Structural brain correlates of obstructive sleep apnoea in older adults at risk for dementia

Nathan E. Cross[1,2,3,4,5], Negar Memarian[2,3,4,5], Shantel L. Duffy[2,3,4,5], Casey Paquola[3], Haley LaMonica[1,3,5], Angela D'Rozario[1,2,4,5], Simon J.G. Lewis[3,4], Ian B. Hickie[3], Ronald R. Grunstein[2,4,6] and Sharon L. Naismith[1,3,4,5]

Affiliations: [1]School of Psychology, The University of Sydney, Camperdown, Australia. [2]Woolcock Institute of Medical Research, The University of Sydney, Camperdown, Australia. [3]Brain and Mind Centre, The University of Sydney, Camperdown, Australia. [4]Neurosleep, NHMRC Centre of Research Excellence, The University of Sydney, Camperdown, Australia. [5]Charles Perkins Centre, The University of Sydney, Camperdown, Australia. [6]Sydney Health Partners, The University of Sydney, Camperdown, Australia.

Correspondence: Sharon L. Naismith, Brain and Mind Centre, The University of Sydney, 94 Mallett Street, Camperdown, NSW 2050, Australia. E-mail: sharon.naismith@sydney.edu.au

@ERSpublications
This study demonstrates how obstructive sleep apnoea might contribute to neurodegenerative processes in older adults http://ow.ly/frH030jWFJn

Cite this article as: Cross NE, Memarian N, Duffy SL, *et al*. Structural brain correlates of obstructive sleep apnoea in older adults at risk for dementia. *Eur Respir J* 2018; 52: 1800740 [https://doi.org/10.1183/13993003.00740-2018].

ABSTRACT This study aimed to investigate associations between obstructive sleep apnoea (OSA) and cortical thickness in older adults with subjective and objective cognitive difficulties, who are considered "at-risk" for dementia.

83 middle-aged to older adults (51–88 years) underwent neuropsychological testing, polysomnography assessment of OSA and a structural magnetic resonance imaging brain scan. A principal components analysis was performed on OSA measures. Cortical thickness and subcortical volumes were compared to extracted components of "oxygen desaturation" and "sleep disturbance".

Oxygen desaturation was significantly related to reduced cortical thickness in the bilateral temporal lobes (left: r=−0.44, p<0.001; right: r=−0.39, p=0.003). Conversely, sleep disturbance was associated with increased thickness in the right postcentral gyrus (r=0.48, p<0.001), pericalcarine (r=0.50, p=0.005) and pars opercularis (r=0.46, p=0.009) and increased volume of the hippocampus and amygdala. Decreased thickness in the bilateral temporal regions was associated with reduced verbal encoding (r=0.28, p=0.010).

Given the clinical significance of this sample in terms of dementia prevention, these changes in grey matter reveal how OSA might contribute to neurodegenerative processes in older adults.

This article has supplementary material available from erj.ersjournals.com

Received: Jan 26 2018 | Accepted after revision: May 04 2018

Introduction

Obstructive sleep apnoea (OSA) is a sleep disorder characterised by repetitive airway obstructions, resulting in sleep disturbance and hypoxaemia. The prevalence of OSA increases with age, and longitudinal evidence indicates that OSA is associated with an increased risk of cognitive decline and dementia in the elderly [1, 2]. Although sleep disturbances have not traditionally been considered as modifiable risk factors for dementia [3], such evidence now warrants more detailed studies elucidating the mechanisms by which OSA may contribute to brain degeneration.

Studies conducted in younger and middle-aged adults indicate that the effects of sleep fragmentation and nocturnal hypoxaemia probably underpin the cognitive deficits associated with OSA [4]. Emerging data highlight the critical role that sleep serves for maintaining a healthy brain, for example the clearance of neurotoxic waste products (including β-amyloid) [5] and moderating synaptic strength [6]. Sleep disruption with the compounding effect of hypoxaemia could thus have deleterious effects on brain integrity and morphology [7]. A wide range of cerebral grey matter changes have been associated with OSA, including reductions in volume or thickness across the temporal lobe and prefrontal cortex [8–10], in addition to subcortical structures including the hippocampus, thalamus and cerebellum [9–11]. In older adults specifically, one study reported grey matter reductions in the brainstem only [12], while another reported that hypertrophy of various cortical regions was associated with increasing OSA severity [13].

However, there is a relative paucity of work examining the inter-relationships between OSA, brain integrity and cognitive decline in older adults. As adults age, they may experience neurodegenerative processes resulting in measurable atrophy of cortical grey matter in the temporal lobes and posterior cingulate cortex, as well as subcortical structures such as the hippocampus, amygdala and thalamus [14, 15]. These changes are evident even in the transitional or "at-risk" stage between normal ageing and dementia, defined as those with subjective memory concerns and mild cognitive impairment [16–18].

The aim of the current study was firstly to explore grey matter changes in relation to key mechanistic markers of OSA in a clinical sample of middle-aged to older adults at risk for dementia. Secondly, we aimed to determine whether any identified grey matter changes are correlated with memory performance. We hypothesised that OSA would be associated with reduced grey matter thickness and volume in regions associated with memory, specifically the frontotemporal cortex and the hippocampus.

Methods

Study subjects

90 middle-aged to older adults at-risk for dementia were recruited from an ageing research clinic for people aged >50 years with subjective concerns about cognition and/or mood. As described previously [19], at-risk was defined as those who are seeking help for assessment and/or intervention for cognitive decline, including those with subjective and/or objective cognitive complaints. Exclusion criteria were a dementia diagnosis or a Mini-Mental State Examination (MMSE) score <24 [20]; neurological disease (*e.g.* Parkinson's disease, epilepsy); psychosis; prior stroke or head injury (with loss of consciousness >30 min); current treatment for OSA (*e.g.* with continuous positive airway pressure); and inadequate English. This study was approved by the University of Sydney institutional ethics committee, and all participants gave written informed consent prior to study participation.

