datasets and modeling age-specific, sex-stratified structural brain trajectories using generalized additive models for location, scale, and shape (Bethlehem et al. 2022). These reference charts aggregate MRI data to establish sex- and age-specific centile-based normative trajectories for key brain phenotypes, allowing an individual's brain structure to be benchmarked against the population

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distribution of their age group (Cole 2012). Such tools permit the sensitive detection of atypical neuroanatomical patterns that may reflect atypical development, accelerated aging, or the influence of occupational and environmental exposure (Chen et al. 2021; Larkin 2022; Kim et al. 2025).

Emerging evidence indicates that occupational factors, including work schedules, working hours, physical and cognitive demands, and psychosocial stress, have measurable impacts on brain structure and function across the lifespan (Habeck et al. 2019; Choi et al. 2025). Studies on occupational neuroplasticity have revealed that diverse work environments are associated with structural and functional brain changes, affecting individuals from skilled professionals such as bus and taxi drivers to those exposed to prolonged working hours or high-stress conditions (Maguire et al. 2006; Jang et al. 2025). Among occupational exposures, shift work has garnered particular attention owing to its well-established link to circadian disruption and the associated risks of metabolic, cardiovascular, and mental health conditions (Han et al. 2024; Cho et al. 2025). However, previous studies have largely relied on region-of-interest or exploratory whole-brain approaches without systematically benchmarking individual brain phenotypes against population-normed, age- and sex-specific reference standards. Consequently, the degree to which shift work confers measurable deviation from normative brain reference charts across the adult lifespan has not been systematically evaluated.

Therefore, we aimed to assess whether shift workers exhibit brain structural profiles that diverge more frequently from normative reference brain lifespan chart trajectories than do nonshift workers. The central hypothesis is that a shift in the working population is associated with a higher probability of accelerated aging based on population norms. Such deviations may indicate altered or accelerated brain aging trajectories relative to the established reference standards. This study aims to fill a critical gap in occupational neuroepidemiology by leveraging the brain chart methodology to quantify the neurobiological impacts of shift work at the population level.

Methods

Dataset and participants

This study involved using data collected in 2023 from healthcare workers at a regionally representative tertiary hospital in South Korea (Lee et al. 2022). The study population comprised 111 individuals, including shift and nonshift workers. The inclusion criteria were healthcare professionals aged ≥ 18 years who had completed MRI scans and had

available demographic information without any mental health problems. Occupational information included work type and shiftwork status. Shiftwork status was determined from the hospital duty roster, which included rotating night shifts, irregular schedules, and on-call assignments. Participants were classified as shift workers if they had any documented shiftwork patterns in the hospital roster records. Work type was stratified into three categories, namely healthcare workers, nurses, and physicians. Health and lifestyle covariates included smoking status, alcohol consumption, and obesity. Smoking status was classified as none, past, or current. Alcohol consumption was categorized as none, moderate, or binge. Obesity was defined as a body mass index > 25 kg/m². Hypertension was recorded as a yes or no variable based on clinical diagnosis or blood pressure measurements. Fasting glucose levels were measured in mg/dL. Cognitive function was assessed using the Prescreening Korean Dementia Screening Questionnaire (Lee et al. 2025), with a cutoff score of four or more indicating possible cognitive impairment. Participants with known neurological conditions, significant head trauma, or contraindications for MRI were excluded from the analysis. This study was approved by the Institutional Review Board, and all participants provided informed consent before enrollment.

MRI data acquisition

Structural MRI data were acquired using a 3 Tesla Siemens MAGNETOM Vida scanner (Siemens Healthineers, Erlangen, Germany). A 3D T1-weighted magnetization-prepared rapid gradient echo sequence was obtained with the following parameters: repetition time = 1,970 ms; echo time = 2.84 ms; inversion time = 991 ms; field of view = 256×256 mm²; flip angle = 9°; voxel resolution = $0.5 \times 0.5 \times 1$ mm³; number of slices = 192; and scan time = 4 min 34 s. All MRI scans were acquired in DICOM format and converted to NIfTI format prior to preprocessing.

Lifespan curve estimation

Ventricular volume (VV), gray matter volume (GMV), white matter volume (WMV), subcortical GMV (sGMV), cortical surface area (SA), and cortical thickness (CT) were extracted using FreeSurfer version 7.4 (Fischl 2012) with the standard automated 'recon-all' pipeline. This pipeline includes automated motion correction, intensity normalization, skull stripping, cortical surface reconstruction, and anatomical segmentation. All processed outputs were systematically visually inspected by trained researchers to identify major reconstruction errors (e.g., gross skull-stripping failures, severe surface misplacements, or segmentation collapse). Scans with major processing failures were

excluded from analysis. No manual edits or corrections were applied in order to maintain full reproducibility and consistency with the normative reference framework, and to avoid operator-dependent bias. This approach is consistent with large-scale population-based neuroimaging studies using automated pipelines.

To assess the brain structures of the participants relative to their age, we applied an existing normative model developed in a large-scale international project (<https://github.com/ucam-department-of-psychiatry/Lifespan>) (Bethlehem et al. 2022). This reference model, derived from 123,984 MRI scans of 101,457 individuals (aged 115 days to 100 years). These centile scores indicate an individual's percentile rank within an age- and sex-matched normative reference population, reflecting relative brain structure rather than an estimated brain age or predicted biological age. Centile scores were estimated as a function of age and sex for all measurements (VV, GMV, WMV, sGMV, SA, and CT). We applied this normative model to our participants' data to obtain centile scores for each measure, which indicated each individual's percentile rank within the age- and sex-matched reference population. The model and accompanying code were adopted as released by the original authors, and no retraining or modification was performed in the present study.

