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Neuropathological investigation of cell layer thickness and myelination in the hippocampus of people with obstructive sleep apnea FREE

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Abstract

Obstructive sleep apnea (OSA) is commonly associated with memory impairments. Although MRI studies have found volumetric differences in the hippocampus of people with OSA compared with controls, MRI lacks the spatial resolution to detect changes in the specific regions of the hippocampus that process different types of memory. The present study performed histopathological investigations on autopsy brain tissue from 32 people with OSA (17 females and 15 males) to examine whether the thickness and myelination of the hippocampus and entorhinal cortex (EC) vary as a function of OSA severity. Increasing OSA severity was found to be related to cortical thinning in the molecular layer of the dentate gyrus ($r^2 = 0.136$, $p = 0.038$), the CA1 (overall, $r^2 = 0.135$, $p = 0.039$; layer 1, $r^2 = 0.157$, $p = 0.025$; layer 2, $r^2 = 0.255$, $p = 0.003$; and layer 3, $r^2 = 0.185$, $p = 0.014$) and in some layers of the EC (layer 1, $r^2 = 0.186$, $p = 0.028$; trend in layer 3, $r^2 = 0.124$, $p = 0.078$). OSA severity was also related to decreased myelin in the deep layers but not the superficial layers of the EC (layer 6, $r^2 = 0.282$, $p = 0.006$; deep white matter, $r^2 = 0.390$, $p = 0.001$). Patients known to have used continuous positive airway pressure (CPAP) treatment showed no significant reductions in cortical thickness when compared with controls, suggesting that CPAP had a protective effect. However, CPAP did not protect against myelin loss. The regions of decreased cortical thickness and demyelination are locations of synaptic connections in both the polysynaptic (episodic and spatial) and direct (semantic) memory pathways and may underpin the impairments observed in episodic, semantic, and spatial memory in people with OSA.

CPAP, cortical thickness, gray matter, hippocampus, myelin, obstructive sleep apnea, white matter

Statement of Significance

Memory deficits are common in people with obstructive sleep apnea (OSA), and although MRI studies have reported hippocampal shrinkage in OSA, they lacked the resolution to investigate individual cell layers that process specific types of memory. The present study used autopsy brain tissue from people with OSA to investigate the thickness and myelination of cell layers in the hippocampus and associated cortex. As OSA severity increased, so did hippocampal atrophy and demyelination. Since the specific cell layers affected are involved in memory processing, they likely underpin the memory impairments. People with OSA that adhered to continuous positive airway pressure therapy showed less hippocampal atrophy but similar demyelination. This irreversibility of white matter damage implies that some memory deficits might be permanent.

Introduction

Obstructive sleep apnea (OSA) involves the intermittent cessation of breathing throughout sleep, leading to frequent episodes of hypoxia, severe sleep disruption, and consequent deficits in memory, attention, and executive functioning [1, 2]. Memory processing occurs in the hippocampus, a structure in the inferior part of the temporal lobe of the brain. Neuroimaging studies have found gross volumetric changes in the brains of people with OSA [1]. Specifically, there is reduced hippocampal volume in people with OSA when compared with controls [3–6], which correlate with memory deficits [1, 7]. In contrast to the bulk of studies, increased hippocampal volume has been reported by a few imaging studies of people with OSA [8, 9].

It has been suggested that in OSA the loss of gray matter may vary between regions of the hippocampus [10, 11], but such regional loss has not been demonstrated directly. MRI studies have reported that in people with OSA the hippocampal sulcus is wider, and the extent of this width is correlated with OSA severity [10]. An increased sulcus width could indicate reduced volume of the gray matter on either side of the hippocampal sulcus, which includes the dentate gyrus and CA1 or subiculum. In this context, it is interesting that continuous positive airway pressure (CPAP) treatment of people with OSA increases the volume of their CA1 and dentate gyrus [11]. However, MRI studies lack the spatial resolution to be able to resolve differences in the thickness of individual cortical cell layers. A capacity to do this would be very useful, since specific layers are associated with particular aspects of the memory circuitry, and hence reductions in the thickness of specific layers might provide insights into which circuits are most affected in OSA.