Clinical and neuropsychological assessment

A medical specialist conducted a physical examination and recorded medical history and current medication use *via* a semi-structured interview. Psychiatric history was assessed and current major depression was determined using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition [21]. In addition, patients self-reported their depressive symptoms using the Geriatric Depression Scale (15-item) [22]. The MMSE was conducted for reporting and screening purposes.

As detailed previously [19], a neuropsychologist administered a comprehensive standardised test battery. While the broader battery encompassed a variety of tests, in this study we were specifically interested in verbal memory, as it is particularly associated with OSA in later life [23]. From this test battery, the Rey Auditory Verbal Learning Test (RAVLT) [24] was used to assess verbal declarative memory performance. The RAVLT requires the participant to learn unstructured verbal material (a 15-item word list) over five learning trials, and to recall the list after a time delay of 20 min. From this test, we defined encoding ability as the summed score for the five learning trials (A1–5), and delayed recall as the number of words recalled at delay (A7). All scores were transformed to age- and education-adjusted z-scores based on appropriate normative data [25] and these transformed scores were used for all subsequent analyses.

Magnetic resonance imaging acquisition

Participants completed the magnetic resonance imaging (MRI) protocol within 4 weeks of the neuropsychological assessment. All scanning was conducted using a 3 Tesla General Electric (GE) Discovery MR750 scanner (GE Medical Systems, Milwaukee, WI, USA) with an eight-channel phased array head coil. The following images were acquired in order. 1) Three-dimensional sagittal whole-brain scout for orientation and positioning of subsequent scans; 2) T1-weighted magnetisation prepared rapid gradient-echo sequence producing 196 sagittal slices (repetition time 7.2 ms; echo time 2.8 ms; flip angle 10; matrix 256×256; 0.9 mm isotropic voxels) for anatomic analysis. For each patient, two T1-weighted MRI scans were obtained in a single scanning session, out of which the image with the higher signal-to-noise ratio was used.

Cortical thickness and subcortical volume segmentation

Grey and white matter segmentation, cortical reconstruction and subcortical labelling were conducted using FreeSurfer (v. 5.3) [26] (http://surfer.nmr.mgh.harvard.edu/). The FreeSurfer analysis pipeline has been described previously [26] and is available online. The standard FreeSurfer pipeline "recon-all" was utilised on every T1-weighted scan for the removal of non-brain tissue, alignment to Talairach space, intensity normalisation and tessellation of the grey matter/white matter boundary. Topology correction was performed and all images were visually inspected for any inaccuracies in segmentation and parcellation, which were subsequently edited manually. Parcellation of the cortex into gyral and sulcal features for the creation of cortical thickness statistics was calculated as the closest distance from the grey/white boundary to the grey/cerebrospinal fluid boundary at each vertex on the tessellated surface [26]. Volumetric segmentation and labelling of subcortical tissue class was performed in the undeformed brain of each subject, and were based on voxel intensities and a registered probabilistic atlas [27]. Following segmentation, subcortical and intracranial volumes were extracted from the aseg.stats file of every subject.

Polysomnography

Participants underwent polysomnography (PSG) in a sleep clinic, which was performed within 4 weeks of the neuropsychology assessment. Nocturnal PSG recordings were collected on an ambulatory recording system (Compumedics Siesta, Melbourne, Victoria, Australia; Embla Titanium, Mortara Instruments, Milwaukee, WI, USA). In addition, nasal airflow was recorded using a nasal pressure transducer and respiratory effort was assessed using thoracic and abdominal bands. Blood oxygen saturation was recorded using pulse oximetry.

Patients were required to maintain their usual bedtime and wake-up schedule during the study, and were asked to abstain from caffeinated beverages for the 8 h prior to and during PSG data collection. Sleep architecture and respiratory events were scored manually in 30-s epochs by an experienced sleep technician using standardised scoring criteria [28]. Studies were reported on by an accredited sleep physician. Primary outcome measures for this study were oxygen-desaturation index (ODI; number of saturations >3% per hour of sleep); lowest oxygen saturation level; percentage of total sleep time (%TST) with an oxygen saturation <90%; apnoea–hypopnoea index (AHI; total number of apnoeas and hypopnoeas per hour of total sleep); sleep efficiency (%); awakening index (total number of transitions from sleep to wake ⩾30 s, per hour of sleep); and arousal index (total number of abrupt shifts in electroencephalogram frequency ⩾3 s, per hour of sleep). Hypopnoeas were scored per American Academy of Sleep Medicine criteria [28], as a reduction in airflow ⩾30% for ⩾10 s, measured *via* pressure transducer, with either an arousal or ⩾3% desaturation.

Principal components analysis of OSA severity metrics

We followed a similar approach to that of a recent study [13] and conducted a principal components analysis (PCA) to extract prinicipal components of OSA severity from a range of common OSA metrics. This was because 1) it has been argued that the sole use of AHI as a measure of OSA severity is inconsistent [29]; 2) other measures of OSA severity may relate to the same concept (*e.g.* ODI and %TST <90% oxygen saturation); and 3) this reduced the number of factors entered into statistical models. Common respiratory and sleep variables were entered into the PCA. Two variables (lowest oxygen saturation, sleep efficiency) were inverted so that all variables loaded in the same direction. The number of components extracted was based on eigenvalues >1. A varimax rotation was used to preserve the independence of resulting components. The variables with the highest loadings in the rotated component matrix were used to facilitate the naming and interpretation of the components.

Regional cortical thickness

Statistical maps were generated using the FreeSurfer application Qdec 1.4 (query, design, estimate, contrast; http://surfer.nmr.mgh.harvard.edu). Qdec fits a general linear model (GLM) at each surface vertex to

predict regional cortical thickness across all subjects. Regional cortical thickness in each hemisphere of the brain was compared with the components from the PCA. Age and intracranial volume were accounted for and the moderating effect of sex was assessed. The results were obtained with a full-width/half maximum of 10 mm. A multiple-comparison Monte Carlo simulation with 5000 iterations and a threshold of 1.3 was used to make inferences at a corrected p=0.05. Clusters were labelled based on the location of the vertex of most significant thickness variation. Clusters where thickness significantly varied with the OSA components were masked and mapped to individual subjects. The subject-specific estimates of cluster thickness were subsequently exported into SPSS (IBM SPSS Statistics, New York, NY, USA) for further statistical analysis with behaviour.