Statistical analysis

Descriptive statistics were calculated for all the demographic, occupational, and health-related variables. Normality of continuous variables was assessed using the Shapiro–Wilk test, complemented by visual inspection of histograms and Q–Q plots. Homogeneity of variances between groups was evaluated using Levene's test. Independent two-sample t-tests were used for group comparisons when assumptions of normality and equal variances were satisfied. When variance homogeneity was violated, Welch's t-test was applied. For variables showing marked deviations from normality, nonparametric alternatives were considered. In addition to p-values, effect sizes were reported to quantify the magnitude of group differences. Cohen's d was calculated for continuous variables, and Cramér's V was reported for categorical variables based on chi-square tests. Continuous variables are presented as means with standard deviations, and categorical variables as frequencies with percentages. Between-group comparisons of baseline characteristics according to shiftwork status were performed using the chi-square test for categorical variables and the independent t-test for continuous variables.

Age-related trajectories of global brain structural metrics were visualized using locally weighted scatterplot smoothing (LOWESS). A fixed smoothing parameter (span=0.5)

was applied to balance bias and variance in the context of the modest sample size. To estimate uncertainty around the smoothed curves, 95% confidence intervals were constructed using bootstrap resampling (1,000 iterations) of the full sample, with pointwise percentile-based confidence bands derived from the bootstrap distribution. LOWESS curves were used solely for descriptive visualization of age-related patterns and were not intended for formal statistical inference. Group-specific LOWESS fits for shift and non-shift workers were generated separately to facilitate visual comparison, but no statistical tests were performed to compare the smoothed trajectories. Given the age distribution of the cohort, primary analyses focused on age-referenced centile outcomes, and additional sensitivity analyses were conducted within restricted working-age strata to assess the robustness of findings to age imbalance.

Statistical tests were selected according to the level of analysis and distributional characteristics of the data. Independent two-sample t-tests were used for comparisons of global brain structural metrics, which exhibited approximately symmetric distributions and stable variance. In contrast, regional cortical volume measures showed greater skewness and variability, particularly in the context of modest subgroup sample sizes; therefore, the nonparametric Mann–Whitney U test was applied for regional analyses to provide robust inference without assuming normality.

To enable comparisons across individuals of varying ages and sexes, all brain metrics (VV, GMV, WMV, sGMV, SA, and CT) were transformed into population-based centile values. For each participant, centiles were computed relative to a reference distribution of same-sex individuals within a ± 5 -year age range. Within each subgroup, raw values were ranked using the local percentile function:

$$\text{centile} = \frac{\text{rank}(x_i)}{N + 1}$$

where x_i denotes the individual metric value and N is the number of participants in the subgroup.

Higher centile values indicate larger brain structures, and lower centiles represent smaller or more atrophic structures relative to peers. Group differences in brain structural indices between shift and nonshift workers were examined using unadjusted and adjusted analyses. Initially, independent two-sample t-tests were performed to compare raw distributions of each brain metric between groups. Regression models including chronological age and intracranial volume as a covariate were conducted as sensitivity analyses to assess the robustness of findings to residual age-related variation within the study cohort, rather than as primary age-adjustment models. Sensitivity analyses were conducted by additionally adjusting for smoking status,

alcohol consumption, exercise level, educational level, and chronic diseases (hypertension, diabetes, and dyslipidemia), given their established associations with brain aging. These extended models were used to assess the robustness of the primary findings, while the main analyses retained a parsimonious covariate set to minimize overfitting in the context of a modest sample size.

Regional cortical volumetric measurements were performed using the Desikan–Killiany Atlas. For each participant, cortical volume (mm^3) was calculated for 34 parcellated regions per hemisphere and averaged across hemispheres to yield region-wise cortical volume indices. The volumes were adjusted for total intracranial volume and age. For each volume of the cortical region, group differences between shift and nonshift workers were assessed using a two-sided Mann–Whitney U test. Separate analyses were conducted for men and women to examine sex-specific volumetric patterns. The effect direction was defined as the mean volume difference (Shift–Nonshift). The negative log-transformed p-values [$-\log_{10}(p)$] were plotted for each cortical region to visualize regional deviations. Regions were sorted using $-\log_{10}(p)$ to prioritize the most significant deviations at the top of the plot. Given the modest sample size, primary inference was based on pooled regression analyses including all participants, with shift work status as the main exposure and adjustment for age and intracranial volume. Sex was included as a covariate in adjusted models, and sex-stratified analyses were conducted as exploratory sensitivity analyses to examine potential effect modification. Multiple testing correction was applied according to the level of analysis. For global brain structural metrics, which comprised a small number of predefined outcomes, no formal correction for multiple testing was applied, and results were interpreted with caution alongside effect size estimates. For regional cortical analyses involving multiple comparisons across Desikan–Killiany atlas regions, false discovery rate (FDR) correction was performed using the Benjamini–Hochberg procedure, with an adjusted q-value threshold of 0.05. All regression models were evaluated for key assumptions. Linearity and homoscedasticity were assessed using residual-versus-fitted plots, normality of residuals was examined using Q–Q plots, and multicollinearity was assessed using variance inflation factors (VIFs). VIF values were below commonly accepted thresholds, indicating no substantial multicollinearity among covariates.

