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# Cerebral perfusion is not impaired in persons with moderate obstructive sleep apnoea when awake

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## Abstract

**Purpose** It is well established that, together with a multitude of other adverse effects on health, severe obstructive sleep apnoea causes reduced cerebral perfusion and, in turn, reduced cerebral function. Less clear is the impact of moderate obstructive sleep apnoea (OSA). Our aim was to determine if cerebral blood flow is impaired in people diagnosed with moderate OSA.

**Methods** Twenty-four patients diagnosed with moderate OSA ($15 \leq$ apnoea-hypopnea index (AHI) $< 30$) were recruited (aged 32–72, median 59 years, 10 female). Seven controls (aged 42–73 years, median 62 years, 4 female) with an AHI $< 5$ were also recruited. The OSA status of all participants was confirmed at baseline by unattended polysomnography and they had an MRI arterial-spin-labelling scan of cerebral perfusion.

**Results** Neither global perfusion nor voxel-wise perfusion differed significantly between the moderate-OSA and control groups. We also compared the average perfusion across three regional clusters, which had been found in a previous study to have significant perfusion differences with moderate-severe OSA versus control, and found no significant difference in perfusion between the two groups. The perfusions were also very close, with means of 50.2 and 51.8 mL/100 g/min for the moderate-OSAs and controls, respectively, with a negligible effect size (Cohen's $d = 0.10$).

**Conclusion** We conclude that cerebral perfusion is not impaired in people with moderate OSA and that cerebral flow regulatory mechanisms can cope with the adverse effects which occur in moderate OSA. This is an important factor in clinical decisions for prescription of continuous positive airway pressure therapy (CPAP).

**Keywords** Obstructive sleep apnoea · Cerebral perfusion · MRI arterial spin labelling · Polysomnography

## Introduction

Obstructive sleep apnoea (OSA) is a widespread sleep-related breathing disorder with prevalence rates for moderate-to-severe OSA of 23·4% for women and 49·7% for men [1]. OSA is considered one of the most important of all sleep disorders where non-treatment can lead to a prolonged assault on the brain [2]. It is characterized by repeated

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episodes of either complete (apnoeas) or partial closures (hypopnoeas) of the upper airway during sleep due to muscles that normally maintain airway patency become atonic. The level of severity of OSA is defined by the number of apnoeas/hypopnoeas per hour (AHI). When AHI is 5–15, the level of severity is considered mild. When AHI is 15–30, the severity is considered moderate, and when AHI > 30 the OSA is considered severe.

When untreated, OSA can result in fragmented sleep, hypoxia, hypertension, hypoperfusion, endothelial dysfunction, inflammation, and oxidative and endoplasmic-reticulum stress [3]. It can also lead to physiological changes in the brain involving widespread synaptic loss in the neocortex and the hippocampus as well as impairment of the several other brain regions, including structural integrity of the medial temporal lobe [4]. Moreover, as has been shown in studies involving severe apnoeics [5–8] or a mix of moderate and severe apnoeics [9–12], OSA can have a detrimental impact on cerebral perfusion whilst awake. Impaired cerebral perfusion has been independently associated with reduced cognition, smaller total brain volume, and reduced cortical thickness in older adults [13]. Moreover, OSA and/or impaired cerebral perfusion has been associated with an increased risk and/or progression of neurodegenerative disorders [14–16], including Alzheimer's disease [17–19], Parkinson's disease [16–22], and vascular dementia [23].

However, a striking feature of the studies that have investigated reduced cerebral perfusion whilst awake is the inconsistent distribution of brain regions affected (Table 1). With the exception of Baril et al. [8], the cohorts all comprised severe OSA or a mix of moderate and severe OSA. Baril et al. found regional perfusion changes in their severe cohort but not their moderate-OSA cohort.

Because of the inconsistency surrounding the various regions where affected perfusion was found, and the fact that, of all the studies investigated, only one study had separated out moderate OSA as a standalone group, questions surrounding the role of moderate OSA remained. We hypothesized that cerebral perfusion would be impaired in patients with moderate OSA, albeit to a lesser extent than in severe OSA.

