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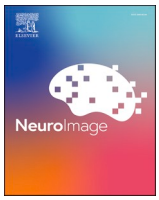

Shift work is associated with selective brain volume loss: a longitudinal study

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ABSTRACT

Introduction: Global work patterns are changing, with more individuals engaged in shift work and remaining in the workforce later in life. Shift work is linked to disrupted sleep, impaired cognition, and greater risk of metabolic and neurodegenerative disease; effects that are amplified by aging. However, the neural correlates of shift work remain poorly characterized, leaving a critical gap in understanding how occupational schedules may shape the aging brain.

Objectives: We aimed to determine the relationship between shift work on brain structure in healthy adults, and how brain structure changes over time in older-aged shift workers.

Methods: We analysed data from a population-based longitudinal cohort study. We included data for employed individuals with no serious medical conditions. Participants completed self-report questionnaires on health, sleep, cognition and employment, and brain MRI. We used linear regression to compare shift workers and non-shift workers on 153 structural brain parameters, controlling for age, sex, chronotype, intracranial volume, smoking history, MRI head motion, hypertensive status and socioeconomic status.

Results: We included $n = 14{,}198$ individuals (aged median 47 [IQR=7] years) comprising non-shift workers ($n = 12{,}076$) and shift workers ($n = 2122$). In shift workers, we detected a symmetrical pattern of volume loss in the right thalamus (Cohen's d=-0.10, adjusted $p = 0.026$) and left amygdala (Cohen's d=-0.11, adjusted $p = 0.010$). In subjects who ceased shift work after the baseline, we observed a halting of shift work-related volume loss within 2.4 years. Secondary analyses revealed microstructural degradation in the corticospinal tract, cerebral peduncle and right sagittal stratum, and negative correlation of volume loss with cognitive performance.

Conclusion: Shift workers have selective volume loss of the thalamus and amygdala, which is halted within 2.4 years of stopping shift work. Monitoring, counselling and interventional measures, including adjustment of work schedules, could minimise brain volume loss in shift workers.

1. Introduction

The demands of a 24-hour modern society have led to the transformation of work patterns. Two prominent trends are the increased presence of shift work and the increasingly older age of the workforce. Indeed, in Europe, the proportion of shift workers increased from 17 % in 2010 to 21 % in 2015 (Parent-Thirion et al., 2016), and has remained stable until 2024 (Eurofound 2025), while retirement age and length of working life have steadily increased (OECD 2023; Eurostat 2024). In the US, the proportion of shift workers increased from 14.8 % in 2004 (US

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Bureau of Labor Statistics 2005) to 16.4 % in 2019 (US Bureau of Labor Statistics 2019). Older workers are the fastest-growing segment of the workforce (Fry and Braga, 2023). Shift workers are at greater risk for health problems that affect the brain (Yang et al., 2024; Costa, 2010; Jin et al., 2017), and these are compounded by aging (Shi et al., 2022; Karhula et al., 2021). However, the relationship between shift working and the structure of the brain is not known.

The first neuroimaging study in healthy shift workers reported temporal lobe atrophy among flight attendants (n = 20), which correlated with reaction time (Cho, 2001). However, subsequent studies have found no evidence for effects of shift work on brain structure or function in healthy individuals (Bittner et al., 2022; Jeong et al., 2024) and were performed in small samples (n = 13 and n = 63 current shift workers, respectively). Studies may have been limited by statistical power, heterogeneous samples and lack of detailed data for working patterns, health, sleep and cognition. These limitations could be addressed through the use of large population-level biobank datasets, such as the UK Biobank (Sudlow et al., 2015). The UK Biobank includes brain MRI, as well as rich data on employment, health, sleep, and cognition for a large cohort that would provide greater power to detect changes associated with shift work. Better knowledge about the impacts of shift work could help to identify at-risk individuals or optimise working patterns to improve workers' health and performance.

Here, we compared brain structure between shift workers and non-shift workers in a healthy, employed, British, middle-to-older aged population-based sample (n = 14,198). We hypothesised that shift workers would have reduced brain volumes and abnormal microstructure. We proposed that cessation of shift working would be associated with the halting of shift work-related changes to brain structure and that the effects on brain structure would correlate with the number of hours worked, and with cognitive deficit.

2. Methods

2.1. Study design

We conducted a population-based longitudinal observational study of structural brain MRI parameters, employment, cognitive and health data to determine the changes in brain structure associated with shift work in the set of UK Biobank participants who were healthy and in full-time employment (Fig. 1). We followed the "STrengthening the Reporting of OBservational studies in Epidemiology" (STROBE) reporting guidelines (von Elm et al., 2007).

2.2. Participants

Data were accessed via the UK Biobank Research Analysis Platform (application ID 72354) in December 2024. The UK Biobank is a population-based biobank of over 500,000 individuals aged 40–70 years who were recruited between March 2006 and July 2010 from among the general UK population. One of 22 assessment centres were attended by all participants at baseline (2006–2010), by a subset of participants for an initial imaging visit (2014+), and by a subset of those participants for a repeat imaging visit (2019+). At each visit, participants completed a self-administered touch-screen questionnaire, interview and measurement-taking by trained staff. Except for longitudinal analysis, we used data from the initial imaging visit.