Results

The study included 111 participants, comprising 33 shift workers and 78 nonshift workers (Table 1). The proportion of male and female participants aged 20–40 years was

comparable, with a higher representation among shift workers (84.8% vs. 64.1%); however, those aged 41–60 years were less represented (15.2% vs. 35.9%), with a marginal difference in age distribution ($p=0.0502$). Educational status, handedness, smoking and drinking habits, obesity, blood pressure status, and fasting glucose levels were comparable between the groups, with all variables having nonsignificant p-values >0.05 . Most participants had a college or university education (75.8% were shift workers and 65.4% were nonshift workers). Obesity affected 21.2% and 28.2% of shift and nonshift workers, respectively, whereas hypertension was rare in both groups (2.7% overall). Occupational distribution differed significantly between groups ($p=0.0139$), with 87.9% of shift workers being health workers compared with 35.9% of nonshift workers. Nurses comprised 60.6% of the shift workers and 34.6% of the nonshift workers, whereas physicians accounted for 27.3% and 25.6%, respectively. All participants were screened as cognitively normal according to the Korean Dementia Screening Questionnaire (score of <4). Effect size estimates indicated that baseline characteristics were largely well balanced between shift and nonshift workers, with negligible to small effect sizes for most variables, except for work type, which showed a small-to-moderate association.

Figure 1 shows the age-related trajectories of the six global brain structural metrics in shift and nonshift workers. Across all participants, the normative reference (solid black line) reproduced the expected adult pattern of progressive expansion of VV and gradual declines in GMV, sGMV, SA, and CT with increasing age. Compared with nonshift workers, shift workers (red lines) exhibited larger VV and WMV, particularly in mid-adulthood, and slightly higher GMV and SA values in early adulthood, whereas CT showed a more pronounced age-related decline in shift workers. Although group differences did not reach statistical significance after FDR correction for multiple testing, the overall pattern suggested subtle deviations in brain-aging trajectories associated with shift work, characterized by relatively preserved or enlarged tissue volumes but thinner cortices. Given the modest sample size, LOWESS-based trajectories should be interpreted as descriptive visual summaries rather than inferential evidence of group differences.

Figure 2 shows sex-stratified split-violin plots of brain structural centile distributions according to shiftwork status. When stratified by sex, significant differences emerged only among females, with shift workers showing a lower GMV ($p=0.002$) and increased SA ($p=0.008$) than nonshift workers did. However, these associations were not statistically significant after adjusting for age and intracranial volume.

Figure 3 illustrates the regional distribution of cortical volume deviations between shift and nonshift workers, expressed as mean differences and corresponding $-\log_{10}(p)$

Table 1 General characteristics of study participants according to shift work

Characteristics	Total (<i>n</i> = 111)	Shift work		<i>p</i> -value	Effect size (Cramér's <i>V</i> or Cohen's <i>d</i>)
		Yes (<i>n</i> = 33)	No (<i>n</i> = 78)		
Sex				0.998	0.008
Male	41 (36.9%)	12 (36.4%)	29 (37.2%)		
Female	70 (63.1%)	21 (63.6%)	49 (62.8%)		
Age (years)				0.050	0.094
20–40	78 (70.3%)	28 (84.8%)	50 (64.1%)		
41–60	33 (29.7%)	5 (15.2%)	28 (35.9%)		
Education level				0.165	0.075
College or university	76 (68.5%)	25 (75.8%)	51 (65.4%)		
Graduate school or Higher	34 (30.6%)	8 (24.2%)	26 (33.3%)		
Handedness				0.092	0.014
Right	104 (93.7%)	30 (90.9%)	74 (94.9%)		
Left or both	7 (6.3%)	3 (9.1%)	4 (5.1%)		
Smoking				0.183	0.060
None	95 (85.6%)	28 (84.8%)	67 (85.9%)		
Past or current	16 (14.4%)	5 (15.2%)	11 (14.1%)		
Drinking				0.575	0.077
None	28 (25.2%)	7 (21.2%)	21 (26.9%)		
Moderate or binge	83 (74.8%)	26 (78.8%)	57 (73.1%)		
Obesity ^a				0.571	0.013
No	81 (73.0%)	26 (78.8%)	55 (70.5%)		
Yes	29 (26.1%)	7 (21.2%)	22 (28.2%)		
Hypertension ^b				0.999	0.153
No	108 (97.3%)	32 (97.0%)	76 (97.4%)		
Yes	3 (2.7%)	1 (3.0%)	2 (2.6%)		
Fasting glucose level (mg/dL)	86.7 ± 9.0	85.5 ± 8.5	87.2 ± 9.3	0.364	0.190
Cognitive dysfunction ^c				1.000	-
No	0 (0.0)	0 (0.0)	0 (0.0)		
Yes	111 (100.0)	111 (100.0)	111 (100.0)		
Work type				0.014	0.153
Health worker	57 (51.4%)	29 (87.9%)	28 (35.9%)		
Nurse	47 (42.3%)	20 (60.6%)	27 (34.6%)		
Physician	29 (26.1%)	9 (27.3%)	20 (25.6%)		

Data are presented as *n*, %, or mean ± standard deviation

Effect sizes are reported as Cohen's *d* for continuous variables and Cramér's *V* for categorical variables. Effect size estimation was not applicable for cognitive dysfunction because no participant met the criterion in either group

^aObesity defined as body mass index over 25 kg/m²

^bHypertension defined as diagnosis or systolic blood pressure over 140 mmHg or blood pressure over 90 mmHg

^cCognitive function test was based on Prescreening Korean Dementia Screening Questionnaires, with cutoff score of ≥ 4 used for further evaluation

values across the Desikan–Killiany atlas. Among male participants, shift workers had higher relative cortical volumes in several prefrontal and parietal regions, including the frontal pole, medial orbitofrontal cortex, and inferior parietal lobule. Female shift workers exhibited nominally lower cortical volumes in the limbic and occipital regions, such as the entorhinal, posterior cingulate, and lateral occipital cortices. Although none of these regional effects survived multiple-comparison FDR correction, the observed pattern suggests sex-specific tendencies in the spatial distribution of volumetric alterations associated with shift work.