Subcortical volumes

Grey matter volume was calculated for 19 subcortical structures using FreeSurfer, namely the brainstem and bilateral structures of the nucleus accumbens, amygdala, caudate, cerebellum, hippocampus, pallidum, putamen, thalamus and ventral diencephalon. Grey matter volume estimates of these regions were entered as dependent variables into a multivariate GLM. Age, sex, intracranial volume and the PCA components were entered as covariates. In order to confirm that depression was not mediating the findings, also analysed the relationship between depressive symptoms and antidepressant use with "oxygen desaturation", "sleep disturbance", RAVLT performance and thickness/volume. Bootstrapping was performed with 1000 samples to account for the sample variance and provide 95% confidence intervals for significance and thus correcting for multiple comparisons. All significance values reported are bootstrap-corrected for multiple comparisons.

Statistical analysis

All statistical analysis was performed in SPSS version 22, except for regional cortical thickness, which was performed using Qdec. Figures were produced from screenshots taken in Qdec.

Results

Participants

Of the 90 participants recruited for this study, one participant was excluded due to poor quality of the MRI scan, while another was excluded due to hydrocephalus. During the diagnostic PSG, five participants had a total sleep time <3 h and were excluded. As such, the final sample consisted of 83 participants (53 females). Table 1 details the demographic characteristics of the sample. 36 (43%) participants had a diagnosis of hypertension, 11 (13%) had a diagnosis of diabetes mellitus, 15 (18%) were diagnosed with cardiovascular disease and 12 (15%) met criteria for current major depression. Seven (8%) participants were taking medication for diabetes, 31 (37%) were taking medication for hypertension and 27 (33%) were taking antidepressant medication. Three (4%) participants were current smokers, 30 (36%) had previously been regular smokers but no longer smoked and eight (10%) had previously been occasional smokers. Based on the classical measure of AHI, the average OSA severity was moderate, but there was a broad range from mild to severe (mean 18.7 events·h^{-1}, median 12.9 events·h^{-1}, range 0–111 events·h^{-1}). Although we analysed severity measures across the whole sample, for reporting purposes 20 (24.1%) participants had an AHI <5 events·h^{-1} (no OSA); 30 (36.1%) had an AHI 5–15 events·h^{-1} (mild); 17 (20.5%)

TABLE 1 Demographic and clinical statistics of the sample

Age years	51.1–88.5	67.4±7.5
Education years	4.0–23.0	13.3±3.2
Body mass index kg·m^{-2}	15.7–64.4	27.8±6.8
Mini-Mental State Examination total score	24.0–30.0	28.6±1.6
Geriatric Depression Scale total score	0.0–15.0	4.1±3.6
Cumulative Illness Rating Scale total score	0.0–17.0	4.8±3.8
Alcohol consumption drinks per week	0.0–35.0	4.7±6.8
Epworth Sleepiness Scale total score	0.0–19.0	7.6±4.4
Apnoea–hypopnoea index events·h^{-1}	0.0–111.0	18.7±20.2
Oxygen desaturation index events·h^{-1}	0.0–109.7	15.1±19.1
Lowest oxygen saturation %	71.0–97.0	85.6±6.1
Oxygen saturation <90% %TST	0.0–46.1	4.4±8.2
Sleep efficiency %	37.4–96.0	75.7±12.1
Awakening index events·h^{-1}	1.8–49.4	6.6±6.8
Arousal index events·h^{-1}	5.4–78.9	19.8±14.7

Data are presented as range or mean±SD. n=83. %TST: percentage of total sleep time.

had an AHI 15–30 events·h^{-1} (moderate); and 16 participants (19.3%) had an AHI >30 events·h^{-1} (severe). No demographic or clinical characteristics were significantly different across these OSA severity groups apart from age. However, as expected, all PSG variables of sleep quality and oxygen desaturation levels were significantly different across these OSA severity groups (online supplementary table S1).

The overall mean±SD z-score on the encoding section of the RAVLT was −0.09±−1.03, while the mean±SD delayed recall score was −0.01±1.13. On objective neuropsychological testing, half of the sample (n=41) met criteria for multiple domain mild cognitive impairment. No demographic or clinical characteristics were significantly different between subjects with or without mild cognitive impairment, except that sleep efficiency was significantly lower in the mild cognitive impairment group (online supplementary table S2). As expected, patients with mild cognitive impairment exhibited significantly lower z-scores on the RAVLT (−0.2 *versus* 0.5, p=0.01).

Principal components analysis

The PCA resulted in two components with eigenvalues >1 explaining 72.8% of the total variance. The size of the loadings of included variables demonstrated that the first component related to "oxygen desaturation" and the second component related to "sleep disturbance". The loadings of variables to each component are listed in table 2.

Relationship between OSA severity and regional cortical thicknesses

The two OSA severity components exhibited opposing relationships with spatially independent clusters of cortical thickness. Increased severity of the oxygen desaturation component was significantly related to reduced thickness in the left temporal pole (r=−0.44, 95% CI −0.66–−0.11; p<0.001) and the right fusiform gyrus (r=−0.39, 95% CI −0.58–−0.09; p=0.003) (figure 1). Meanwhile, greater severity of the sleep disturbance component was significantly associated with increased thickness in the postcentral gyrus (r=0.46, 95% CI 0.28–0.60; p<0.001), pericalcarine (r=0.48, 95% CI 0.20–0.68; p=0.005) and pars opercularis (r=0.50, 95% CI 0.07–0.75; p=0.010) in the right hemisphere (figure 2).