The precise neural circuitry involved in memory formation, storage, and retrieval is complex and not entirely understood. However, two functional neural circuits have been identified: the polysynaptic (trisynaptic) and direct (monosynaptic) pathways (see Figure 6a in Discussion). The polysynaptic pathway is thought to process memories that involve spatial reference, as well as episodic memories (memory of personal experiences and events). The polysynaptic pathway may be important for the acquisition of new memories [12]. This pathway begins in the entorhinal cortex (EC), specifically in layer 2 neurons of the six-layered cortex. These neurons send axons to the molecular layer of the dentate gyrus via the so-called “perforant pathway.” In turn, neurons in the dentate gyrus project to the CA3 region via specialized axons called “mossy fibers.” Pyramidal neurons in the CA3 region then project to CA2 and CA1 via branched axons called “Schaffer collaterals.” Pyramidal neurons in CA1 send axons through the subiculum to terminate in layer 5 of the EC, completing the loop [12, 13].

The circuitry of the direct hippocampal pathway is more straightforward. It originates in neurons located in layer 3 of the EC, which project to and synapse in the CA1 region. Pyramidal neurons in CA1 then send efferents back to the deep layers of EC, with some traveling via the subiculum [13]. Semantic memory (memory of facts and general knowledge) is processed via this pathway, and it may also be involved in maintaining the stability of older memories [12].

The decreased hippocampal volume in OSA may be due to the loss of either gray or white matter (WM) or both. WM damage can arise from the loss of myelin, axons, or oligodendrocytes. Decreased integrity of the WM is seen in the hippocampus, parahippocampal gyrus, and temporal lobe of people with OSA compared with age-matched controls [14–16]. This loss is thought to be the result of hypoxia rather than sleep fragmentation. Indeed, whole brain ischemia causes demyelination [17]. Additionally, animal studies have shown that exposure to intermittent hypoxia (IH) causes hypomyelination and reduces the expression of myelin-associated proteins in the cerebral cortex [18, 19]. However, neither of these studies investigated the hippocampus.

Interestingly, hippocampal degeneration and memory impairments are common features of Alzheimer’s disease (AD). The two neuropathological hallmarks of AD are the deposition of extracellular Aβ plaques and intraneuronal NFTs in the hippocampus. Furthermore, there is significant loss of gray matter in the hippocampus, as evidenced by neuropathological studies of autopsy brain tissue from people with AD [20, 21]. Hippocampal regions that lose gray matter include the CA1, subiculum, and EC [22, 23]. Although some of the neuronal loss is associated with the development of NFTs, other loss appears to be independent of NFTs [24]. Recently, with advances in the resolution of neuroimaging, volumetric losses have been confirmed in the EC, CA1, CA2, CA3, and CA4 regions of the hippocampus in people with AD [25, 26]. The most consistent difference in people with AD is a reduced CA1 volume compared with that in healthy elderly controls [27, 28]. Histology studies from autopsy tissue show that WM deteriorates in brain tissue from people with AD [29, 30], including in the hippocampus and adjacent cortex [31], with all components of the WM (myelin, oligodendrocytes, and axons), showing signs of degeneration [32, 33].

OSA stands out as a potential contributor to the demyelination that occurs during the prodromal stage of AD. As noted above, OSA and IH are associated with injury to the cerebral WM, and there is also a strong comorbidity between OSA and AD, with the presence of OSA in midlife being associated with the development of AD or dementia in later life. Furthermore, the prevalence of OSA in people with AD or dementia is more than double the prevalence of OSA in the general elderly population [34–36], and people with AD have a fivefold increased risk of also having OSA [37].

In people with OSA, treatment with CPAP is effective at eliminating hypoxic episodes and sleep disruption [38]. Restoring proper oxygenation to the brain via CPAP can alleviate the cognitive symptoms associated with OSA [1], but it is not consistently effective at restoring all of the affected cognitive domains [39]. Neuroimaging research suggests that the effectiveness of CPAP treatment to reverse the volumetric loss and WM damage seen in OSA may vary between regions [1, 11, 40]. For example, CPAP was shown to increase the volume of the dentate gyrus of people with OSA [11]. Those authors suggested that neurogenesis was the cause of the volume increase observed, as the dentate gyrus is a known site of neurogenesis in the adult brain.

MRI measurements generally correlate well with cortical thickness measurements determined by histological methods [41]; however, the large confidence intervals suggest that the method would be unreliable to estimate the thickness of individual cortical layers [42]. Given that reductions in the thickness of certain cell layers can affect specific neural circuits, it is important to be able to determine the thickness of cortical layers individually. Histological measurements are commonly utilized for determining regional gray matter atrophy and neuronal loss in cases of epilepsy and hippocampal sclerosis [43, 44] and can be used to differentiate specific cell layers [45]. Myelin is a key component of WM and although changes in WM can be determined through diffusion tensor MRI, the specific components of WM (myelin, oligodendrocytes, and axons) cannot be reliably differentiated [46]. The immunohistochemical detection of myelin-associated proteins is commonly used to identify the location of demyelinating lesions in multiple sclerosis brains [47] and histopathological quantification of myelin loss has been used to investigate WM injury in neurodegenerative diseases, including AD [32, 33, 48].