Discussion

Building upon prior studies that have linked occupational exposures to brain structural alterations and accelerated brain aging the present study applies a population-referenced, centile-based normative framework to examine brain structural variation associated with shift work in a relatively healthy working population. We evaluated six global brain structural metrics and regional cortical volumes in 111 healthcare workers (33 shift workers and 78 nonshift workers) using centile-based benchmarking derived from a reference sample of over 123,000 individuals. Contrary to

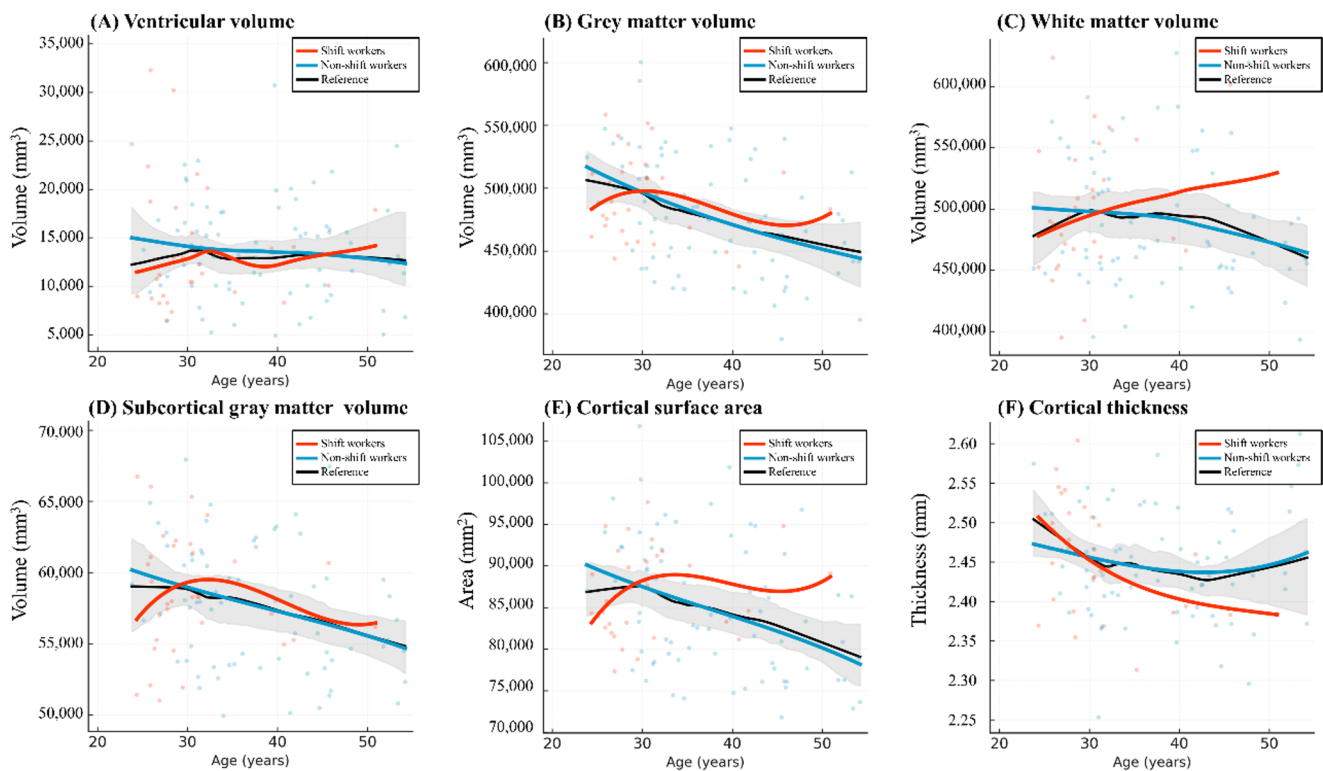


Fig. 1 Age-related trajectories of six global brain structural metrics among shift and nonshift workers. Reference brain lifespan trajectories and 95% confidence intervals are represented using solid black lines and grey bands, respectively. Scattered points represent individual participants (blue, nonshift; red, shift). Reference trajectories and 95% confidence intervals were estimated using LOWESS smoothing

(span=0.5) with 1,000 bootstrap iterations. Confidence intervals represent pointwise percentile-based bands derived from bootstrap resampling. Smoothed curves are provided for descriptive visualization only and were not statistically compared between groups. All brain volume measures are displayed in cubic millimeters (mm^3), and cortical thickness is displayed in millimeters (mm)