We investigated this hypothesis by undertaking a study to determine the impact of moderate OSA on cerebral perfusion in a group of participants with untreated moderate OSA and in a control group of participants without OSA (AHI < 5). Arterial spin-labelling (ASL) was used to estimate global and regional cerebral perfusion.

## Methods

### Participants

Twenty-four participants with an AHI between 15 and 30 events per hour were recruited to form the moderate-OSA group. A further seven participants with an AHI < 5 were recruited as a control cohort. Their study data were collected over July 2015 – October 2018.

**Table 1** Regions of reduced cerebral perfusion in moderate and severe OSA patients

| Study | Scan type | OSA severity | Affected cerebral regions |
|---|---|---|---|
| Joo et al. [5] | ECD SPECT | Severe | Bilaterally in the parahippocampal gyri<br>Unilaterally in the left lingual gyrus |
| Yadav et al. [10] | ASL | Moderate/severe | Bilaterally near the corticospinal tracts, pontocerebellar fibres, and superior cerebellar peduncles<br>Unilaterally in the right medial lemniscus, right midbrain, right red nucleus, and left dorsal fornix/stria terminalis, left inferior cerebellar peduncle, and left tapetum |
| Shiota et al. [6] | ECD SPECT | Severe | Bilaterally in the right middle and superior frontal gyri |
| Baril et al. [8] | HMPAO SPECT | Severe<br>Moderate | In the severe cohort only: Bilaterally in the post-central gyri. Unilaterally in the left inferior parietal lobules (supra marginal gyrus), and right praecuneus<br>*No differences in regional cerebral perfusion compared to controls* |
| Innes et al. [9] | ASL | Moderate/severe | Bilaterally in the cingulate gyri, paracingulate gyri, and in the subcallosal cortex<br>Unilaterally in the left frontal cortex, left putamen, right hippocampus, right parahippocampal gyrus, right temporal fusiform cortex, and right thalamus |
| Nie et al. [7] | ASL | Severe | Bilaterally in the parahippocampal gyri<br>Unilaterally in the left cerebellum posterior lobe, left medial frontal gyrus and left temporal lobe |
| Chen et al. [11] | ASL | Moderate/severe | Right putamen/insula, right cerebellum, left thalamus, right caudate, right medial, superior and inferior frontal gyrus, right superior temporal gyrus, right fusiform gyrus, left and right cingulate gyrus |

ASL: Arterial spin labelling magnetic resonance imaging; BOLD: Blood oxygen level dependent functional magnetic resonance imaging; HMPAO SPECT: $^{99m}$Tc-HMPAO single photon emission computed tomography; ECD SPECT: $^{99m}$Tc-ethylcysteinate dimer single photon emission computed tomography

Participants for the moderate-OSA group were recruited from patients referred to Christchurch Hospital's Sleep Unit by their general practitioner with sleep problems. They had been assessed via unattended polysomnography as having moderate OSA but no other comorbid sleep disorders, which might have confounded the results. They were all naïve to treatment.

Control participants were confirmed by unattended polysomnography as having an AHI < 5 and, by interview, no other sleep disorder. They were recruited from the general public through word of mouth, public presentations, and from a list of voluntary research subjects held by the School of Medicine at University of Otago, Christchurch.

All subjects (i) were 18–80 years of age, (ii) had a usual bedtime between 9.00 pm and 12.00am, (iii) had a usual time in bed of 7–9 h, (iv) had an understanding of verbal and written English, (v) were not receiving nor had previously received treatment for OSA, (vi) did not have a history of physiological, psychiatric, or neurological disorders unrelated to OSA, which could affect sleep behaviour, fatigue, cerebral perfusion or brain structure such as chronic obstructive pulmonary disease, congestive heart disease, diabetes, heart failure, hypertension > 150/90, migraine, myocardial infarction, stroke, previous brain surgery, stroke, and traumatic brain injury, and (vii) were not taking medication that could impact cerebral perfusion (e.g., ACE inhibitors, nitrates) or cognition.