In this study, we only included data from participants who met all of the following criteria: (a) had completed the brain MRI at the initial imaging visit, (b) had no prior cancer diagnosis, stroke, heart attack or

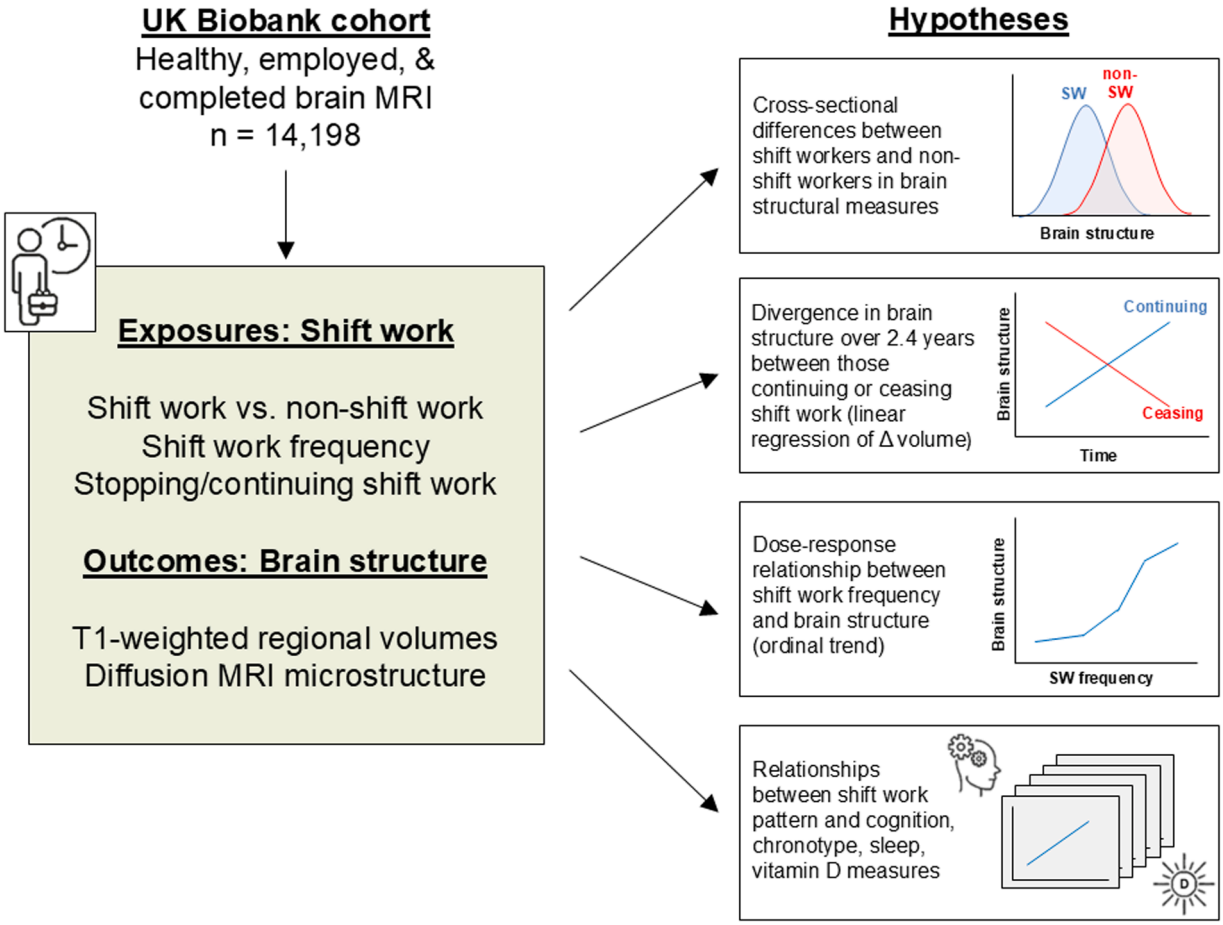

Fig. 1. Conceptual diagram summarising the study hypotheses and analytical framework.

any other serious medical conditions (self-reported response to "Has a doctor ever told you that you have had any other serious medical conditions or disabilities?"; question L5C in the UK Biobank touchscreen questionnaire), (c) had "excellent", "good" or "fair" general health, (d) were in full-time paid employment or self-employed, and (e) had no reported incidental findings from either MRI scan.

Of the 502,132 individuals who consented to the UK Biobank, 58,746 individuals had completed the initial brain MRI, and 39,379 of those did not have serious medical conditions (cancer, heart attack, stroke, or "other serious conditions") or "poor" general health. Of those, 14,198 individuals were in paid employment or self-employed (Fig. 2). The sample characteristics are detailed in Table 1.

2.3. Ethics statement

The UK Biobank is has approval from the North West Multi-centre Research Ethics Committee as a Research Tissue Bank (RTB), which was granted in 2011, and renewed in 2016 and 2021. Written informed consent was obtained from all participants. All research was conducted in accordance with the established RTB approval, ensuring participant confidentiality and anonymisation. We signed a material transfer agreement and accessed de-identified data.