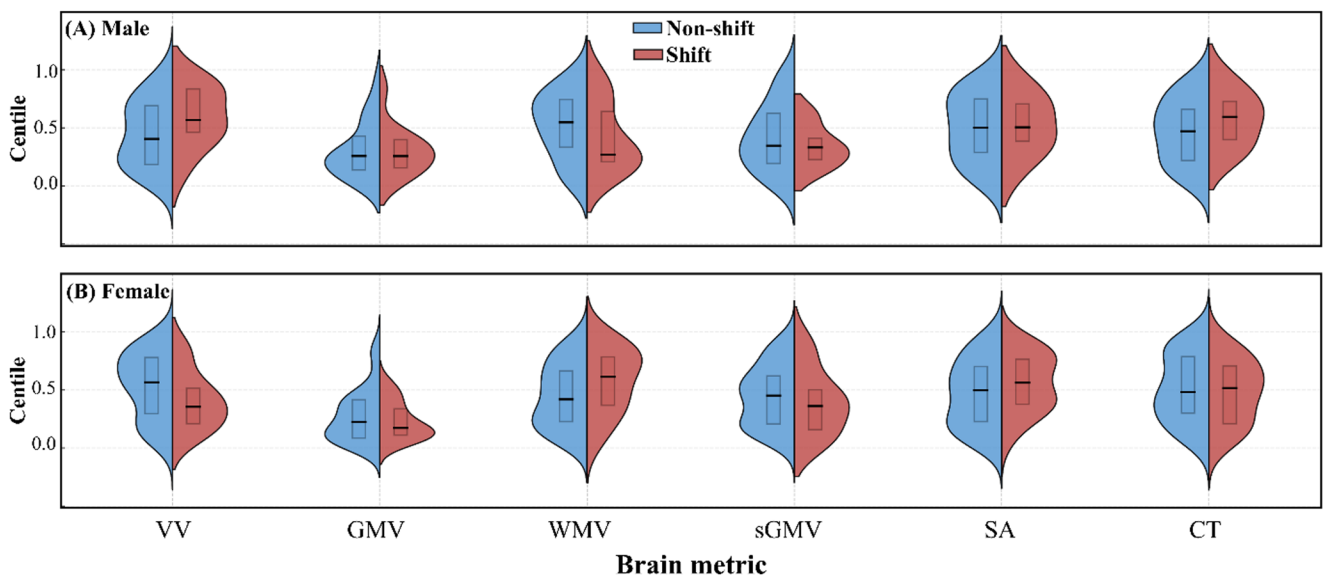


Fig. 2 Sex-stratified split-violin plots showing brain structural centile distributions in six metrics according to shiftwork status. **A** Male participants. **B** Female participants. Blue and red colors indicate nonshift and shift workers, respectively. Black boxes represent the interquartile

range and median. VV: ventricular volume, GMV: gray matter volume, WMV: white matter volume, sGMV: subcortical gray matter volume, ST: cortical surface area, CT: cortical thickness

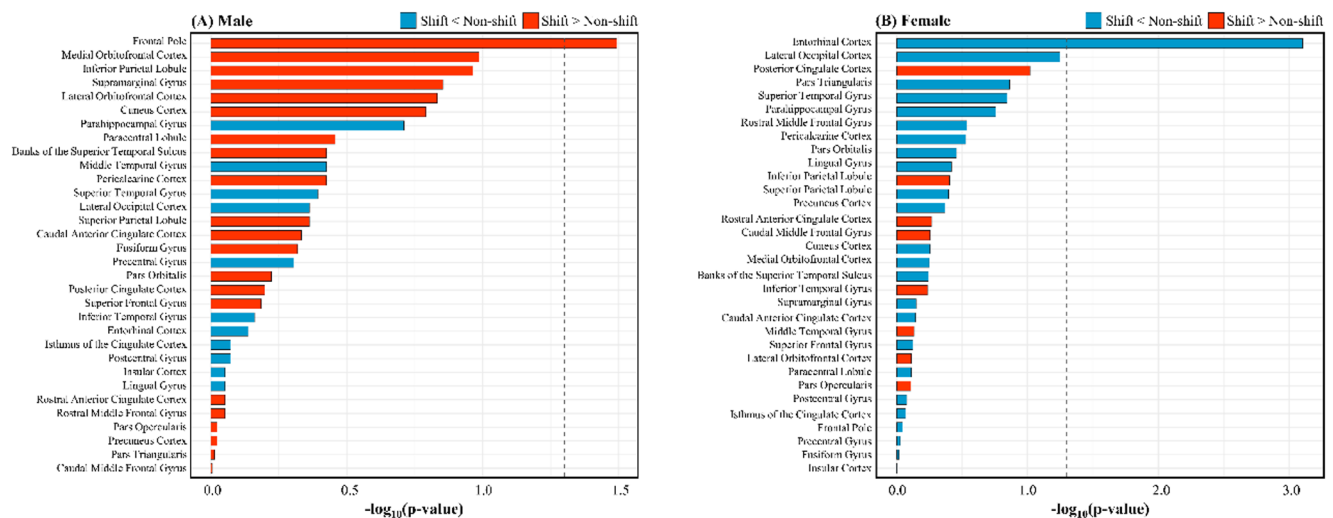


Fig. 3 Regional distribution of cortical volume deviations between shift and nonshift workers with sex stratification. **A** Male participants. **B** Female participants. Bars represent $-\log_{10}(\text{p-value})$ from Mann-Whitney U tests comparing each volume of brain region (Shift vs.