To assess whether these associations may have been moderated by clinical comorbidities that are associated with OSA, we conducted further GLMs independently for each of the identified clusters identified and exported from the Qdec analysis. For both the left temporal pole and right fusiform clusters, the main effect of the oxygen desaturation component was tested accounting for the following variables: age; sex; education; mild cognitive impairment diagnosis; body mass index; Epworth sleepiness scale score; diagnosis of hypertension, diabetes, cardiovascular disease or depression; or hypertension, diabetes or antidepressant medication use. Oxygen desaturation remained significantly associated with cortical thickness in both clusters (temporal pole F=9.59, r=−0.31, p=0.003; fusiform gyrus: F=7.45, r=−0.25, p=0.009). For the postcentral gyrus, pericalcarine and pars opercularis clusters, the same analyses were performed with the sleep disturbance component. All regions remained significantly associated with sleep disturbance (postcentral gyrus: F=16.62, r=0.49, p<0.001; pericalcarine: F=19.89, r=0.51, p<0.001; pars opercularis: F=26.22, r=0.56, p<0.001).

To compare these analyses with traditional measures of OSA severity, we reran the GLM analyses in Qdec with AHI as a main variable. Comparing the two groups, <15 events·h^{-1} and ⩾15 events·h^{-1}, there were

TABLE 2 Rotated component matrix of the principal components analysis of obstructive sleep apnoea severity metrics

	Component	
	"Oxygen desaturation"	**"Sleep disturbance"**
Apnoea–hypopnoea index	**0.774**	0.489
Oxygen desaturation index	**0.856**	0.311
%TST saturation oxygen <90%	**0.842**	0.154
Lowest oxygen saturation (inverted)	**0.855**	−0.115
Sleep efficiency (inverted)	0.001	**0.768**
Awakening index events·h^{-1}	0.115	**0.780**
Arousal index events·h^{-1}	0.454	**0.734**
Variance explained %	42.8	30.1

Extraction method: principal component analysis; rotation method: varimax with Kaiser normalisation. Variables with a loading >0.5 on each component are presented in bold. %TST: percentage of total sleep time.

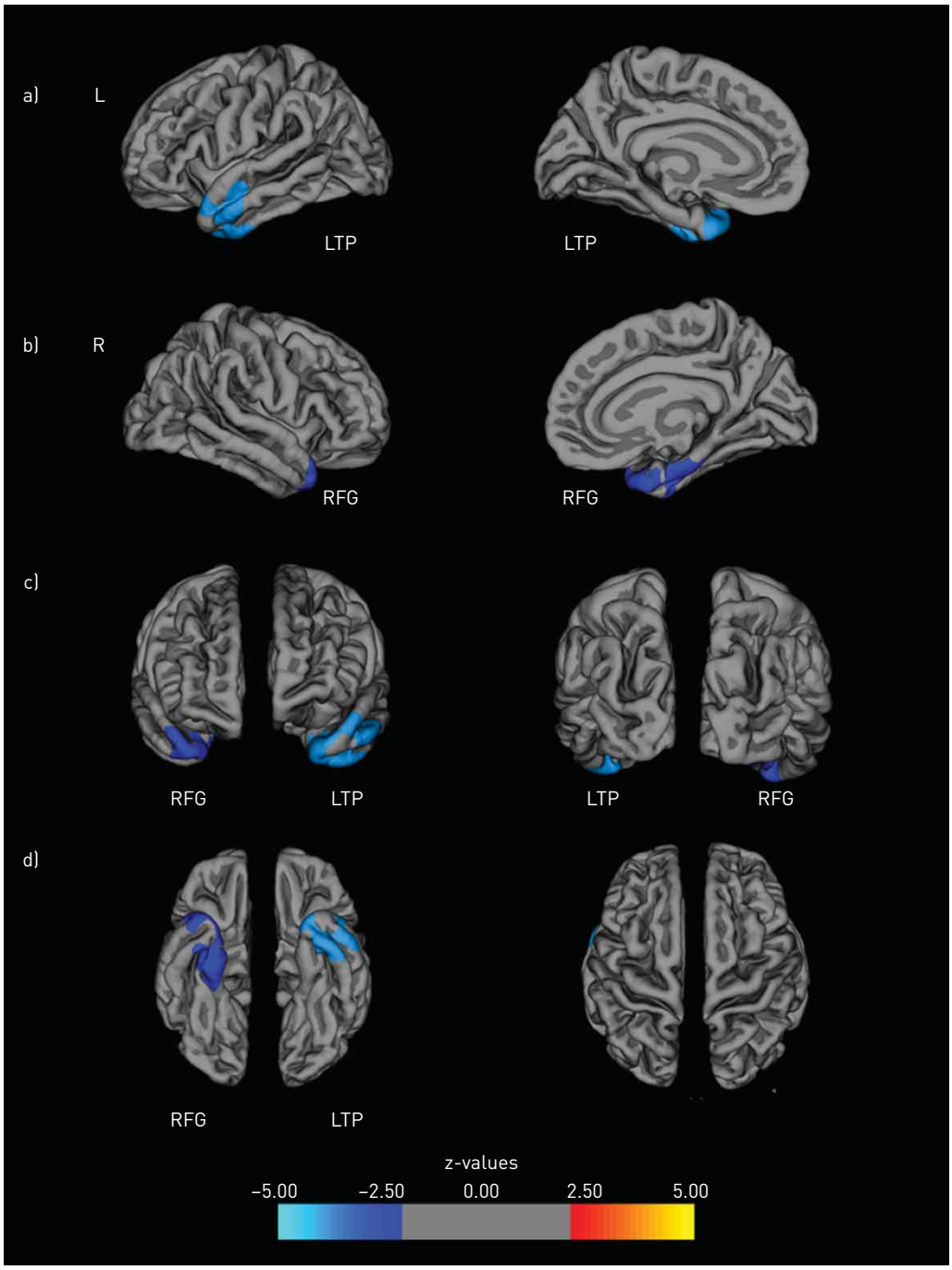

FIGURE 1 Significant atrophy in the left temporal pole (LTP) and right fusiform gyrus (RFG) related to "oxygen desaturation" in older "at-risk" patients; displayed on Qdec's (query, design, estimate, contrast) semi-inflated cortical surfaces. a) Left lateral and left medial; b) right lateral and right medial; c) anterior and posterior; d) inferior and superior views. Results were obtained using Monte Carlo simulation, with a threshold of $p<0.05$, to provide cluster-wise correction for multiple comparisons. Clusters are labelled based on the location of the vertex with the greatest association as defined by Qdec.

no significant differences in cortical thickness in any region. When AHI was also included as a continuous variable in the analysis, there were also no significant associations with any regional cortical thickness.