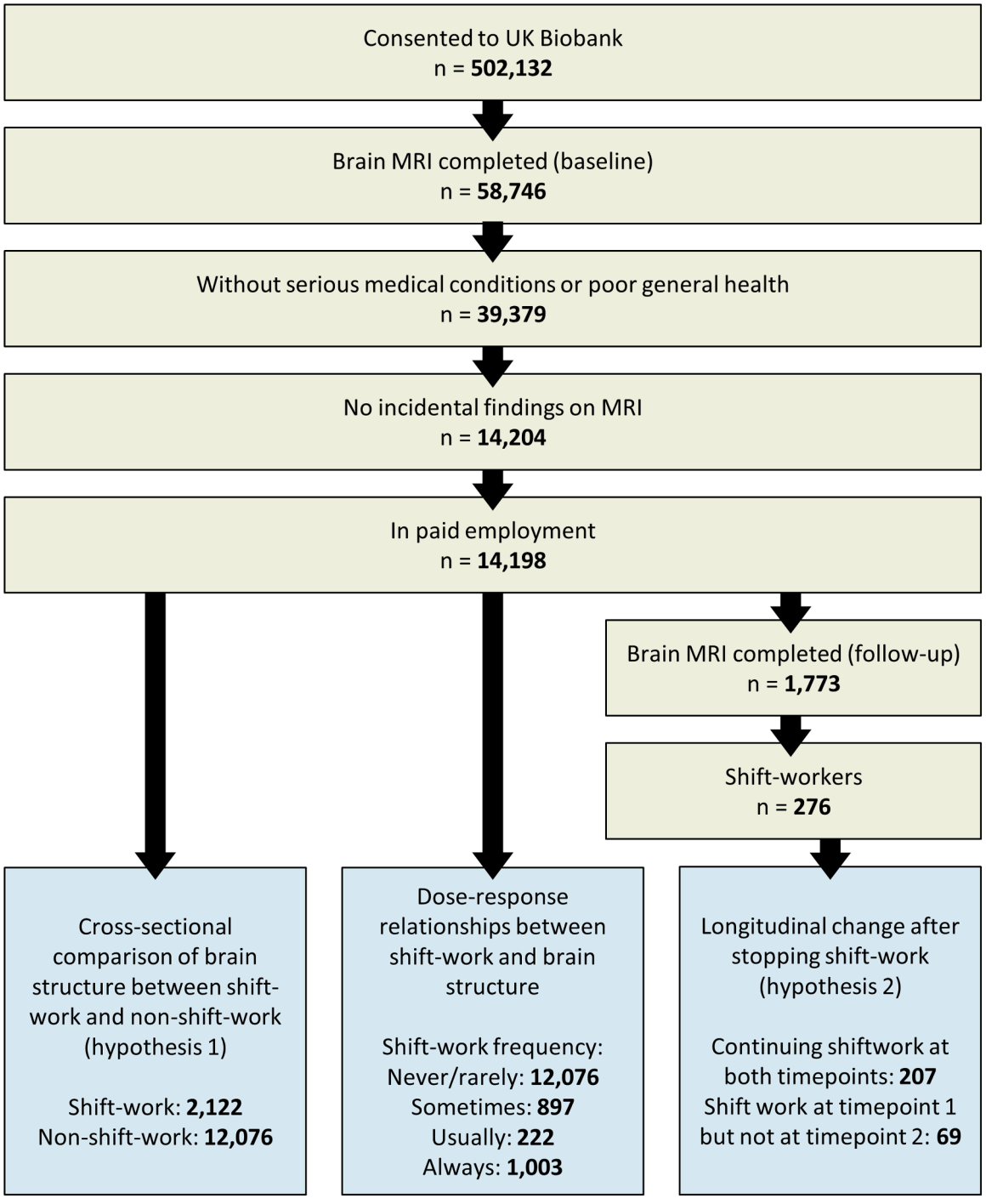

Fig. 2. Flowchart of inclusion criteria and sample sizes at each stage and analysis. Breakdown of sample size used in each stage of analysis.

Table 1
Sample characteristics.

	All subjects	Shift workers	Non-shift workers	P (shift vs. non-shift)
n	14,198	2122	12,076	-
Age, years [b]	47 (7)	47 (6)	47 (7)	0.007 **
Sex, % male [c]	49.9	54.8	49.0	< 0.001 **
Socioeconomic Deprivation Index [a, d]	0.61 ± 3.57	0.75 ± 3.50	0.58 ± 3.58	< 0.001 **
Chronotype, % evening [c]	13.0	15.6	12.5	0.001 **
Intracranial volume, mm^3 [a]	1189,895 ± 110,944	1191,817 ± 111,298	1189,596 ± 110,854	0.469
Serum vitamin D, nmol/L [a]	47.7 ± 21.0	47.6 ± 21.5	47.7 ± 20.9	0.832
Insomnia, % sometimes/usually [c]	74.1	75.4	73.8	0.151
Diffusion MRI head motion (mean absolute motion), mm [a]	1.12 ± 0.47	1.14 ± 0.49	1.12 ± 0.43	0.053
T1 MRI estimated head motion [a]	0.34 ± 0.17	0.35 ± 0.18	0.34 ± 0.15	0.006 **
Smoking history, % previous or current [c]	44.2	46.7	43.3	< 0.001 **
Hypertensive, % positive [c]	51.8	53.1	51.2	< 0.001 **
Numeric memory [a]	7.19 ± 1.4	7.10 ± 1.5	7.20 ± 1.4	0.071
Fluid intelligence [a]	6.74 ± 2.12	6.28 ± 2.13	6.81 ± 2.10	< 0.001 **
Pairs matching [a]	0.53 ± 1.05	−0.59 ± 1.06	−0.52 ± 1.04	0.065
Symbol-digit substitution [a]	22.34 ± 4.80	21.2 ± 4.91	22.5 ± 4.76	< 0.001 **
Trail-making [a]	34.7 ± 13.0	−36.9 ± 11.9	−34.3 ± 13.1	< 0.001 **

[a] Normally-distributed continuous variables are shown as mean ± SD, with the p-value for a *t*-test.
[b] Median (IQR) with the p-value for a Mann-Whitney U test.
[c] Categorical variables are shown as a percentage with the p-value for a Chi-square test.
[d] Log transformed variable, showing geometric mean and geometric standard deviation.

2.4. MRI data

Brain MRI acquisition was performed on Siemens Skyra 3T MRI machine with a standard Siemens 32-channel RF receive head coil. We used data from the T1-weighted and diffusion-weighted (DW) sequences, which are available online (https://www.fmrib.ox.ac.uk/ukbiobank/protocol/). T1-weighted images have good contrast between gray and white matter, allowing more accurate segmentation of brain regions and quantification of their volumes. The DW MRI signal is affected by the random motion of water molecules in the brain tissue, and allows quantification of tissue microstructural parameters which can inform us about the integrity of white matter. Diffusion MRI data from Phase 2 and earlier were not analysed due to a protocol change, otherwise no significant changes were made to MRI scanners during the study.

MRI images were processed in the UKB Brain Imaging Pipeline (Alfaro-Almagro et al., 2018). In short, both T1 and DW MRI data were converted to NIFTI format for analysis, anonymised, and corrected for gradient distortion. For the T1 images, non-brain tissues were removed, the images were registered to a standard template, and then segmented into regions using FSL FAST, FIRST, SIENAX (Jenkinson et al., 2012) and FreeSurfer (FreeSurfer, 2012). Volumes of each region were calculated and provided in the UK Biobank. From T1-weighted images, an estimate of head motion was used as a covariate in our analyses (Alfaro-Almagro et al., 2021).