Nonshift). The dashed vertical line indicates the nominal significance threshold ($p=0.05$). Blue bars indicate regions where shift workers showed lower volumes than did nonshift workers, and red bars indicate regions where shift workers showed higher volumes

our hypothesis of significant group-level deviations, global brain metrics showed no significant differences between shift and nonshift workers after adjusting for age and intracranial volume. However, sex-stratified analyses revealed nuanced patterns consistent with occupational neuroplasticity, in which female shift workers exhibited lower GMV and higher SA before covariate adjustment, suggesting a potential reorganization of cortical architecture associated with circadian disruption. These observations, although not robust to adjustments for age and brain size, suggest that the neurobiological signature of shift work may manifest as subtle, sex-specific alterations in the normative brain structure rather than wholesale deviations from established reference trajectories.

The observed sex-specific pattern in the unadjusted analyses, in which female shift workers exhibited lower GMV ($p=0.002$) and higher SA ($p=0.008$) than did female nonshift workers, warrants mechanistic consideration, particularly given the absence of comparable differences in males. This sexual dimorphism is consistent with that of a previous study, demonstrating the increased physiological sensitivity of women to circadian misalignment (Gunn et al. 2016). Women exhibit a shorter intrinsic circadian period than men do (24.09 vs. 24.19 h) and consequently display greater circadian amplitude disruption and increased nocturnal melatonin suppression when exposed to shift work schedules (Duffy et al. 2011). This enhanced vulnerability to phase desynchronization may render women more susceptible to chronic circadian dysrhythmia than their male counterparts (Gamble et al. 2013; Walton et al. 2022). At the neurobiological level, estrogen directly modulates serotonin and dopamine signaling in cortical networks through

estrogen-responsive elements and nuclear receptor mechanisms; therefore, circadian disruption combined with perturbed estrogen secretion may intensify the dysregulation of monoaminergic tone, causing downstream consequences for cortical plasticity, dendritic remodeling, and synaptic refinement (Begemann et al. 2025). The observed neuroanatomical pattern, characterized by reduced GMV with preserved or increased SA, is consistent with selective cortical thinning, reflecting adaptive synaptic pruning in response to chronic occupational and circadian stress. This process of synaptic pruning, which involves the activity-dependent elimination of less-utilized synaptic connections, represents a fundamental mechanism of brain development and plasticity across the lifespan, causing measurable reductions in CT (Malik et al. 2024). However, these unadjusted sex-specific associations were substantially attenuated to statistical nonsignificance following adjustment for age and ICV, suggesting that observed female-specific neuroanatomical differences may largely reflect underlying variations in brain size or developmental trajectories rather than shift work-specific pathophysiological processes. This ICV dependency suggests that female shift workers differ in overall brain scaling and volumetric architecture, rather than displaying genuine parenchymal remodeling attributable to occupational exposure. Although centile scores are inherently age-normalized, we additionally examined models including chronological age to evaluate robustness against residual age-related variation arising from cohort-specific sampling. This approach did not materially change the results, suggesting that observed findings were not driven by residual age confounding. Future studies may benefit

from exploring allometric or population-specific scaling approaches to further refine age-related adjustment.

The absence of significant global brain structural deviations in shift workers across VV, GMV, WMV, and CT measures warrants interpretation within contemporary frameworks of occupational neuroimaging and adaptive plasticity (Winkler et al. 2010; Kim, Choi et al. 2025). Global brain metrics reflect whole-brain tissue volumes and organization that demonstrate robust age-related trajectories, and the lack of shift work effects on these measures suggests that occupational circadian disruption does not substantially alter macrostructural brain phenotypes (Choi et al. 2025). This null finding is consistent with that of neural compensation models, in which adaptive neuroplasticity permits individuals to maintain a normative structural anatomy despite chronic occupational challenges. In contrast to occupational exposures that cause overt structural pathology (e.g., chronic substance use and traumatic brain injury), shift work may preferentially affect functional neural organization, such as network connectivity architecture and neurotransmitter regulation, rather than gross structural parameters (Hylin et al. 2017). Alternatively, the adaptive and relatively long-term nature of occupational shift work exposure in healthy young adults may trigger compensatory neuroplastic mechanisms, enabling individuals to maintain structural brain reserves and developmental trajectories despite ongoing circadian dysrhythmia (Jang et al. 2025). This interpretation is consistent with the cognitive reserve frameworks, which distinguish between neural reserves (intrinsic structural brain capital) and neural compensation (functional reorganization of existing networks) (Barulli and Stern 2013). These considerations suggest that measurable associations between shift work and accelerated brain aging, when detected using brain age algorithms in complementary studies, may reflect functional or computational changes in neural information processing rather than morphological brain atrophy or volumetric loss (Geerligs et al. 2015; Ranasinghe and Mapa 2024). The observation of lower GMV alongside higher SA should be interpreted cautiously, particularly given the largely nonsignificant results. Rather than reflecting compensatory neurobiological mechanisms, this pattern likely reflects the geometric relationship among cortical morphometric measures. GMV is mathematically determined by the product of CT and SA, and small, independent variations in these components can produce divergent volumetric patterns without implying functional adaptation or compensation. Accordingly, these findings are best regarded as descriptive and hypothesis-generating. In the context of a modest sample size, mechanistic interpretations are premature, and future studies incorporating longitudinal designs and multimodal imaging will be required

to clarify the biological significance of such morphometric patterns.