The present study has investigated archived autopsy brain tissue from people with a medical history of OSA and CPAP use. The aim of the study was to investigate the cell layer thickness and extent of myelination in specific hippocampal regions, and to relate these measures to OSA severity and CPAP use.

Methods

This project was approved by the National Bioethics Committee, Iceland (reference 09-087-CM) and the RMIT Human Research Ethics Committee, Australia (reference ASEHAPP 71-16).

Study sample

Since 1987 a total of 8853 patients aged 18 years and older have been registered with a diagnosis of OSA in Iceland (total population 320 000) by December 2013. By March 2014, 1322 of these patients had died. Among the deceased, 121 underwent autopsy at the Department of Pathology, Landspitali University Hospital and 61 of these autopsies included brain tissue that had been preserved and stored. Brain samples were sent to RMIT University, Melbourne, Australia. Patients were excluded from this study if they had been diagnosed with dementia (one patient), AD (one patient), or multiple sclerosis (one patient), if their clinical records could not be found, if no hippocampal tissue was available, or if evidence of hemorrhagic stroke could be seen in the area of interest. The study sample consisted of autopsy brain tissue from 32 patients with a mean age of 67.0 ± 11.0 years (ranging from 41.7 to 83 years): there were 17 females (mean age 66.7 ± 12.5 years) and 15 males (mean age 67.4 ± 9.5 years). One case was excluded from WM analysis due to tissue damage. Six cases were excluded from EC analysis due to insufficient tissue being present; however, the cases were used for the other hippocampal regions.

The OSA diagnoses were all performed using full polysomnography at the sleep laboratory of Landspitali University Hospital during the time period 1988 to 2010 and scored by a laboratory technician. OSA diagnoses during this time period were always based on whole night sleep studies involving oximetry and a variable number of other parameters depending on the time period they were performed. Due to the archival nature of this study, not all of the AHI records could be retrieved, whereas all of the oxygen desaturation index (ODI) records were recovered. Therefore, the present study uses ODI as the measure of OSA severity.

Landspitali University Hospital has been the sole provider of CPAP therapy in Iceland since 1987. During the study period, all patients were taken care of by one of the authors (T.G.) and his team. People with CPAP paid a monthly usage fee and hospital records registered when treatment was started, the settings used, and all follow-up visits. If CPAP devices were returned, this was recorded. Among the 32 patients in the present study, 18 were known to have regularly used CPAP until they died, that is, their CPAP machines were being used at the time of death or admission to hospital. Of the remainder, three were known to have never used CPAP, whereas 11 were not using CPAP at the time of death but may or may not have used CPAP for some period of time between diagnosis and death. For the purposes of this study, only those patients known to have regularly used CPAP were included in the “CPAP-users” group. All other patients were considered to be “CPAP non-users/unconfirmed.”

Tissue processing

Brains were dissected at autopsy. Details of the postmortem interval are unknown. Samples of tissue were formalin-fixed paraffin-embedded and archived. Blocks from the medial part of the temporal lobe (including rostral hippocampus and parahippocampal gyrus) were used in the present study. Tissue was sectioned at 20 μm on a microtome, dried onto glass microscope sides, then dewaxed in Histolene (two changes), rehydrated in graded ethanols (100% two changes, 95%, 70%, H_2O), and then processed for histology or immunohistochemistry, as described below.

Cresyl violet histology

Sections were stained with cresyl violet in order to visualize cell bodies. After deparaffinisation, sections were incubated for 20 min at room temperature in 0.5% cresyl violet solution. Sections were washed briefly in H_2O, then in 70% ethanol, and then differentiated in 95% ethanol + glacial acetic acid for 5 min. Slides were then dehydrated in 100% ethanol (two changes) and histolene (two changes) before being coverslipped with Depex. After being left to dry, sections were viewed under the microscope.