DW MRI data were corrected for eddy currents and head motion, and used to fit a diffusion tensor model (DTIFIT) to create FA (fractional anisotropy) data. A second model (Neurite Orientation Dispersion and Density Imaging) was used to create the ICVF (intra-cellular volume fraction - an index of white matter neurite density), ISOVF (isotropic or free water volume fraction) and ODI (orientation dispersion index, a measure of within-voxel tract disorganisation) diffusion metrics. A white matter tract skeleton was created using TBSS (tract-based spatial statistics) and used to calculate the average of each diffusion metric in various subregions of the white matter tracts. Head motion during diffusion MRI scanning (mean absolute motion), measured by eddy (Andersson and Sotiropoulos, 2016), was used as a covariate in statistical analysis.

We divided the structural imaging variables into "primary" and "secondary" sets. The primary set included regional cerebral brain volumes from T1-weighted MRI (subcortical nuclei and cortex), and diffusion microstructure (FA) from a white matter tract "skeleton", totalling 153 variables. The secondary set included all variables from the primary set plus the MD, OD and ICVF diffusion parameters for the regions in the same skeleton, totalling 321 variables. We used MRI data from the initial imaging visit for the main analyses and from the first repeat imaging visit in the longitudinal analyses. Data points outside of five interquartile ranges of the median were removed. Data points with high head motion or low contrast-to-noise ratio were removed (five interquartile ranges above or below the median, respectively).

2.5. Shift work data

The frequency of shift work was recoded from a self-reported Likert scale into a binary variable by grouping "Always", "Usually" and "Sometimes" together to comprise "shift workers" and "Never/rarely" as "non-shift workers". Among shift workers, we classified those who ceased or continued shift work between the two imaging visits based on employment data. We calculated the time interval between both imaging visits in days, based on the dates the MRI scans were performed. Among shift workers, a new variable was created to categorise those who "Always" or "Usually" worked day shifts ("day shift workers") and those who "Always" or "Usually" worked night shifts ("night shift workers"). We gathered data on the number of hours of shift work completed per week and the length of time consecutively doing shift work. All empty, "do not know" or "prefer not to answer" responses were excluded. The variables used in this study are listed in Supplemental Table 1.

2.6. Demographic, sleep, cognitive and health data

Demographic data (age, sex, and socioeconomic status) were gathered. Socioeconomic status was determined by the Index of Multiple Deprivation which includes crime, education, employment, health, housing, income, safety, access to services and environment, with higher scores indicating greater deprivation (e.g. lower socioeconomic status) and vice-versa (Townsend et al., 2023). Socioeconomic status was strongly right skewed, so it was transformed using the natural logarithm. We gathered self-reported general health ratings with four options; "excellent", "good", "fair" and "poor". We combined self-reported and inpatient diagnosis records to ascertain previous diagnoses of cancer, stroke, heart attack, or "other serious medical conditions or disabilities". We binarised the chronotype variable, encoding those who were "definitely" or "more of a" morning or evening person, as "morning" or "evening". We determined the clashing of chronotype with usual shift pattern by classifying "morning types who usually worked night shifts" and "evening types who usually worked morning shifts" as having a chronotype clash, and others as not having a clash. We gathered data on serum vitamin D levels which were measured by chemiluminescence immunoassay, the number of hours slept per day, daytime sleepiness

and insomnia symptoms (all self-reported; sleepiness and insomnia were a selection from "Never/rarely", "Sometimes" or "Usually"). For cognitive data, we used scores from five different domains, which were gathered by touchscreen test (Fawns-Ritchie and Deary, 2020): numeric memory, fluid intelligence, trail making, symbol-digit substitution and pairs matching (Valentine et al., 2020; Llinàs-Reglà et al., 2017). We gathered data for smoking status ("never", "previous", "current") and hypertensive status for use as covariates.

2.7. Statistics

We hypothesised that chronic exposure to shift work is associated with regionally specific reductions in brain volume within circuits regulating sleep, emotion, and memory, and that these effects would diminish or reverse after cessation of shift work. To test this, we used a stepwise analytic approach. (Hypothesis 1) Cross-sectional comparison of brain volumes between current shift workers and non-shift controls to identify structural correlates of exposure. This was supported by investigation of dose-response relationships for shift work frequency. (Hypothesis 2) Longitudinal analysis of individuals who stopped shift work to assess potential reversibility. We supplemented our findings with analysis of correlation between brain structure and cognitive performance, mood and vitamin D.

All data processing and statistical analyses were performed using R version 4.3.1. For the cross-sectional comparison of brain volumes between current shift workers and non-shift controls (hypothesis 1), we compared shift workers and non-shift workers using the primary and then the secondary imaging variables. After excluding individuals with missing neuroimaging data, the final sample sizes used in the comparison of shift workers and non-shift workers ranged from 9774 to 10,228. We used linear regression with the following covariates: age, sex, chronotype, intracranial volume, smoking history, hypertensive status and socioeconomic status. Head motion from T1 and diffusion MRI scans were used as covariates for the respective modalities. The sample size varied across tests due to scrubbed data-points. We confirmed that the variance inflation factor was <2 for all tests. The false discovery rate (FDR) was controlled at 5 %. The same analysis was repeated with shift-work frequency coded as an ordinal numeric variable, allowing testing for a linear trend across increasing frequency of shift work (dose-response effect).

Within shift workers only, we then tested the association of the primary imaging variables with the number of hours of shift work performed per week, the total length of time doing shift work, and the shift pattern. This was carried out using linear regression with the same set of covariates, and correction for 5 % FDR.

We then compared continuing and ceasing shift workers (hypothesis 2). This was performed only for participants with MRI data available at both imaging timepoints. We used linear regression with an additional covariate which was the inter-timepoint interval in days. We then tested the secondary set.