Regional cortical volumetric analyses revealed exploratory sex-specific spatial patterns in shift workers compared with nonshift workers, although none of them survived multiple comparison corrections. Male shift workers demonstrated nominally higher cortical volumes in several prefrontal and parietal regions, including the frontal pole, medial orbitofrontal cortex, and inferior parietal lobule. These prefrontal regions are crucial for executive function, sustained attention, cognitive control, and cognitive domains, which are essential for occupational performance during vigilant night-shift work (An et al. 2025). The pattern of elevated prefrontal volumes in male shift workers may reflect occupational neuroplasticity, in which chronic demands for sustained executive attention during night shifts elicit compensatory cortical expansion or increased synaptic density in the brain regions that support cognitive control. Conversely, female shift workers exhibited nominally lower cortical volumes in the limbic and occipital regions, including the entorhinal, posterior cingulate, and lateral occipital cortices. The entorhinal cortex and posterior cingulate are components of the default mode network and medial temporal lobe memory system, which are stress-responsive and undergo volumetric reductions with chronic circadian disruption and elevated glucocorticoid exposure (Rolls 2019). The sex-specific regional pattern, in which males show prefrontal expansion and females show limbic contraction, suggests divergent neurobiological responses to shift work: a top-down compensatory mechanism in males involving enhanced executive control versus a bottom-up vulnerability in females characterized by altered limbic-affective processing and memory consolidation (Dong et al. 2022). However, the lack of multiple comparison correction and modest sample size within sex-stratified subgroups substantially limit the statistical reliability of these regional observations, making them exploratory findings that require replication in larger cohorts.

From a mechanistic perspective, circadian disruption impairs nocturnal melatonin secretion, which is critical for synaptic plasticity and dendritic spine density in the hippocampus and prefrontal cortex (Valdés-Tovar et al. 2018). Similarly, chronic circadian misalignment disrupts the 24-h glucocorticoid rhythm, causing elevated nocturnal cortisol and blunted circadian amplitude, with consequences for dendritic retraction and cortical thinning in glucocorticoid receptor-dense regions (Oster et al. 2017). Additionally, circadian disruption activates microglial neuroinflammation through dysregulation of clock genes that normally suppress proinflammatory cytokines, causing impaired synaptic plasticity (Lull and Block 2010; Samanta and Bagchi 2024). However, the mechanistic pathways linking shift work to

neurobiological changes cannot be directly evaluated using the structural brain lifespan chart methodology alone.

The present findings should be interpreted in the context of prior occupational neuroimaging studies, including investigations conducted in World Trade Center responder cohorts, which have reported more pronounced brain aging and neurostructural alterations in populations exposed to severe, traumatic, or highly toxic occupational environments (Invernizzi et al. 2023, 2025). These studies typically involve individuals with substantial clinical burden, including post-traumatic stress symptoms, chronic systemic inflammation, and long-term neuropsychiatric sequelae, all of which may contribute to detectable acceleration of brain aging as assessed by brain age prediction models. In contrast, the current study focuses on a relatively healthy working population with predominantly nontraumatic occupational exposure, where circadian disruption rather than acute toxic or psychological injury represents the primary exposure of interest. Differences in exposure intensity, duration, and qualitative characteristics, as well as variations in clinical vulnerability, demographic composition, and study design, may partially explain why the brain structural deviations observed here are more subtle and do not manifest as robust global deviations from normative reference trajectories. These contrasts underscore the importance of considering exposure severity and cohort context when interpreting occupational neuroimaging findings and suggest that population-referenced normative approaches may be particularly informative for detecting early or mild neurobiological alterations in otherwise healthy worker populations.

The largely null findings observed in age-related trajectories, sex-stratified analyses, and regional cortical comparisons should also be interpreted in the context of limited statistical power. Based on the small effect sizes observed across global brain metrics (typically in the range of Cohen's $d \approx 0.2$ – 0.3), substantially larger sample sizes would likely be required to reliably detect occupational circadian effects on brain structure. For example, detecting a small-to-moderate effect size ($d = 0.25$) with 80% power at a two-sided α of 0.05 would require approximately 250–300 participants per group, with even larger samples needed for sex-stratified or region-level analyses after correction for multiple comparisons. These considerations suggest that future studies investigating the neurobiological effects of shift work will benefit from multi-center collaboration, population-based cohorts, or large biobank-scale datasets. Longitudinal designs may further improve statistical efficiency by enabling within-subject comparisons, thereby reducing between-subject variability and improving sensitivity to subtle occupational effects. Although the present cohort was not powered to detect such small differences, the

current findings provide a useful empirical basis for planning adequately powered future studies.

Despite the null findings regarding global brain structural measures, this study has substantial implications for occupational neuroscience and worker health. The absence of overt macrostructural brain deviation does not exclude clinically meaningful neurobiological impacts. Complementary functional neuroimaging, including resting-state functional MRI, may reveal circadian effects on neural information processing that are not captured through volumetric assessment. Clinically, neurocognitive screening of shift workers should include assessments of attention, executive function, and processing speed with structural brain imaging (Vlasak et al. 2022). For occupational policy, the findings support continued efforts to optimize shift schedules through forward rotating systems, adequate recovery intervals between shifts, and evidence-based interventions, including appropriately-timed light therapy during night shifts (900–6000 lx for ≥ 1 h) (Zhao et al. 2025), which has demonstrated efficacy in circadian phase realignment and sleep improvement in shift workers. Future longitudinal investigations should integrate multimodal biomarker assessments, including actigraphy-derived circadian phase, saliva cortisol, and melatonin profiling, and larger sample sizes to reveal neuroplastic signatures not evident in this relatively young cohort.