Immunohistochemistry

The immunohistochemistry protocol was modified from that described previously [49]. After deparaffinisation, sections to be immunostained for myelin basic protein (MBP) underwent antigen retrieval for 40 min at 80°C in EDTA buffer, prepared as described previously [50], and then washed in 0.1 M phosphate-buffered saline (PBS) (3 × 10 min). Sections were then incubated with blocking solution (0.1 M PBS, 1% bovine albumin serum [BSA], 1% Triton X-100, 1% ethanolamine, and 4% serum) for 3 hr at room temperature. Serum from the host animal of the secondary antibody was used in the blocking solution, primary and secondary antibody dilutants to reduce nonspecific background staining. After blocking, sections were incubated with primary antibody for anti-MBP (Abcam, ab7349) diluted at 1:1000 in primary antibody dilutant (0.1 M PBS, 1% BSA, 0.5% Triton X-100, and 4% serum) for 18 hr at room temperature. Following this, sections were incubated with goat anti-rat secondary antibody (Merck Millipore, AP183B) diluted at 1:300 in secondary antibody dilutant (0.1 M PBS, 1% BSA, and 4% serum) for 6 hr, and followed by streptavidin-biotinylated horseradish peroxidase (GE Healthcare, RPN1051) diluted at 1:300 in 0.1 M PBS and 1% BSA for 3 hr. Between each of the above steps, sections were washed for 3 × 10 min in 0.1 M PBS. After incubation with streptavidin-biotinylated horseradish peroxidase, sections were washed for 2 × 5 min in 0.1 M PBS and then for 2 × 10 min in 0.175 M sodium acetate buffer (NaOAc). Sections were then incubated with the chromagen DAB diluted in NaOAc buffer at 0.05% for 10 min and then 0.05% DAB in NaOAc buffer with 0.004% H_2O_2 for 15 min. Immunolabelled sections were then washed in NaOAc buffer for 2 × 5 min, then 0.1 M PBS for 2 × 10 min, and left overnight in 0.1 M PBS at 4°C. On the following day, sections were dehydrated in graded ethanols (70%, 95%, 100%; two changes in 100% only) and histolene (two changes) before being coverslipped with Depex. After being left to dry, sections were viewed under the microscope.

Neuronal counts

Cresyl violet–stained sections were used to estimate the number of neurons present in the pyramidal cell layer of each of the four regions of the hippocampus, CA1-4. Due to the very limited amount of tissue available, three-dimensional stereological estimates of total neuronal numbers could not be conducted. Instead, image analysis was used to provide estimates of neuronal numbers from photomicrographs of defined regions. Photomicrographs were taken at 200× magnification (1200 × 1600 pixels) converted to grayscale and autocontrasted. Based on careful histological examination at high magnification, it was determined that most objects with an area greater than 200 pixels [2] in size were neurons. Based on this criterion, Olympus CellSens software was used to estimate the number of neurons in an image. Cell bodies that were bisected by the left hand or top margins of the micrograph were not included in the counts. Each image was visually examined to ensure that all of the obvious neurons had been selected, and that no other cell types or other features had been included.

Hippocampus size measurements

Cresyl violet–stained sections were used for measurements of cell layer thickness and area. Three different parts of a section containing the hippocampus and parahippocampal gyrus were measured: the dentate gyrus, CA1, and EC (Figure 1a). Photomicrographs of the dentate gyrus and CA1 were taken at 40× magnification, and EC micrographs were taken at 64× magnification. Olympus CellSens software was used to measure distances and areas of specific regions, as detailed below for each region.

Figure 1.

Cresyl violet and MBP images of hippocampal regions. Low magnification cresyl violet (a–d) and MBP (e) images of hippocampus (a) with boxes indicating the areas sampled for the dentate gyrus (A), CA1 (B), and EC (C). Dentate gyrus (b) including measurements taken for the hilus length (solid arrow), hilus opening (dashed arrow), and the depth of the hilus perpendicular to the hilus opening (dotted arrow). CA1 (c) indicating the four different layers measured. EC (d and e) indicating the six cortical layers measured and the deep white matter. Scale bar in (d) applies to (e).

Features measured in the dentate gyrus were as follows: the width of the opening of the hilus, the depth perpendicular to the opening of the hilus, the length of the hilus, and the area of the molecular and granule cell layers (Figure 1b). The layers of the dentate gyrus were identified from histological features, as described previously [13]. The granule cell layer is prominent in cresyl violet–stained sections due to the dense clustering of cells. The molecular cell layer was defined as the region between the outer border of the granule cell layer and the hippocampal sulcus.