In shift workers only, we compared cognitive performance across the five cognitive domains using linear regression with age, sex, chronotype, smoking history, hypertensive status and socioeconomic status covariates. In shift workers, we tested the relation of the primary imaging measures to serum vitamin D levels and the presence of self-reported insomnia symptoms using a linear model with age, sex, chronotype, intracranial volume and socioeconomic status covariates. In the same model without chronotype covariate, we tested the impact of chronotype, and the chronotype clashing/matching, number of hours slept, and daytime sleepiness. We also performed the same tests in non-shift workers and in the whole cohort together to evaluate generalizability. Effect sizes were quantified using Cohen's d, which expresses the standardized mean difference between two groups in units of pooled standard deviation ($d = 0.2$ small, 0.5 medium, 0.8 large).

3. Results

3.1. Volume loss of the thalamus and amygdala in shift workers

We first sought to identify shift work-related structural abnormalities in the brain using linear regression. The main results are summarised in Table 2.

When comparing the 153 primary structural brain imaging parameters between healthy British middle-older aged shift workers ($n = 2122$) and non-shift workers ($n = 12{,}076$) at the baseline imaging visit, we found that shift workers had significantly smaller volumes of the left amygdala (Cohen's d=−0.11, adjusted $p = 0.010$) and right thalamus (Cohen's d=−0.10, adjusted $p = 0.026$) compared to non-shift workers (Fig. 3A-B), consistent with our primary hypothesis. Although statistically significant, these volume differences were small in magnitude, indicating subtle structural differences at the group level.

When including the secondary imaging parameters (total 321

Table 2
Summary of main findings.

	Total n	Standardised Beta	Effect size (Cohen's d)	Adjusted p
Cross-sectional comparison of shift-workers and non-shift workers				
Volume of thalamus (right)	10,221	−0.0209	−0.100	0.0265
Volume of amygdala (left)	10,222	−0.0309	−0.111	0.0096
Mean OD in corticospinal tract on FA skeleton (right)	9807	0.0352	0.101	0.0250
Mean OD in cerebral peduncle on FA skeleton (right)	9797	0.0341	0.096	0.0378
Mean OD in cerebral peduncle on FA skeleton (left)	9807	0.0376	0.107	0.0170
Mean OD in sagittal stratum on FA skeleton (right)	9796	0.0417	0.118	0.0100
Correlation of brain structure with the number of hours of shift-work per week				
Mean FA in superior fronto-occipital fasciculus on FA skeleton (left)	1460	−0.1066	−0.009	0.0190
Dose-response relationship between brain structure and shift work frequency				
Volume of amygdala (left)	10,222	−0.0248	0.010 [a]	0.0445
Mean FA in posterior thalamic radiation on FA skeleton (right)	9410	−0.0385	0.016 [a]	0.0206
Mean FA in medial lemniscus on FA skeleton (right)	9410	−0.0337	0.012 [a]	0.0306
Mean FA in sagittal stratum on FA skeleton (right)	9417	−0.0346	0.012 [a]	0.0306
Mean FA in superior fronto-occipital fasciculus on FA skeleton (right)	9419	−0.0344	0.012 [a]	0.0306
Volume of gray matter in Brain-Stem	9796	−0.0271	0.011 [a]	0.0362
Comparison of 2.4-year change in brain strucutre between continuing or ceasing shift-workers				
Volume of gray matter in Cingulate Gyrus, posterior division (right)	208	−0.2926	−0.784	0.0019
Volume of thalamus (left)	208	−0.2003	−0.528	0.0027
Volume of amygdala (left)	208	−0.2156	−0.540	0.0022

[a] Cohen's F^2. All other effect sizes are Cohen's d.