This study has some limitations. First, the relatively small number of shift workers represents an important limitation with respect to statistical power, particularly for subgroup and sex-stratified analyses. In a relatively healthy working population, brain structural measures are inherently heterogeneous, reflecting individual differences in biological susceptibility, occupational exposure history, and adaptive or compensatory neuroplastic mechanisms. Such variability may attenuate detectable group-level effects in cross-sectional analyses, particularly when exposure-related changes are subtle. To mitigate this limitation and reduce potential confounding, our primary conclusions are based on pooled regression models adjusting for age and intracranial volume, with sex included as covariate. Although smoking, alcohol consumption, exercise level, educational level, and chronic diseases (hypertension, diabetes, and dyslipidemia) are known contributors to accelerated brain aging, additional adjustment for these factors in sensitivity analyses did not materially change the observed associations. This suggests that the findings are unlikely to be driven solely by lifestyle or past history confounding. Nonetheless, residual confounding cannot be fully excluded, particularly in a relatively small cohort. Importantly, the observed variance should not be interpreted solely as statistical noise but may reflect meaningful heterogeneity in vulnerability to circadian disruption. Future studies with larger sample

sizes, longitudinal follow-up, and repeated measures will be essential to disentangle true exposure-related effects from individual variability and to identify subgroups with heightened susceptibility. Second, the cross-sectional design precluded inferences regarding the temporal relationships and causality between shift work and neurobiological changes. The duration and cumulative intensity of circadian rhythm disruption are likely key determinants of when measurable brain structural changes emerge. In the present study, shift work was defined based on current duty rosters, and detailed information on cumulative exposure duration, rotation patterns, and lifetime shift work history was not available. As a result, the findings reflect cross-sectional associations related to the presence of shift work rather than dose–response or temporal effects. Emerging evidence suggests that prolonged or chronic circadian misalignment may exert cumulative neurobiological effects, potentially leading to detectable brain structural alterations only after sustained exposure. Future studies should incorporate detailed longitudinal assessments of shift work duration, intensity, and recovery periods, along with repeated neuroimaging measures, to identify critical exposure windows and thresholds for brain aging–related changes. Third, occupational exposure was dichotomized as shift versus nonshift status rather than being characterized using dose-response metrics, including the duration of shift work exposure, frequency of night shifts, or rotation pattern type, limiting the ability to model exposure gradients and identify critical exposure windows. Fourth, this cohort comprised relatively young healthcare workers (mean age, approximately 35 years) who were presumably selected through healthy worker effects, potentially limiting generalizability to older workers or occupations with more severe or prolonged circadian disruption. Fifth, an important methodological consideration concerns the population specificity of normative brain reference models. Although the brain lifespan charts developed by Bethlehem et al. represent the largest available normative resource and incorporate data from multiple international cohorts, the majority of contributing datasets originate from Western populations. Emerging evidence suggests that brain structural trajectories may differ across populations due to genetic, cultural, socioeconomic, and environmental factors, and that population-specific normative references may provide improved accuracy (Choi et al. 2021; Turney et al. 2023). In the present study, centile scores were used as a relative benchmarking framework to compare shift and nonshift workers within the same cohort, rather than as absolute indicators of abnormal brain aging. This within-cohort comparison mitigates, but does not eliminate, potential bias related to cross-population differences. Future studies should prioritize the development and validation of population-specific or multi-ethnic normative

brain reference models, particularly for occupational and environmental health research. Sixth, participants in this study skewed in both age and gender distribution due to the nature of shift work. Older participants were less likely to be engaged in shift work, reflecting workforce structure rather than selection bias; analyses therefore emphasize within-age relative comparisons rather than absolute differences across the entire age range. Sex-stratified findings should be interpreted cautiously, as the number of older shift workers within each sex was limited. Accordingly, these analyses are exploratory and intended to generate hypotheses regarding potential sex-specific susceptibility rather than to establish definitive biological differences.

Normative brain lifespan charts from a cohort of 111 healthcare workers revealed no significant global brain structural deviations associated with shift work status after adjusting for age and intracranial volume. However, sex-stratified analyses revealed exploratory patterns suggesting divergent neurobiological responses to shift work, with female shift workers showing reduced GMV and altered limbic organization and males showing elevated prefrontal volumes compatible with cognitive demand-related neuroplasticity. These findings contribute to the emerging field of occupational neuroscience by demonstrating the utility and feasibility of normative modeling approaches for detecting potential neurobiological signatures of occupational exposure. The results indicate that the absence of macrostructural brain deviation does not exclude meaningful circadian impacts, suggesting that future investigations should involve integrating functional neuroimaging, circadian phase biomarkers, and neurocognitive assessments to comprehensively characterize the effects of shift work on brain aging and inform evidence-based occupational health policies.

Author contributions Youjin Kim: Investigation, Data curation, Formal analysis, Visualization, Interpretation of data, Manuscript writing – original draft preparation. Joon Yul Choi: Methodology, Validation, Imaging analysis, Technical support for MRI data acquisition and interpretation, Critical revision of the manuscript for important intellectual content, and Writing – review and editing. Wanhyung Lee: Conceptualization, Study design, Funding acquisition, Project administration, Supervision, Interpretation of results, Critical revision of the manuscript for important intellectual content, and Writing – review and editing.

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Data availability Data will be made available on request.

Code Availability All analyses were conducted using publicly available software and open-source tools. The normative brain lifespan

chart model is available at <https://github.com/ucam-department-of-psychiatry/Lifespan>. Structural MRI processing was performed using FreeSurfer (version 7.4). No custom code or trained models were developed for this study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval The study protocol was approved by the Institutional Review Board of Chung-Ang University (IRB 1041078-20231024-HR-287). Written informed consent was obtained from all participants before enrollment.

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