As a part of the screening process, information on the subject's current neurological, psychiatric, and sleep status was obtained during personal interviews.

## Apparatus and tests

**Polysomnography** Unattended polysomnography of all participants was completed overnight in the participant's home using a Nox polysomnograph (Model Nox A1, Nox Medical, Reykjavík, Iceland). Central and occipital EEG, ECG, bilateral EOG, submental and tibialis anterior EMG, and body position were recorded using the standard polysomnography montage recommended by the American Academy of Sleep Medicine (Scoring Manual Version 2.0). A nasal cannula/pressure transducer was used to measure nasal airflow, whilst oral airflow was measured using a thermistor. Respiratory effort was measured using chest and abdominal piezoelectric belts. A pulse oximeter (Nonin 3150 WristOx2, Nonin Medical Inc, Plymouth, Minnesota, USA) was used to monitor oxyhaemoglobin saturation (SpO2). Hypopneas were scored if there was a 30% reduction in flow and a 3% oximetry drop.

**MRI – structural imaging** High-resolution, anatomic images of the whole brain were acquired from a Signa HDxt 3.0 T MRI Scanner (GE Medical Systems, Milwaukee, WI, USA) using an 8-channel head coil. This included a T1-weighted spoiled gradient recalled echo (SPGR) acquisition with an echo time of 2.8 ms, a repetition time of 6.6 ms, inversion time of 400 ms, flip angle of 15 deg, acquisition matrix of $256 \times 256 \times 170$, field of view of 250 mm, slice thickness of 1 mm, voxel size of $0.98 \times 0.98 \times 1.0$ mm$^3$, and a scan time of 5 min 3 s.

**MRI – arterial spin labelling** On the same MRI scanner, whole-brain perfusion was measured using a stack of spiral fast-spin-echo-acquired images prepared with pseudo-continuous ASL with static background signal suppression, a repetition time of 6 s, echo spacing of 9.2 ms, post-labelling delay of 1.525 s, labelling duration of 1.5 s, eight interleaved spiral arms with 512 samples at 62.5 kHz bandwidth, field of view of 240 mm, 30 phase-encoded 5-mm-thick slices, reconstructed in-plane resolution of $1.88 \times 1.88$ mm, five excitations, and a scan time of 7 min. Perfusion units were mL/100 g/min.

Baseline and follow-up images were treated cross-sectionally, as opposed to longitudinal within-subject co-registrations. Structural and perfusion MRI data were pre-processed using CAT12 (http://dbm.neuro.uni-jena.de/cat12/) – a toolbox of SPM12 (Wellcome Trust Centre for Neuroimaging, University College London, UK) – and custom MATLAB scripts (Mathworks, Natick, MA, USA) as follows: (i) structural images were bias corrected, tissue classified, and normalized using linear and nonlinear transformations (DARTEL) within a unified model, (ii) grey-matter segments for each subject were modulated, thereby preserving actual tissue values locally by accounting for warping, (iii) both modulated and unmodulated, normalized grey matter segments were smoothed with a 10-mm full-width at half-maximum (FWHM) Gaussian kernel to improve signal-to-noise ratio and to minimize the effect of any residual misalignment. In addition, perfusion images (i) were quantified and co-registered to the SPGR images, (ii) had the brain extracted (using the inverse brain mask method, in which the SPM ICV brain mask in MNI space is inverse normalized to each subject's space using the DARTEL-derived deformations and nearest neighbour interpolation and normalized using the deformation fields generated during segmentation and normalization of the SPGR images, (iii) were smoothed with a 10-mm FWHM Gaussian kernel, (iv) were visually inspected for completeness and alignment, (v) had non-grey matter contributions excluded via a study-specific grey-matter mask. The study-specific grey-matter mask was created by averaging the modulated normalized grey matter segments from all subjects, with values < 0.10 excluded, as were all slices inferior to the superior cerebellum and periventricular white matter regions.