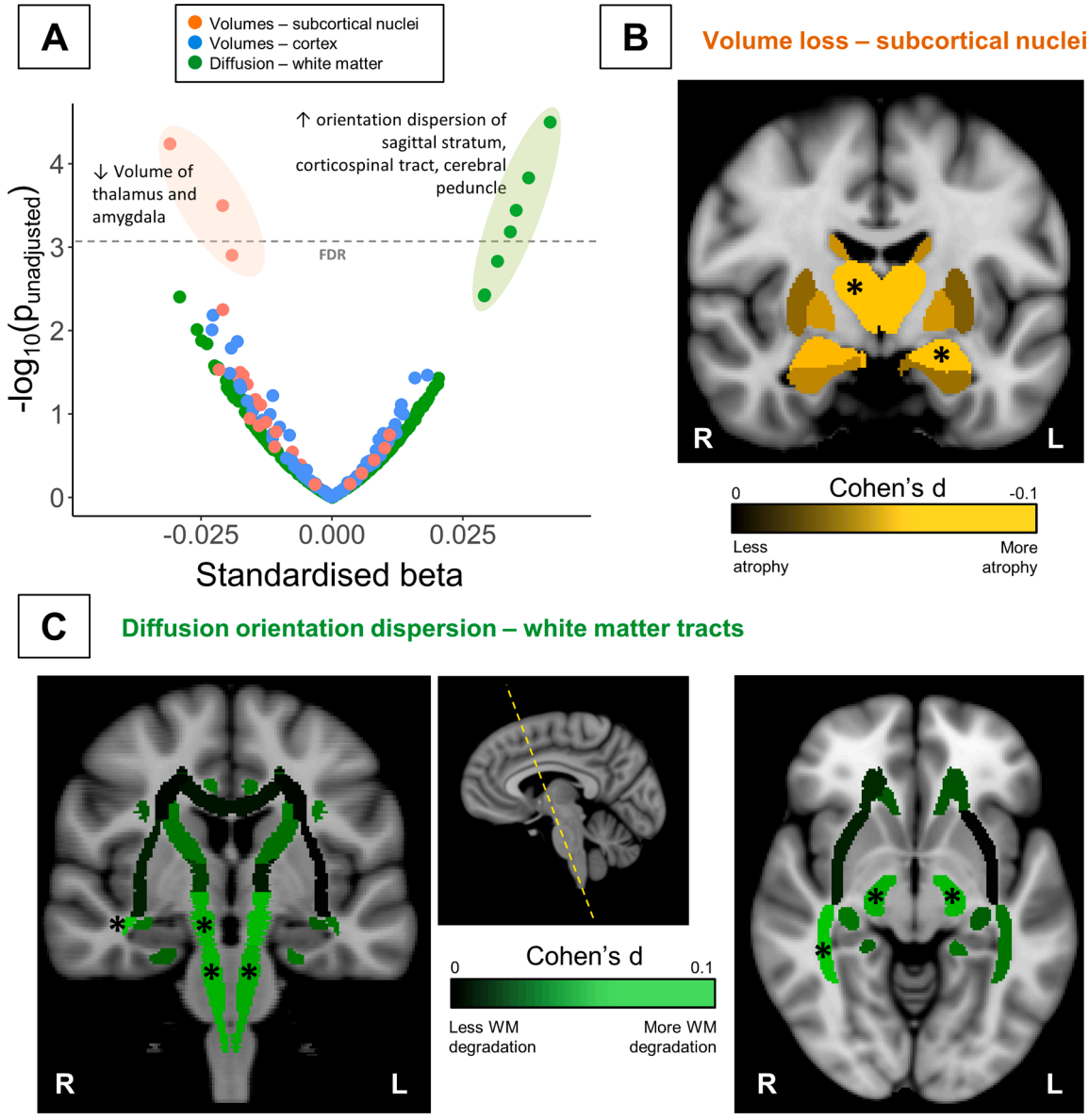

Fig. 3. Comparison of brain imaging measures between shift workers and non-shift workers. (A) Volcano plot highlighting significant volume loss and microstructural changes, with colours indicating the type of imaging measure. (B-C) Brain mapping of significant neuroimaging changes showing symmetrical spatial patterns of (B) volume loss in the amygdala and thalamus bilaterally (MNI coordinate y=−7) and (C) microstructural degradation (increases in orientation dispersion) in corticospinal tract bilaterally, cerebral peduncle bilaterally and right sagittal stratum (left: non-orthogonal slice showing whole corticospinal tract; right: MNI coordinate z=−5.7). Brain image overlays were generated by colouring regions in the relevant atlases based on the effect sizes calculated for our primary hypothesis, and overlaid on the MNI standard brain. The volcano plot shows the p-values and betas for the same data.

variables including the MD, OD, ISOVF and ICVF diffusion metrics), we found five additional significant differences, all of which showed increased OD in white matter pathways in shift workers, suggestive of degradation (Fig. 3A&C). These were in the right corticospinal tract (Cohen's d = 0.10, adjusted p = 0.025), cerebral peduncle bilaterally (right: Cohen's d = 0.10, adjusted p = 0.038; left: Cohen's d = 0.11, adjusted p = 0.017) and the right sagittal stratum (Cohen's d = 0.12, adjusted p = 0.010). Mapping of effect sizes across all tested regions revealed symmetrical patterns of volume reductions and white matter changes (Fig. 3B-C).

In shift workers, the number of hours of shift work per week was weakly but significantly associated with decreased FA in the left fronto-occipital fasciculus (Cohen's d=−0.009, adjusted p = 0.019), although the distribution of hours worked was tightly clustered around 40. Other employment variables (length of time doing shift work, day or night shift) were not significantly associated with any imaging variable after FDR correction (Supplemental Tables 2–6).

3.2. *Dose-response relationship between brain structure and shift work frequency*

Among the same 153 brain structure variables, we tested for dose-response (ordinal trend) associations with the frequency of shift work ("Never/rarely" n = 12,076, "Sometimes" n = 897, "Usually" n = 222 and "Always" n = 1003). The subgroups did not differ in intracranial volume, hypertensive status, or MRI head motion, but differed in age, sex, socioeconomic status, smoking history, and chronotype (Supplemental Table 7). We adjusted for these covariates and corrected for a 5 % false discovery rate.

We observed a significant dose-response relationship between shift

work frequency and six brain structural measures after FDR correction, indicating monotonic effects of increasing shift work on brain structure. Notably, the amygdala volume showed a robust dose-response effect, consistent with the shift work vs non-shift work comparison. Regression modeling revealed a negative association for a small but significant effect (β=−6.87 mm^3 per category increase, Cohen's F^2=0.01, adjusted p = 0.045), reflecting a graded reduction in amygdala volume. Other regions also demonstrated lower volumes and lower FA with higher shift-work frequency (Supplemental Table 8). This supports our secondary hypothesis of reversibility of effects.

3.3. Stopping shift work is associated with halting of volume loss within three years

We then tested whether the cessation of shift work was associated with any change in the above significant effects compared to workers who continued shift work. Among the group with longitudinal data available for imaging and all covariates, the number of individuals who ceased shift work between the two time points was 69, while the number who continued was 207. The median interval between baseline and follow-up imaging time-points in this subgroup was 2.40 years with a long right tail (IQR=2.41 years). For this test, we added the time interval between imaging sessions as an additional covariate in the regression model. The subgroups did not differ demographically, except for a greater socioeconomic deprivation in the continuing shift-work group (Supplemental Table 9).

We found that the left thalamic and amygdalar volume change was significantly different between those who ceased and those who continued shift work, with moderate effect sizes (thalamus: Cohen's d=−0.53, p = 0.003; amygdala: Cohen's d=−0.37, p = 0.034; Table 3). Those who continued shift work had an average volume decrease over time, but those who ceased shift work had a reversal in shift work-related volume loss, as shown by an average increase in volume of 21 mm^3 for the thalamus and 34 mm^3 for the amygdala (compared to 115 mm^3 and 22 mm^3 volume losses in continuers, respectively). After adjustment for a 5 % FDR, the right posterior cingulate gyrus also had a significant volume reduction in continuing shift workers (Cohen's d=−0.78, adjusted p = 0.002). Volume in the PCG was retained and slightly increased in individuals who ceased shift work (by 101 mm^3) while volume was lost in individuals who continued shift work (by 82 mm^3; Supplemental Table 10). The longitudinal change in OD of the corticospinal tract, cerebral peduncle and sagittal stratum did not differ between those who ceased or continued shift work.