The total cortical thickness of the CA1 and EC was calculated as the mean of three measurements of the cortex from pia matter to the deep WM on each micrograph. The boundary of each layer of the cortex was then estimated, from histological characteristics, such as the presence or absence of certain cell types [13] with agreement between two investigators (J.E.O. and S.R.R.). The percentage area of each layer was calculated using the sum area of all cortical layers across the same lateral distance (width of the micrograph, 1200 pixels). The percentage area occupied by each layer was divided by the mean total cortical thickness that was initially recorded, in order to give measurements for the cortical thickness of each layer of cortex. Figure 1, c and d illustrates the measurements taken from typical cresyl violet images at the CA1 and EC, respectively.

In the CA1, four cortical layers were measured (Figure 1c). Layer 1: the alveus consists mostly of WM and is directly underneath the pial surface. Layer 2: stratum oriens consists of mostly basket cells and axons although there is less WM than layer 1. Layer 3: stratum pyramidale is the largest layer and contains pyramidal neurons. The molecular zone is made up of layers 4 (stratum radiatum), 5 (stratum lacunosum), and 6 (stratum moleculare). These layers are very difficult to distinguish from each other in the CA1, and for this reason they are collectively referred to as the molecular zone [13]. In the present study, the term “molecular zone” is used.

In the EC, six cortical layers were measured, as described by Vanderah et al. [51]; layer 1 (molecular layer), layer 2 (external granule cell layer), layer 3 (external pyramidal cell layer), layer 4 (internal granule cell layer), layer 5 (internal pyramidal cell layer), and layer 6 (polymorphic layer). Layer 1 is directly beneath the pial surface; it contains mostly axons and few neuronal cell bodies. Layers 3 and 5 contain pyramidal neurons; layers 2 and 4 consist mainly of granule cells rather than pyramidal cells; whereas layer 6 contains modified pyramidal cells as well as many axons (Figure 1, d and e).

MBP quantification and analysis

Micrographs of MBP staining were taken at the same magnification and in the same regions as the cresyl violet–stained sections. These images were converted to grayscale and the mean gray intensity of the area of each cortical layer was measured. The area of the cortical layer was copied as a template from the cresyl violet image and pasted onto the MBP image. Minor adjustments were made to the area where the borders of the layers did not line up exactly with the cresyl violet image (Figure 1e). Measurements were also made of the mean gray intensity in the deep WM of the EC. The deep WM was defined as being below the boundary of layer 6 of the cortex. The area of this region was not defined individually; rather a standard area (0.34 mm^2) was used for all images to obtain a value for the mean gray intensity. The inverse mean gray intensity was used for all graphs so that lower gray intensity values correspond to lighter staining, indicating decreased myelin content. The inverse mean gray intensity was calculated by subtracting the mean gray intensity from 256 (the maximum value of any grayscale image).

Statistical analysis

As the variable ODI was found to be non-normally distributed, a log transformation was performed to normalize the distribution, and therefore, all correlations were performed with log ODI. All statistical analysis was performed using the IBM SPSS version 22.

Results

Descriptive statistics

Descriptive statistics for the sample are given in Table 1 . A significant correlation was found between ODI and age, $r = 0.421$, $p = 0.016$. No other significant correlations were found between the descriptive variables. CPAP users and nonusers/unconfirmed were compared using two-tailed

student *t*-tests. CPAP users were found to have a significantly higher body mass index (BMI) than CPAP nonusers/unconfirmed (Table 1). No differences were found for age, ODI, or interval from diagnosis to death. No significant differences were found between males and females for any descriptive statistics (Supplementary Table 1). Scatterplots for all negative findings in the subsequent sections are presented in Supplementary Figures 1 and 2.

Table 1.

Descriptive statistics for total sample and separated by CPAP use

	Total	CPAP users	CPAP nonusers/unconfirmed	Significance CPAP users vs. nonusers/unconfirmed
n	32	18	14	
Gender	F=17, M=15	F=12, M=6	F=5, M=9	
Age at death (years)	67.0 ± 11.0	69.9 ± 11.1	63.3 ± 10.2	p=0.096
BMI kg/m^2	29.9 ± 5.9 n=28	32.6 ± 5.8 n=16	26.3 ± 4.0n=12	p=0.004*
Time from OSA diagnosis to death (years)	7.6 ± 5.9	7.1 ± 6.2	8.3 ± 5.6	p=0.563
ODI (events/hr)	26.5 ± 21.4	32.0 ± 18.8	19.5 ± 23.2	p=0.104

Mean ± standard deviation.