The quantified CBF map for each participant was overlaid on the T1-weighted SPGR structural image and visually inspected for artefacts and errors in registration (Fig. 1). This was done by verifying that the contours of the brain were in the right place and the interhemispheric fissure appeared in the middle of the image.

**Eye-video recording** To estimate level of participant drowsiness, eye-video was recorded during the ASL sequence via a Visible Eye system incorporating a fibre-optic camera (Avotec Inc., Stuart, FL, USA). The video-capture software recorded 352 × 288-resolution eye-video at 25 fps. Each participant's 7-min eye-video was visually rated for signs of, and level of, drowsiness by an experienced rater (RB). Drowsiness was subjectively rated according to the visual scoring method proposed by Wierwille [24]. This rating system is based on observable personal characteristics including eye blinks, eye closures, and saccadic movement. The rating system has five levels of drowsiness on an analogue scale of 0 to 100 (not drowsy = 0, slightly drowsy = 25, moderately drowsy = 50, very drowsy = 75, and extremely drowsy = 100). We first rated the level of drowsiness as an average over each min, which was then collated into an overall average rating across the 7 min.

## Procedure

**Polysomnographic testing** Prior to ASL, all participants had their OSA severity status assessed by a registered polysomnographic technologist via an unattended/home polysomnography test. The polysomnography sleep records were manually scored in accordance with American Academy of Sleep Medicine guidelines, including confirmation of moderate OSA ($15 \leq AHI \leq 30$).

**ASL** All participants underwent MRI protocols scheduled in afternoon sessions. The sequence of scans at both baseline and follow-up included an initial localizer scan followed by a T1-weighted spoiled gradient recalled echo structural scan (T1 SPGR), and then the pseudo-continuous ASL (PCASL). All scans were conducted by a registered MRI technologist and clinically reviewed by a registered radiologist.

Drowsiness during the ASL was assessed via a video recording of the participant's left eye. Participants were instructed to keep their eyes open, except for normal blinks, during which background music was muted.

## Statistics

For the ASL, a general linear model (GLM) for unpaired two-sample t-tests (one-sided) was used to investigate baseline voxel-by-voxel differences between the moderate-OSA and the control groups in grey-matter volume and concentration, and grey-matter perfusion. Age, sex, and BMI were included as explanatory variables (EVs) in all models. ICV was included as an additional covariate in the grey matter volume (modulated grey matter) and concentration (not modulated grey matter) models. The perfusion model also included voxel-dependent grey matter volume. Separate models with and without the additional EVs of drowsiness during the ASL scan and total grey matter perfusion were also run.

We also tested whether the total sleep time with oxygen saturation < 90% (ST90) was correlated with changes in regional blood flow (RBF). This was done using a GLM with voxel-by-voxel correlations, including age and sex as covariates.