These longitudinal effect sizes (Cohen's d = 0.37–0.53) were notably larger than the small cross-sectional effects (d~0.10). This reflects the fact that longitudinal analyses capture within-person changes over time, making them more sensitive to divergent trajectories between groups, even when baseline brain volumes are similar. The larger cross-sectional sample provides high power to detect very small effects, whereas the longitudinal subgroup yields moderate effect sizes due to the greater contrast in change over time rather than large absolute volume differences.

3.4. Shift work-related volume loss is related to cognitive impairment, insomnia and vitamin D

The significant regions we had identified and the spatial distribution of shift work-related changes corresponded to emotion- and memory-related functional brain networks (Pessoa, 2017; Li et al., 2012), which are known to be dysfunctional in individuals with disrupted sleep (Vlasak et al., 2022). To substantiate this, we compared cognitive performance in five different cognitive assessments between shift workers and non-shift workers. We found differences in numeric memory (Cohen's d=−0.12, p = 0.042), fluid intelligence (Cohen's d=−0.31, p < 0.001) and trail making (Cohen's d=−0.34, $p \leq 0.001$), but did not find differences in symbol-digit substitution (Cohen's d=−0.06, p = 0.334) or pairs matching (Cohen's d=−0.09, p = 0.110).

Then, we sought to understand the relation of brain structure to sleep and wakefulness-related parameters in shift workers (insomnia and serum vitamin D levels), since sleep is often disrupted in shift workers (Wickwire et al., 2017). A nominal association was observed between serum vitamin D and amygdalar volume (Cohen's d = 0.01, adjusted p = 0.038), although the effect magnitude was negligible. This effect was specific to shift workers, as there was no significant association among non-shift workers (adjusted p = 0.663) or among the whole cohort together (adjusted p = 0.239). We also found significantly reduced volume of the left medial frontal cortex in shift workers with insomnia versus those without (Cohen's d=−0.23, adjusted p = 0.014). Again, this effect was specific to shift workers (non-shift workers: adjusted p = 0.907; whole cohort: adjusted p = 0.697).

In shift workers, chronotype had a moderate but non-significant association to the volume of the right inferior frontal gyrus (Cohen's d=−0.31, adjusted p = 0.051), with morning types having smaller volumes than evening types. Other sleep-related variables (clashing of chronotype with usual shift timing, number of hours slept, daytime sleepiness) were not significantly associated with the brain imaging measures after FDR correction (Supplemental Tables 11–17).

4. Discussion

In the "era of longevity", it is critical to understand the relationship between shift work and structure of the middle-older aged brain. We used a large population-based dataset of older adults to test whether shift workers had abnormal brain structure, and found that they had small selective volume reductions and microstructural changes, in support of our primary hypothesis. The identified pattern of structural changes overlapped functional brain networks related to emotion and memory, and correlated with weakening of the same cognitive domains, and presence of insomnia symptoms, supporting the validity and clinical relevance. Importantly, we detected a halting of these changes when shift work was ceased, even over the relatively short time frame of <2.5 years, which supported our secondary hypothesis. These data characterise the pattern of structural brain abnormalities in healthy shift workers, and suggest that closer monitoring, counselling and lifestyle intervention may help to preserve brain volume loss in this growing demographic.

Table 3
Longitudinal volume differences between shift workers who continued shift work over 2.4 years, and shift workers who ceased shift work during the 2.4 year interval.

	Continuing shift-workers			Ceased shift-work during interval			Continuing vs. Ceasing Shift-work difference in Δvolume		
	Baseline, mm3	Follow-up, mm3	Difference, mm3	Baseline, mm3	Follow-up, mm3	Difference, mm3	n	p-value	Cohen's d
Thalamus	8093	7978	−115	8131	8152	21	208	0.003	−0.53
Amygdala	1243	1222	−22	1196	1231	35	207	0.034	−0.37
Posterior cingulate	5548	5466	−82	5512	5612	101	208	0.002	−0.78

Specifically, we identified modest volume losses in the amygdala and thalamus, and microstructural degradation in white matter pathways that relay information within memory and emotion-related brain networks. The primary hypothesis was further supported by a significant dose-response relationship for reduced volume of the amygdala with more frequent shift work. Whether or not these changes can be considered "atrophy" is not clear, as there are a range of possible causes and confounds. First, smaller brain structures do not necessarily indicate poorer brain health, and may reflect healthy reorganisation or compensatory changes due to linked behaviours. Second, it is possible that individuals who fail to acquire these brain changes are unable to tolerate shift work and are therefore biased toward non-shift working roles. Similarly, the observed 2.4-year halting of loss in volume could also be framed as a loss of brain adaptation causing cessation of shift work in specific individuals. Third, there is a possibility that differences in brain structure and cognition could be explained by unequal effects of ageing between the two cohorts, since the observed changes are similar to a prototypical ageing-related thalamic-amygdalar-corticospinal pattern of atrophy. Finally, while we controlled for many confounds in our study, the MRI data can be affected by other factors, such as diet, exercise, differences in blood flow, job stressors, dehydration, scanner drift and others which we did not account for.

Nonetheless, the validity of our findings was supported by shift workers' correlated poorer emotional and memory performance in cognitive testing. Specific deficits in these cognitive domains have been highlighted by previous studies of shift workers of all ages (Vlasak et al., 2022), but have not, until now, been corroborated by evidence of structural brain abnormalities. While ceasing shift work is not a practical recommendation for most people, we did find that this limited the shift work-related structural brain volume loss and, in fact, partially recovered it over 2.4 years, with a moderate effect size, supporting our hypothesis. This suggests that older shift workers with cognitive impairment might be at risk for brain volume loss. In those individuals, closer monitoring and intervention may be pertinent, which should include cognitive training or the recommendation to cease shift work. However, given the small effect sizes observed here, any individual-level clinical implication should be limited.