*$p < 0.05$ CPAP users compared with CPAP nonusers.

F = female; M = male.

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Hippocampus size

In the dentate gyrus, there was a significant negative relationship between the length of the hilus and log ODI (Figure 2a). When the sample was divided into CPAP users and CPAP nonusers/unconfirmed (Figure 2b), the relationship strengthened (higher r^2 value) when only CPAP nonusers/unconfirmed were considered and it approached significance ($p = 0.053$), whereas the relationship weakened (lower r^2 value) when only CPAP users were considered. These trends indicate that CPAP use may protect against shrinkage of the length of the hilus. No relationship was seen for the width of the opening of the hilus, the depth perpendicular to the opening or the area of the granule cell layer. However, a significant negative relationship was found between log ODI and the area of the molecular layer of the dentate gyrus (Figure 2c), indicating that the area of the molecular layer decreased with increasing ODI value. This relationship strengthened (higher r^2 value) when only CPAP nonusers/unconfirmed were considered and did not change (to two decimal places) or reach significance when only CPAP users were considered (Figure 2d). These results indicate that CPAP use may protect against shrinkage of the molecular layer of the dentate. Figure 2, e and f shows representative micrographs of the dentate gyrus from people with lower and higher ODIs, respectively. In the person with lower ODI, the length of the hilus is longer and the area of the molecular layer is larger, compared with the person with higher ODI.

Figure 2.

Dentate gyrus size measurements regressed against OSA severity (ODI). Total length of the hilus (a), area of the molecular layer (c) regressed against OSA severity and stratified by CPAP use (b and d). CPAP users are indicated by red circles and CPAP nonusers/unconfirmed are indicated by blue triangles. Micrographs of sections stained with cresyl violet from a person with a lower ODI score (e) and a higher ODI score (f). Scale bar = 1 mm and applies to (e) and (f). *$p < 0.05$.

There was a significant negative correlation between log ODI and total cortical thickness of the CA1 (Figure 3a). Furthermore, when the sample

was separated into CPAP users and nonusers/unconfirmed (Figure 3b), the correlation strengthened for CPAP nonusers/unconfirmed and weakened in CPAP users. These results suggest that CPAP nonusers/unconfirmed experience a decrease in cortical thickness of the CA1 with increasing ODI, whereas CPAP users do not.

Figure 3.

Overall thickness and individual cortical layer thickness of the CA1. Overall cortical thickness measurements in mm in the CA1 regressed against OSA severity (ODI) (a) and separated by CPAP use (b). Cortical layer thickness of the CA1 of the hippocampus (layers 1–3) regressed against OSA severity (ODI) (c, e, and g), and stratified by CPAP use (d, f, and h). CPAP users are indicated by red circles and CPAP nonusers/unconfirmed are indicated by blue triangles. Micrographs of sections stained for cresyl violet from a person with a lower ODI score (i) and a higher ODI score (j). Scale bar = 500 μm and applies to (i) and (j). *$p < 0.05$.

The thickness of each of the four cortical layers (layers 1, 2, 3, and the molecular zone comprised of layers 4–6) of the CA1 of the hippocampus was measured individually. Significant negative relationships were found between layer thickness and log ODI in layers 1, 2, and 3, but not in the molecular zone (Figure 3). Representative micrographs from a person with lower ODI (Figure 3i) and higher ODI scores (Figure 3j) show the decrease in overall thickness; the distance from the top black line to the bottom black line is larger in the person with less severe OSA (Figure 3i) compared with the person with more severe OSA (Figure 3j). Specifically, there is decreased cortical thickness in layers 1–3 in the person with more severe OSA. The sample was then separated into CPAP users and nonusers/unconfirmed. There was a strengthening of the relationship between log ODI and the CA1 layer thickness for CPAP nonusers/unconfirmed in layers 1, 2, and 3, and no relationship was present among CPAP users. No relationship was seen in the CA1 molecular zone.

Neuronal counts in hippocampus

Neuron numbers were estimated in the pyramidal cell layer of the CA1–CA4 regions of the hippocampus (Supplementary Table 2). No significant relationships were seen between neuron estimates and ODI in any of the four regions, even when separated into CPAP users and nonusers/unconfirmed.