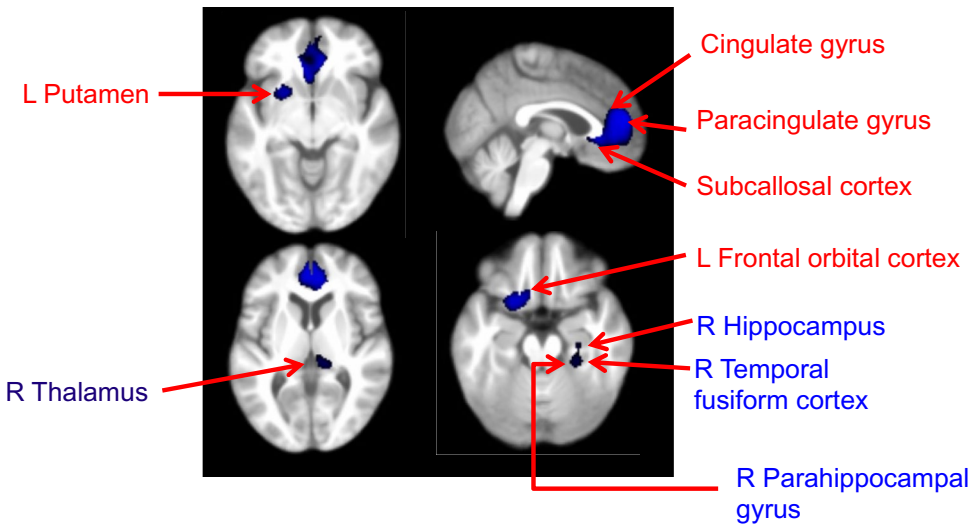


**Fig. 1** Three regional clusters found by Innes et al. [9] to have significantly reduced perfusion when awake in moderate-severe OSA (AHI > 15) versus Controls (AHI < 5)

A permutation-based inference tool was used for nonparametric statistical thresholding ("randomise" in FSL 5.0.2; www.fmrib.ox.ac.uk/fsl). For each contrast, we generated 5000 permutations, corrected for multiple comparisons using family-wise error rate (threshold-free cluster-enhancement TFCE-corrected, $p < 0.05$).

To ensure the appropriateness of parametric testing of global cerebral perfusion using an independent samples t-test, the distributions from the moderate-OSA group and from the control group were subjected to the Kolmogorov–Smirnov and Shapiro–Wilk tests of normality. These indicated that the parametric *t*-test was appropriate.

Other statistical tests used to test for differences between the moderate-OSA and control groups were (i) Z-tests for means of ages, (ii) Chi-square for female-to-male ratios, and (iii) Mann–Whitney U tests for ST90 and for drowsiness. Pearson correlation was calculated between global perfusion and AHI. Spearman correlations were calculated between drowsiness and AHI and between drowsiness and global perfusion.

## Results

### Demographics

The demographics of the moderate-OSA and control groups are given in Table 2. There was no significant difference in the mean ages between the moderate-OSA and control groups ($Z = 0.92$, $p = 0.36$, 2-tailed). Similarly, there was no significant difference between the female-to-male ratios of the moderate-OSA and control groups ($\chi^2_{(1, N=31)} = 3.84$, $p = 0.25$).

### Polysomnography

**AHI** The mean AHI of the moderate-OSA group was 21.7 (SD 4.5, range 15.6–29.9) and of the control group was 2.5 (SD 2.1, range 0.2–4.9) ($t(29) = 10.90$, $p < 0.001$).

**Oximetry – ST90** There was no significant difference in ST90 (sleep time in which oxygen saturation was below 90%) between the moderate-OSA group, median 11.8 min (IQR 28.4), and the control group, median 12.2 min (IQR 27.6) ($U = 70.00$, $z = -0.66$, $p = 0.532$).

**Table 2** Participant demographics and clinical measures

| | |
|---|---|
| OSA n (F:M) | 24 (10:14) |
| Control n (F:M) | 7 (4:3) |
| OSA mean age (range) | 57.9 y (32–79) |
| Control mean age (range) | 62.1 y (42–75) |
| OSA mean BMI (range) | 30.2 (22.6–37.5) |
| Control mean BMI (range) | 24.5 (22.7–25.9) |
| OSA mean AHI (range) | 21.7 (16–29) |

### Drowsiness

The drowsiness of all participants was rated during the ASL sequence of the MRI scan. There was a small but nonsignificant correlation between drowsiness and AHI ($r_s(31) = 0.31$, $p = 0.42$ one-tailed). There was no significant difference in the median drowsiness levels between the moderate-OSA and control groups (13.5 vs. 7.0; $U = 65.5$, $z = -0.88$, $p = 0.39$). This indicates that any difference seen in cerebral perfusion between the two groups could not simply be attributed to differences in drowsiness due to OSA.

A scatter plot of drowsiness levels during the ASL scan and global cerebral perfusion revealed, at most, a weak correlation between these two factors ($r_s(31) = -0.32$, $p = 0.083$).