While it is well established that shift work is linked to poorer neurocognitive function and abnormal brain signals, previous neuroimaging studies on shift work have not found significant associations (Cho, 2001; Bittner et al., 2022; Jeong et al., 2024). The lack of significant findings in previous studies may be due to limited sample sizes (n = 13–63) and inadequate confound modelling. One previous study investigated effects of shift work on neuropsychiatric disorders, and did report smaller brain volumes in shift workers, but did not exclude individuals with serious medical conditions, which comprises a large portion of the cohort (Yang et al., 2024) (we excluded 26 % due to "serious" medical conditions). Their study also did not account for variation in whole-brain volume or chronotype. Our study focused only on healthy, employed individuals, used the largest sample to date, and controlled for known structural brain imaging confounds. We also evaluated a different set of imaging measures, which included diffusion in white matter pathways, and analysed cognition. As such, we find a different set of regions associated with shift working (Yang et al. (Yang et al., 2024) reported differences in lateral orbitofrontal and middle temporal gyri), and it is more likely that our results reflect true shift work-related structural brain changes.

Sleep disturbance is believed to be the primary mechanism for how shift work affects the brain (Wickwire et al., 2017; Knutsson, 2003). Indeed, our data showed, in shift workers, associations of chronotype and self-reported insomnia symptoms with brain abnormalities in the amygdala and PCG that were similar to those found in people with sleep disturbance (Krause et al., 2017). Shift work disrupts circadian hormones (e.g., melatonin and cortisol), and increases inflammatory and stress cascades that can target the hippocampus and related circuits. We did not find significant associations for the clashing of chronotype with usual shift timing, number of hours slept, or specific shift patterns. One possible reason for this is the limited detail in the available data for shift work. Data did not include descriptions of rotating shift patterns, which may be important for brain health, as recent studies have found sleep irregularity (more so than timing or quantity) to underlie academic performance, inflammation and health (Phillips et al., 2017; Dzierzewski et al., 2020; Chaput et al., 2020).

Finally, we observed a nominal association between serum vitamin D concentration and amygdalar volume among shift workers. Although statistically significant, the effect size was trivial and likely reflects the large sample rather than a biologically meaningful relationship. Shift workers are indeed more prone to vitamin D deficiency, which can affect neural integrity through calcium regulation and immune pathways (Aranow, 2011). Previous studies have linked vitamin D deficiency to whole-brain volume loss (Terock et al., 2022) and cognitive impairment (Sultan et al., 2020). Our finding is therefore consistent in direction with these reports but should be interpreted with caution, as the magnitude suggests no substantive structural effect.

These findings should be interpreted cautiously for several reasons. First, because of the large sample size, even small effects can become statistically significant, so it is important to understand how clinically meaningful these changes are, and not to over-interpret small effects. The effects reported here are very small, so should be interpreted cautiously. Second, the generalisability of our findings is limited by the 30-year age range (40–70 years) and the predominantly white European ethnicity of UK Biobank participants. Furthermore, the UK Biobank imaging arm was healthier than the general population, and its representativeness of ages and types of occupations is not clear, as the UK Biobank included only 5 % of the invited population. Third, the non-imaging data used here were self-reported and limited in resolution. Coarse exposure categorisation could have biased the findings. More detailed occupational data were only available for a smaller group that completed an online follow-up and were not large enough to include in this study. Given our findings in motor-related pathways (e.g. corticospinal tract), it may be worthwhile investigating motor reflex markers, but these were not available. Although we adjusted for various confounding factors, there is a possibility of residual confounding that could affect the statistical outcomes in this large sample. While the reversal of thalamic and amygdalar volume loss after cessation of shift work is a key finding, this was based on a relatively small longitudinal subgroup (n = 69) who had stopped shift work after the first MRI assessment. The limited sample size constrains statistical power and the precision of effect estimates. Therefore, these results should be interpreted as preliminary evidence of potential reversibility. Larger longitudinal cohorts with detailed exposure histories and repeated imaging are needed to confirm whether structural recovery consistently follows cessation of shift work. Finally, our findings were based on observational data, and should not be interpreted as causal.

The selective thalamic and amygdalar volume loss observed in healthy shift workers may represent an early, subclinical marker of neural vulnerability linked to chronic circadian disruption. These regions are central to sleep-wake regulation, emotion, and attention, functions that are commonly affected in shift work-related fatigue and mood disturbance. The apparent reversibility of these structural effects within two years of ceasing shift work highlights a potential therapeutic window for prevention and recovery. Clinically, this supports regular assessment of sleep quality, mood, and cognitive performance in long-term or older shift workers, alongside preventive interventions. Integrating these neuroprotective strategies into occupational health programs could reduce neural and cognitive burden, improve wellbeing and work performance, and mitigate long-term risks of cognitive aging associated with circadian misalignment.

We have identified specific sleep, emotion and memory-related structural brain changes that occur in shift workers. These findings could have implications for the way we organise work schedules and for possible lifestyle intervention to alleviate shift work-related brain changes. The impact of shift work on the brain may be reduced by

cognitive training. Other factors (i.e. chronotype, the number of hours worked per week and day/night scheduling) may be comparatively less influential. For shift workers with structural brain volume loss and poor cognitive performance, closer monitoring, counselling and cessation of shift work may be warranted. There is a need for well-designed studies to attempt to replicate these findings and understand the underlying mechanisms, while gathering detailed data on shift and sleep patterns. As our society trends toward later retirement and increased presence of shift work, understanding the relationship between shift work and brain structure could lead to a healthier and more productive workforce.

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Data availability statement

The results generated in this study are available online with this publication (Supplemental Tables 2–16). The original data were from the UK Biobank, for which access is granted for specific projects proposed by bona-fide researchers for health research in the public interest (https://www.ukbiobank.ac.uk/).

CRediT authorship contribution statement

Thomas Welton: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Thomas Wei Jun Teo:** Writing – review & editing, Visualization, Software, Investigation. **Seyed Ehsan Saffari:** Writing – review & editing, Visualization, Software, Methodology, Formal analysis. **Ling-Ling Chan:** Writing – review & editing, Investigation. **Eng King Tan:** Writing – review & editing, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2025.121619.

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