Entorhinal cortex size

Although there was no significant relationship for the total cortical thickness in the EC (Figure 4a), when separated by CPAP use (Figure 4b), the same trend was seen as for the CA1. CPAP nonusers/unconfirmed had a significant negative relationship between the thickness of the EC and log ODI, and no relationship was seen in CPAP users. These results suggest that not using CPAP is associated with a decrease in cortical thickness of the EC with increasing ODI, whereas CPAP use is not.

Figure 4.

Overall thickness and individual cortical layer thickness of the EC. Overall cortical thickness measurements in mm in the EC regressed against OSA severity (ODI) (a) and separated by CPAP use (b). Cortical layer thickness of the EC (layers 1–3) regressed against OSA severity (ODI) (c, e, and g), and stratified by CPAP use (d, f, and h). CPAP users are indicated by red circles and CPAP nonusers/unconfirmed are indicated by blue triangles. Micrographs of sections stained for cresyl violet from a person with a lower ODI score (i) and a higher ODI score (j). Scale bar = 500 μm and applies to (i) and (j). *$p < 0.05$.

Layers of the EC were measured individually to determine whether there were any changes in the thickness of the different cortical layers. A significant negative correlation between log ODI and cortical layer thickness was found in layer 1, and a trend was seen in layer 3 (Figure 4). No significant relationships were seen for layers 2, 4, 5, or 6. When the sample was separated into CPAP users and nonusers/unconfirmed, there were stronger negative correlations for CPAP nonusers/unconfirmed between log ODI and layer thickness in layers 1, 2, and 3 (Figure 4, d, f, and h). However, only the layer 3 correlation reached significance. The correlations for layers 1 and 2 approached statistical significance. Figure 4, i and j shows representative micrographs from a person with lower ODI score and higher ODI score, respectively. No difference in cortical thickness is evident in layers 2, 3, 4, 5, or 6. Layer 1 is thinner in the person with higher ODI.

Myelin staining intensity

The inverse of the mean gray intensity of MBP staining was used to approximate the amount of myelin, where higher values represent more intense staining (more myelin) and lower values represent less intense staining (less myelin). In the dentate gyrus and CA1, no relationships were seen

between MBP staining intensity and ODI. No significant differences were found when stratified by CPAP.

In the EC, layer 6 showed a significant negative correlation between ODI and MBP staining, (Figure 5). Layers 1–5 showed no relationship to ODI, indicating that the deep cortical layer (layer 6) of the EC shows decreasing myelin with increasing ODI, whereas the superficial layers do not (Figure 5, e and f). Lighter myelin staining is seen in the deep WM as well as in layer 6 in a person with a higher ODI (Figure 5e), compared with a person with a lower ODI (Figure 5f). When stratified by CPAP use, no differences were found in layers 1–5. In layer 6, the relationship between MBP staining intensity and ODI strengthened for both CPAP users and CPAP nonusers/unconfirmed compared with the sample as a whole; however, only the relationship for CPAP users reached statistical significance. This indicates that CPAP use is not associated with the decreased myelin staining in this layer.

Figure 5.

The inverse mean gray intensity of MBP staining regressed against OSA severity (ODI), for the EC layer 6 (a) and the deep white mater (c) and separated by CPAP use (b and d). CPAP users are indicated by red circles and CPAP nonusers/unconfirmed are indicated by blue triangles. Micrographs of sections stained for MBP from a person with a lower ODI score (e) and a higher ODI score (f). Scale bar = 500 μm and applies to (e) and (f). *$p < 0.05$.

In the deep WM of the EC, a strong significant negative correlation was seen between ODI and MBP staining (Figure 5c). With increasing OSA severity, less myelin is seen in the deep WM of the EC. When separated into CPAP users and nonusers/unconfirmed (Figure 5d), the relationship was slightly weaker compared with the whole group but is still significant for CPAP users, and is stronger and more significant for CPAP nonusers/unconfirmed. This indicates that CPAP users and nonusers/unconfirmed have a similar decrease in MBP staining intensity in the deep WM.

Age and hippocampal size/demyelination

Given the significant correlation between age and ODI described above, it is possible that the significant relationships with OSA severity were influenced by age-related changes. To investigate this possibility, each of the significant correlations described above was also correlated against patient age. A significant relationship was found between age and the cortical thickness of layer 2 of the CA1, $r^2 = 0.258$, $p = 0.003$. However, none of the other layers of the CA1, the EC, or the dentate gyrus measures were significantly correlated with age, indicating that patient age cannot account for the correlations described in the preceding sections. There are no significant relationships between MBP staining intensity and age in the EC, indicating the patient age cannot account for the correlations described in the preceding sections.