### Global cerebral perfusion

Moderate-OSA and control group perfusion rates were measured to establish if a difference in global perfusion existed between the two groups at baseline. There was no difference in global perfusion scores between the moderate-OSA group and the control group at baseline (mean 49.26 vs 48.73 mL/100 g/min, $t(30) = 0.126$, $p = 0.899$; $d = 0.06$). Moreover, global perfusion was not significantly correlated with AHI ($r(50) = -0.14$, $p = 0.34$).

### Regional cerebral perfusion

Differences in regional cerebral perfusion rates between the moderate-OSA and control groups were tested at baseline. Using a whole-brain, voxel-wise analysis between participants, with AHI, age, sex, and global cerebral perfusion as explanatory variables along with the voxel dependent grey matter, no significant differences were found in regional cerebral perfusion after correction for multiple comparisons. Moreover, using the four explanatory variables of AHI, drowsiness during ASL, sex, and age, as used by Innes et al. [9], there were still no significant differences between the moderate-OSA and control groups ($p > 0.05$).

### Regional cerebral perfusion regions of interest from a previous study

Baseline perfusion data from three regional clusters, previously found by Innes et al. [9] to have significant perfusion differences with moderate-severe OSA (see Fig. 1), were tested for differences between the moderate-OSA and control groups. Those regions are: (1) bilateral paracingulate gyrus, anterior cingulate gyrus, and subcallosal cortex, and,

unilaterally, the left putamen and left frontal orbital cortex, (2) the right-lateralized posterior temporal fusiform cortex, parahippocampal gyrus, and hippocampus, and (3) the right thalamus.

Comparing the average perfusion within these 3 clusters between the mod-OSA group and the control group in the current study, taking age differences into account and assuming no sex effect, demonstrated (see Fig. 2) that there was clearly no significant difference in perfusion between the two groups ($p = 0.71$). The perfusions were very close, with mean 51.8 mL/100 g/min for our controls and 50.2 for our mod-OSAs. Likewise, the effect size of the difference is negligible (Cohen's $d = 0.10$ and partial-$\eta^2 = 0.0053$ (controlling for age and sex)), indicating that the lack of significance cannot be explained by under-powered data.

## Discussion

Cerebral perfusion is substantially distorted by severe OSA [5–8]. Studies of mixed cohorts of people with moderate and severe OSA have also demonstrated that global [25] and regional cerebral perfusion [9–11] are reduced when awake. Conversely, a study by Baril et al. [8] is the only one to have directly investigated the question 'Is cerebral perfusion also reduced in moderate-OSA?'. The current study has provided further evidence to support Baril et al.'s conclusion that cerebral perfusion is not significantly impaired in moderate-OSA. Given the high prevalence of moderate-OSA [1] and the substantial deleterious effects of OSA in general, our result is an element of good news for people with moderate-OSA. However, it's important to note that lack of a deficit in cerebral perfusion does not imply that there are no other adverse effects of moderate-OSA.

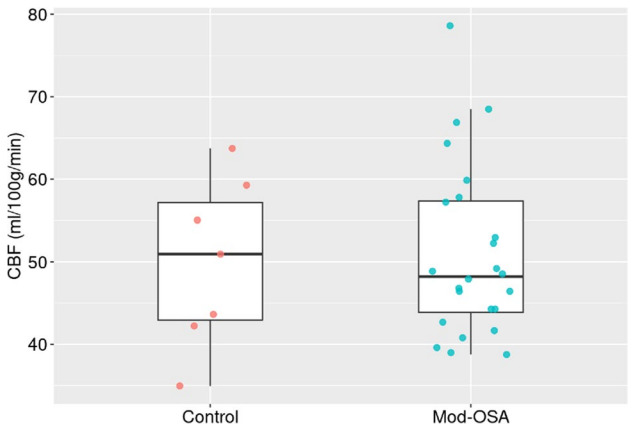


**Fig. 2** Box plot of perfusion in the 3 regional clusters found by Innes et al. [9] to have significantly reduced perfusion when awake in moderate-severe OSA (AHI > 15) versus Controls (AHI ≤ 5)

In their SPECT study, Baril et al. [8] found no significant difference between their cohort of 14 patients with moderate OSA and their cohort of 20 controls without OSA (AHI ≤ 5). However, as did all of the other studies reviewed, they found cerebral perfusion impaired in patients with severe OSA. This suggests that level of OSA severity is a strong and non-linear determinant in adverse manifestations of this disorder on the brain, and that moderate OSA has little or no brain pathology sufficient to reduce regional cerebral perfusion whilst awake.