Relationship between OSA severity and subcortical volumes

Greater oxygen desaturation was associated with smaller right nucleus accumbens volume (r=−0.21, 95% CI −0.35–−0.05; p=0.033). In contrast, greater sleep disturbance was significantly associated with increased volume in the left hippocampus (r=0.34, 95% CI 0.14–0.52; p=0.001; figure 3), right hippocampus (r=0.22,

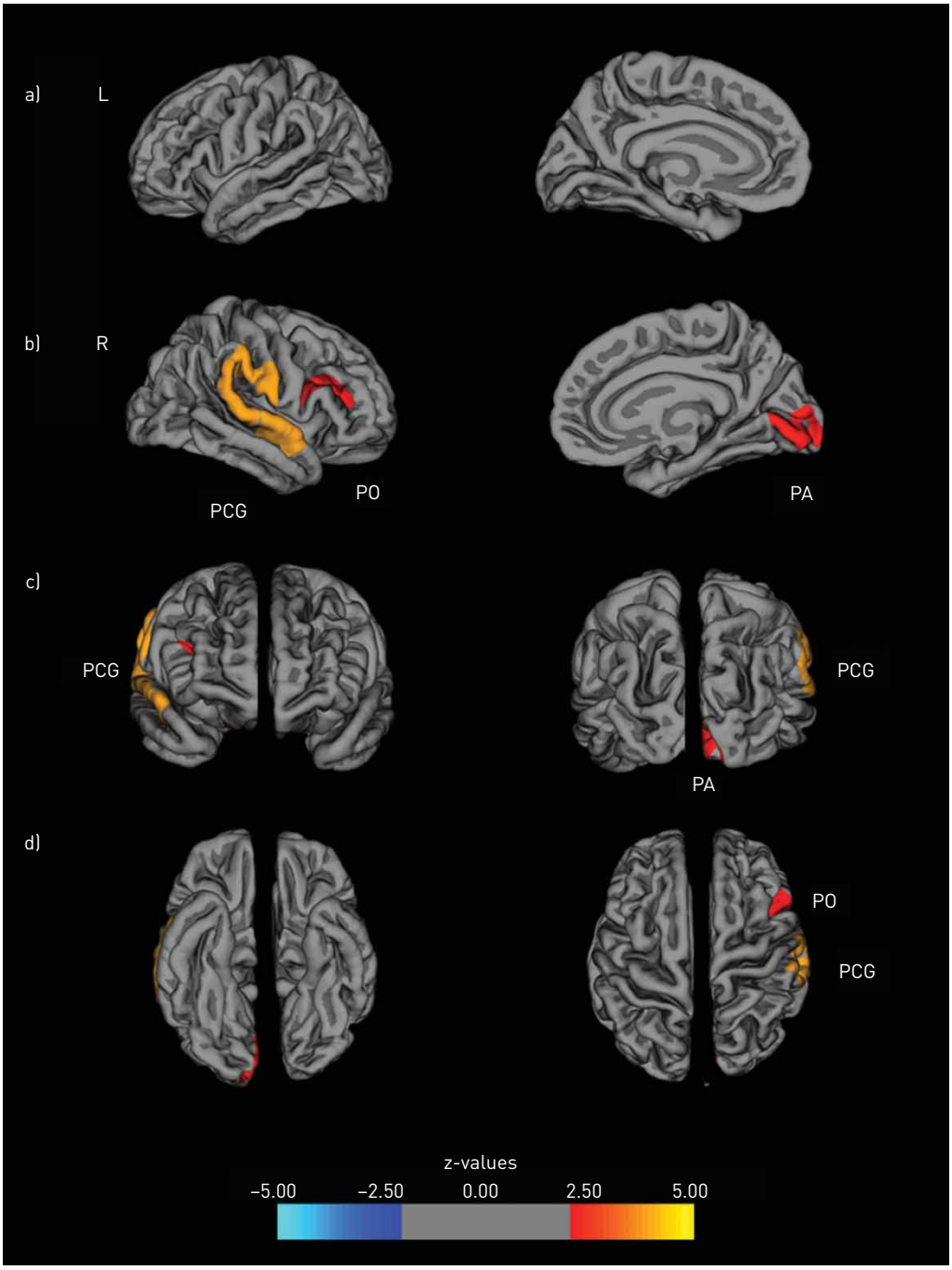

FIGURE 2 Significant hypertrophy in the postcentral gyrus (PCG), pars opercularis (PO) and pericalcarine (PA) related to "sleep disturbance" in older "at-risk" patients; displayed on Qdec's (query, design, estimate, contrast) semi-inflated cortical surfaces. a) Left lateral and left medial; b) right lateral and right medial; c) anterior and posterior; d) inferior and superior views. Results were obtained using Monte Carlo simulation, with a threshold of $p<0.05$, to provide cluster-wise correction for multiple comparisons. Clusters are labelled based on the location of the vertex with the greatest association as defined by Qdec.

95% CI 0.03–0.40; p=0.015) and left amygdala (r=0.25, 95% CI 0.05–0.50; p=0.027; figure 3). Neither component of OSA severity was significantly associated with volume in any other subcortical region.