To confirm this premise, we tested three regions within which the study by Innes et al. [9] had found reduced cerebral perfusion in patients with moderate-severe OSA (4 with moderate OSA (15 ≥ AHI < 30) and 4 with severe OSA (AHI ≥ 30)) in comparison to controls. We found no difference in perfusion in these presumably more OSA-susceptible cerebral regions.

Nevertheless, as the ASL methodologies used in the current study being effectively the same with those used by Innes et al. [9], what can explain the different finding, especially concerning changes in the 3 clusters? The most obvious difference between the two studies is that the clinical cohort in the Innes et al. study comprised a combination of four moderate-OSA and four severe-OSA participants. There are also differences in numbers, in that we have 24 mod-OSAs but only 7 controls, as opposed to the 19 controls in the Innes et al. study. There were also differences between the two studies in terms of male/female ratios, mean ages of the subjects, and BMI of the subjects. All of these variables have been linked to differences in global cerebral perfusion [11] and, therefore, either separately or combined, could account for some of the difference.

Our understanding of the neurophysiology of cerebral perfusion is advanced and we know that it is dependent on intracranial compliance, cerebral autoregulation, and sympathetic tone to maintain cerebral blood flow homeostasis. Conversely, much remains to be answered. Although cerebral autoregulation has been shown to be affected by severe OSA [25–27], the impact of moderate OSA on the efficacy of cerebral autoregulation is equivocal.

Thus, despite an incomplete understanding of the neuropathogenesis of OSA [28] and how cerebral autoregulation works [29], we postulate that any adverse effect of moderate OSA on cerebral perfusion can be adequately compensated for by the normal homeostatic processes responsible for the maintenance of cerebral perfusion, such as intracranial compliance, cerebral autoregulation, and sympathetic tone [30]. This is supported by the lack of correlation between global CBF and AHI in the current study. However, it is proposed that the autoregulatory system breaks down in severe OSA, resulting in reduced cerebral perfusion and, ultimately, irreversible structural changes in the brain.

## Limitations

Despite considerable efforts, the final number of 7 controls was less than originally targeted. Of the 24 prospective 'control' subjects who agreed to enter the study, 17, without overt symptoms, were found to have at least mild OSA when tested formally. Notwithstanding, the negligible difference and effect size between the perfusions in the moderate-OSA and control groups clearly supports there being, at most, a trivial difference in perfusions between moderate-OSA and non-OSA.

A much larger study involving multiple centres, a larger number of non-OSA participants, and cohorts with mild and severe OSA, would, of course, have been desirable. Importantly, such a study would allow determination of the non-linear function between cerebral perfusion and AHI, as well as other measures of OSA severity, such as ST90 and hypoxic burden [31].

## Conclusion

Using MRI arterial spin labelling, we have shown that, in contrast to severe OSA, cerebral perfusion is not impaired in people with moderate OSA. This indicates that cerebral flow regulatory mechanisms are able to adapt to, and cope with, the adverse effects, particularly repeated oxygen desaturations, which occur due to moderate OSA. This is an important factor for clinicians when deciding upon the merits and implications of prescribing CPAP.

**Author contributions** All authors had access to the data and contributed to the writing of the manuscript.

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**Data availability** The data used in this study are available upon reasonable request to the authors.

## Declarations

**Ethics** Approval for this study was obtained from the Health and Disability Ethics Committees, Ministry of Health, New Zealand (14/STH/174/AM02s).

**Consent to participate** Informed consent was obtained from all participants in this study.

**Competing interests** The authors have no relevant financial or non-financial interests to disclose.

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