Associations between cortical thickness, subcortical volume and cognition

Thickness in the left temporal pole cluster was significantly associated with better encoding performance on the RAVLT (r=0.29, 95% CI 0.08–0.47; p=0.010), but not with recall (r=0.16, 95% CI −0.05–0.35;

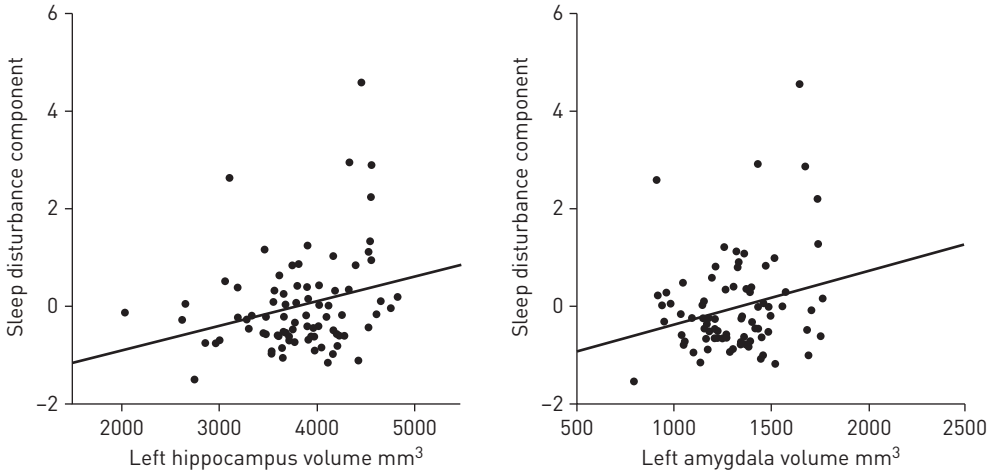

FIGURE 3 Significant linear regressions between "sleep disturbance" in older "at-risk" patients and grey matter volume of a) hippocampal and b) amygdala subcortical regions. Volume was calculated using FreeSurfer automated segmentation. Analysis was conducted accounting for age and intracranial volume.

p=0.153). Thickness in the right fusiform gyrus cluster was also related to improved encoding (r=0.28, 95% CI 0.06–0.46; p=0.030), but not recall (r=0.17, 95% CI −0.04–0.37; p=0.123). None of the regions associated with the sleep disturbance component were significantly associated with any outcome on the RAVLT (all p>0.05).

However, the component corresponding to oxygen desaturation was not significantly associated with encoding (r=−0.04, 95% CI −0.25–0.15; p=0.475) or recall (r=−0.09, 95% CI −0.28–0.10; p=0.685), nor was the sleep disturbance component (r=−0.07, 95% CI −0.24–0.11; p=0.855 and r=−0.07, 95% CI −0.23–0.19; p=0.495, respectively). As such, no further exploratory analysis between measures of OSA severity, cortical thickness, subcortical volume and memory were conducted. The two components of oxygen desaturation and sleep disturbance did not significantly differ between subjects meeting criteria for multiple-domain mild cognitive impairment and those who did not (p>0.200). The associations with depression were all negligible and non-significant (all r<0.15, p>0.150; data not shown).

Discussion

Overall, this study demonstrates that OSA is associated with widespread structural alterations in diverse brain regions in a clinical sample at risk for dementia, but that the detrimental effects of OSA are not likely to be underpinned by only one pathophysiological mechanism. We found that oxygen desaturation is related to reduced cortical thickness in both the left and right temporal lobes. In turn, reduced thickness in these regions was associated with poorer encoding of new information. Conversely, OSA related sleep disturbance was associated with increased cortical thickness in frontal, central and occipital regions of the right hemisphere, and increased volumes of the left hippocampus and amygdala.

Although many studies have examined changes in grey matter integrity in typical middle-aged OSA samples, only two prior studies have specifically included older adults [12, 13]. Neither found any decreases in thickness of any cortical regions; however, one observed hypertrophy across multiple cortical sites associated with OSA-related hypoxaemia and sleep fragmentation [13]. The differences in findings between these two prior studies and this study may be partially attributed to differences in sample characteristics as both prior studies included only healthy or asymptomatic participants. By contrast, our sample is enriched for cognitive impairment and brain degeneration. While in this study we did not specifically examine biomarkers for Alzheimer's disease, it is interesting to note that the temporal lobe is affected early in the progression of Alzheimer's disease [14], and we found that reduced thickness in temporal lobes was, in turn, associated with poorer encoding. This brain region is also known to be particularly susceptible to hypoxic insults, such as those experienced with OSA [30]. Therefore, OSA-related hypoxaemia may contribute to degeneration in this region, a notion that would be aligned with the robust association between OSA and memory decline across older clinical OSA samples [23]. While the mechanisms by which hypoxaemia may exert deleterious effects on the brain are unknown, using MRI spectroscopy we have previously shown oxygen desaturation to be associated with oxidative stress in the brain [31] and compromised brain bioenergetics during sleep [32]. Additionally, recent work has shown that hypoxaemia may be linked to neuroinflammation [33] as well as amyloid and tau deposition in brain tissue [34], all of

which may contribute to neurodegeneration. However, other findings insinuate that a combination of both hypoxaemia and sleep disturbance may be a more critical factor in predicting neurodegenerative changes, such as a build-up of amyloid burden [35]. This is not surprising, given that sleep, particularly deeper slow-wave sleep, has been associated with clearance of neurotoxic waste such as Aβ [5], and that chronic OSA may foster the aggregation of these products within the brain [35].

However, in contrast to the findings pertaining to oxygen desaturation, sleep disturbance was associated with increased thickness in this clinical sample, which could be interpreted as hypertrophy. Grey matter hypertrophy has been reported in previous studies [36, 37]. It has been hypothesised that hypertrophic grey matter findings associated with OSA may represent a disease process involving reactive or maladaptive mechanisms, such as cerebral oedema, neuronal branching, gliosis or even increased β-amyloid deposition [33]. Alternatively, the sleep disturbance measured in this sample could be attributable to neurodegenerative pathology, given such processes are observed to be associated with poorer sleep quality [7], and a proportion of the sample did not have OSA. This may account for the heterogeneity in these structural findings. When patients with an AHI >15 events·h^{-1} were excluded from this analysis, only the postcentral gyrus remained significantly associated with sleep disturbance, suggesting that changes in this region may be not purely related to the consequences of OSA.

In the context of the previous work in older adults, our findings that OSA was associated with increases and decreases in thickness over different cortical regions may indicate a distinct time course within which OSA exerts detrimental effects on brain integrity. In asymptomatic older adults, OSA may lead to enlargement or hypertrophy, reflective of either reactive or inflammatory processes. Later, this may lead to atrophy when clinical symptoms begin to appear (*i.e.* subjective or objective memory decline or excessive daytime sleepiness). Interestingly, recent findings indicate that cortical atrophy also negatively impacts on both the characteristics [38] and coupling of distinct neural oscillations during sleep [39], which are hypothesised to be important for sleep-dependent memory consolidation. Furthermore, oxidative stress, heightened Aβ levels or excessive and prolonged neuronal activity may also interfere with sleep processes that leads to further neurodegenerative processes (for a recent review, see [40]). This suggests that anatomical and neurophysiological changes may develop a maladaptive cycle of age-related changes in brain integrity and cognitive function. Given the cross-sectional design of this study, we do not have data on the duration of OSA symptoms within this sample, and further prospective longitudinal studies may help to further delineate whether a specific time course or cascade of events is apparent. It will also be important to elucidate further the pathophysiological processes that contribute to the observed grey matter changes, either at a cellular level, or with the use of multimodal approaches such as diffusion weighted imaging.

The outcomes of this study have several important implications for clinical practice, particularly in terms of early intervention efforts for preventing cognitive decline in older people with dementia. Prior prospective studies have demonstrated a link between sleep-disordered breathing and the development of mild cognitive impairment [41] and dementia [1, 2] at an epidemiological level. While there were no direct associations between oxygen desaturation and memory, these results do suggest that oxygen desaturation may be a critical aetiological factor in brain deterioration, which could lead to memory decline. Identifying key factors that contribute to or accelerate cognitive decline is of paramount importance, especially given that there are no cures for dementia. A few modifiable risk factors for dementia have been well documented in meta-analytic studies [3]. However, OSA and sleep disturbance more generally are not yet established as risk factors, despite the rapid rise of research and interest in this topic [7, 42, 43]. Efforts to increase screening for OSA and offer targeted treatment in at-risk older adults should be expanded.

This study has a number of strengths, including the diagnosis of OSA severity using gold-standard objective PSG, sophisticated analysis of cortical thickness and subcortical volume using a well-developed and widely used platform, and the combination of a comprehensive and standardised clinical and neuropsychological assessment of a large clinical group of at-risk patients. However, although the current study sample consisted of individuals in a distinct at-risk dementia period, this clinical cohort is quite heterogeneous. While increasing evidence suggests that these older adults are at a greater risk for developing cognitive decline or dementia [44], this is not a definite marker of disease progression and their trajectory is still unclear. Regardless, this is an established health-seeking clinical group within which investigations such as the current study allow for the identification of potential risk factors for dementia.

Conclusion

This study reveals important insights into how sleep disorders such as OSA may impact the brain in older adults. Given the clinical importance of this sample of at-risk older adults, these findings implicate OSA in changes that may be related to neurodegeneration and dementia. The early identification and treatment of

important risk factors for dementia is imperative given the increasing rate of dementia. As there are many treatment options for OSA, further research using larger samples with interventional designs are now required to determine whether this is a truly modifiable risk factor for dementia.

Author contributions: N.E. Cross was involved in the conception and design of the study, acquisition and analysis of data, and drafting a significant portion of the manuscript. N. Memarian was involved with acquisition and analysis of data. S.L. Duffy was involved with acquisition and analysis of data. C. Paquola was involved with analysis of data. H. LaMonica was involved with acquisition of the data. A. D'Rozario was involved with acquisition and analysis of data. S.J.G. Lewis was involved in the conception and design of the study, and acquisition of data. I.B. Hickie was involved with conception and design of the study. R.R. Grunstein was involved with the conception and design of the study. S.L. Naismith was involved in the conception and design of the study and drafting a significant portion of the manuscript. All authors contributed significantly to the interpretation of results and had input into the writing of the manuscript.

Conflict of interest: None declared.

References

1 Chang WP, Liu ME, Chang WC, *et al.* Sleep apnea and the risk of dementia: a population-based 5-year follow-up study in Taiwan. *PLoS One* 2013; 8: e78655.
2 Osorio RS, Gumb T, Pirraglia E, *et al.* Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology* 2015; 84: 1964–1971.
3 Norton S, Matthews FE, Barnes DE, *et al.* Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol* 2014; 13: 788–794.
4 Naismith S, Winter V, Gotsopoulos H, *et al.* Neurobehavioral functioning in obstructive sleep apnea: differential effects of sleep quality, hypoxemia and subjective sleepiness. *J Clin Exp Neuropsychol* 2004; 26: 43–54.
5 Xie L, Kang H, Xu Q, *et al.* Sleep drives metabolite clearance from the adult brain. *Science* 2013; 342: 373–377.
6 de Vivo L, Bellesi M, Marshall W, *et al.* Ultrastructural evidence for synaptic scaling across the wake/sleep cycle. *Science* 2017; 355: 507–510.
7 Macedo AC, Balouch S, Tabet N. Is sleep disruption a risk factor for Alzheimer's disease? *J Alzheimers Dis* 2017; 58: 993–1002.
8 Canessa N, Castronovo V, Cappa SF, *et al.* Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. *Am J Respir Crit Care Med* 2011; 183: 1419–1426.
9 Macey PM, Henderson LA, Macey KE, *et al.* Brain morphology associated with obstructive sleep apnea. *Am J Respir Crit Care Med* 2002; 166: 1382–1387.
10 Yaouhi K, Bertran F, Clochon P, *et al.* A combined neuropsychological and brain imaging study of obstructive sleep apnea. *J Sleep Res* 2009; 18: 36–48.
11 Morrell MJ, McRobbie DW, Quest RA, *et al.* Changes in brain morphology associated with obstructive sleep apnea. *Sleep Med* 2003; 4: 451–454.
12 Celle S, Peyron R, Faillenot I, *et al.* Undiagnosed sleep-related breathing disorders are associated with focal brainstem atrophy in the elderly. *Hum Brain Mapp* 2009; 30: 2090–2097.
13 Baril AA, Gagnon K, Brayet P, *et al.* Gray matter hypertrophy and thickening with obstructive sleep apnea in middle-aged and older adults. *Am J Respir Crit Care Med* 2017; 195: 1509–1518.
14 Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol* 1991; 82: 239–259.
15 Yang J, Pan P, Song W, *et al.* Voxelwise meta-analysis of gray matter anomalies in Alzheimer's disease and mild cognitive impairment using anatomic likelihood estimation. *J Neurol Sci* 2012; 316: 21–29.
16 Nickl-Jockschat T, Kleiman A, Schulz JB, *et al.* Neuroanatomic changes and their association with cognitive decline in mild cognitive impairment: a meta-analysis. *Brain Struct Funct* 2012; 217: 115–125.
17 Ryu SY, Lim EY, Na S, *et al.* Hippocampal and entorhinal structures in subjective memory impairment: a combined MRI volumetric and DTI study. *Int Psychogeriatr* 2017; 29: 785–792.
18 Stewart R, Godin O, Crivello F, *et al.* Longitudinal neuroimaging correlates of subjective memory impairment: 4-year prospective community study. *Br J Psychiatry* 2011; 198: 199–205.
19 Duffy SL, Lagopoulos J, Hickie IB, *et al.* Glutathione relates to neuropsychological functioning in mild cognitive impairment. *Alzheimers Dement* 2014; 10: 67–75.
20 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189–198.
21 First MB, Williams JBW, Spitzer RL, *et al.* Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Clinical Trials Version (SCID-CT). New York, Biometrics Research, New York State Psychiatric Institute, 2007.
22 Yesavage JA, Sheikh JI. Geriatric Depression Scale (GDS): recent evidence and development of a short version. *Clin Gerontologist* 1986; 5: 165–173.
23 Cross N, Lampit A, Pye J, *et al.* Is obstructive sleep apnoea related to neuropsychological function in healthy older adults? A systematic review and meta-analysis. *Neuropsychol Rev* 2017; 27: 389–402.
24 Lezak M. Neuropsychological Assessment. New York, Oxford University Press, 1982.
25 Senior G. Analysing RAVLT Learning and Serial Position Curves using Mahalanobis Distance. Toowoomba, QLD, Australia, University of Southern Queensland, 1999.
26 Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci USA* 2000; 97: 11050–11055.
27 Fischl B, Salat DH, Busa E, *et al.* Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* 2002; 33: 341–355.
28 Iber C, Ancoli-Israel S, Chesson AJ, *et al.* The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Westchester, IL, American Academy of Sleep Medicine, 2007.
29 Asghari A, Mohammadi F. Is apnea-hypopnea index a proper measure for obstructive sleep apnea severity? *Med J Islam Repub Iran* 2013; 27: 161–162.

30 Hodges H, Sowinski P, Fleming P, *et al.* Contrasting effects of fetal CA1 and CA3 hippocampal grafts on deficits in spatial learning and working memory induced by global cerebral ischaemia in rats. *Neuroscience* 1996; 72: 959–988.
31 Duffy SL, Lagopoulos J, Terpening Z, *et al.* Association of anterior cingulate glutathione with sleep apnea in older adults at-risk for dementia. *Sleep* 2016; 39: 899–906.
32 Rae C, Bartlett DJ, Yang Q, *et al.* Dynamic changes in brain bioenergetics during obstructive sleep apnea. *J Cereb Blood Flow Metab* 2009; 29: 1421–1428.
33 Rosenzweig I, Glasser M, Polsek D, *et al.* Sleep apnoea and the brain: a complex relationship. *Lancet Respir Med* 2015; 3: 404–414.
34 Yun CH, Lee HY, Lee SK, *et al.* Amyloid burden in obstructive sleep apnea. *J Alzheimers Dis* 2017; 59: 933–943.
35 Sharma RA, Varga AW, Bubu OM, *et al.* Obstructive sleep apnea severity affects amyloid burden in cognitively normal elderly. A longitudinal study. *Am J Respir Crit Care Med* 2018; 197: 933–943.
36 Lin WC, Huang CC, Chen HL, *et al.* Longitudinal brain structural alterations and systemic inflammation in obstructive sleep apnea before and after surgical treatment. *J Transl Med* 2016; 14: 139.
37 Rosenzweig I, Kempton MJ, Crum WR, *et al.* Hippocampal hypertrophy and sleep apnea: a role for the ischemic preconditioning? *PLoS One* 2013; 8: e83173.
38 Mander BA, Rao V, Lu B, *et al.* Prefrontal atrophy, disrupted NREM slow waves, and impaired hippocampal-dependent memory in aging. *Nat Neurosci* 2013; 16: 357–364.
39 Helfrich RF, Mander BA, Jagust WJ, *et al.* Old brains come uncoupled in sleep: slow wave-spindle synchrony, brain atrophy, and forgetting. *Neuron* 2018; 97: 221–230.
40 Polsek D, Gildeh N, Cash D, *et al.* Obstructive sleep apnoea and Alzheimer's disease: in search of shared pathomechanisms. *Neurosci Biobehav Rev* 2018; 86: 142–149.
41 Yaffe K, Laffan AM, Harrison SL, *et al.* Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA* 2011; 306: 613–619.
42 Mander BA, Winer JR, Jagust WJ, *et al.* Sleep: a novel mechanistic pathway, biomarker, and treatment target in the pathology of Alzheimer's disease? *Trends Neurosci* 2016; 39: 552–566.
43 Pan W, Kastin AJ. Can sleep apnea cause Alzheimer's disease? *Neurosci Biobehav Rev* 2014; 47: 656–669.
44 Mendonça MD, Alves L, Bugalho P. From subjective cognitive complaints to dementia: who is at risk? A systematic review. *Am J Alzheimers Dis Other Demen* 2016; 31: 105–114.