Gender and hippocampal size/demyelination

All hippocampal size and demyelination measures were compared between male and female patients using *t*-tests. Only one significant difference was found: hilus length was significantly longer in males than females (6.96 vs 5.80 μm, $p = 0.023$).

Discussion

OSA is thought to be associated with cortical volume variability and demyelination. However, this has only been investigated using animal models and MRI. Histopathology was used in the present study to directly investigate changes in cortical thickness and myelin in OSA brains. The current study has found that individual layer variations in cortical thickness and myelin staining intensity in the hippocampus are correlated with the severity of OSA.

There is hippocampal loss associated with increasing severity of OSA. In the dentate gyrus, we found that with increasing ODI, the length of the hilus and the area of the molecular layer decreased. In the CA1, the overall cortical thickness decreased as ODI increased, as did the thickness of specific layers of the CA1: layers 1, 2, and 3. In the EC, increasing OSA severity was associated with decreased thickness of layer 1 and a trend towards decreased thickness in layer 3. No neuronal loss was seen in any of the four CA regions examined; therefore, decreased cortical thickness in the CA1 and the dentate gyrus is not due to neuronal loss. Neuronal shrinkage, synaptic loss, or changes in glial cells may account for the cortical thinning; however, further investigation is needed to differentiate between these possibilities. Neuronal loss or atrophy may account for the reduced cortical thickness of layers 1 and 3 in the EC. A loss of axons is unlikely to account for the present results as no reduction in myelin staining intensity was seen in the regions of decreased cortical thickness. Conversely, decreased myelin staining was seen in layer 6 of the EC and the deep WM in the absence of changes in layer thickness, indicating that changes in layer thickness and reductions in myelination occur independently in the present

sample.

MRI studies have variously reported increases or decreases in hippocampal volume in people with OSA [8, 9]. It is possible that volume increases are restricted to younger populations. Participants in studies reporting increased hippocampal volume had a mean age of 41 [9] and 55 years [8], whereas the present sample had a mean age of 67 years. It has been suggested that increased hippocampal volume in people with OSA is due to hippocampal neurogenesis [9]; if so, this factor will decline in importance in older populations, since the rate of adult hippocampal neurogenesis declines steadily with increasing age [52].

The present study found that the extents of cortical atrophy and demyelination are more severe in the CA1 region compared with the EC. Interestingly, the CA1 has been found to be the most vulnerable region of the hippocampus to hypoxic injury [13, 53]. The EC may be protected by the presence of reactive astrocytes. Aviles-Reyes and colleagues suggested that the involvement of reactive astrocytes, specifically the upregulation of S100b and HIF-1α, accounts for the lack of neuronal death seen in animals that are exposed to IH [54].

In the present study, cortical thinning and myelin loss were found in regions involved in the polysynaptic and direct pathways of memory processing (Figure 6a). The molecular cell layer of the dentate and layer 3 of the CA1 are locations of synaptic connections in the polysynaptic pathway; both had decreasing cortical thickness with increasing severity of OSA. Furthermore, we saw decreased myelination in the EC (layers 6 and deep WM), a major output of the polysynaptic pathway. The EC fibers of the direct pathway connect to multiple cortical regions, mostly the association cortices [13, 55]. CA1 layer 3 pyramidal neurons receive synapses from both the polysynaptic and direct memory pathways. The similarity between the locations of synaptic connections and the regions of cortical thinning and demyelination suggests damage to both memory pathways, with implications for episodic, semantic, and spatial memory in people with OSA. Indeed, previous research has found impairment in all three types of memory in people with OSA [56–58].

Figure 6.

Diagram of the polysynaptic (pink) and direct (green) memory pathways in the hippocampus and summarized findings from the present study for the total sample (a), CPAP users (b), and CPAP nonusers/unconfirmed (c) showing regions of decreased cortical thickness (purple boxes) and decreased myelin staining (orange boxes). Notice the overlap between synaptic connections of the memory pathways and regions of cortical thinning and demyelination. Based on circuitry described by Duvernoy et al. [13]. *Trend for a relationship. Thin black arrows denote reduction in cortical thickness or myelination relative to OSA severity. Thick black arrows denote larger reduction in cortical thickness or myelination compared with the total sample.

For cortical thickness measures, there was a general strengthening of the relationship with ODI among CPAP nonusers/unconfirmed, and no change or a weakening of the relationship with ODI for CPAP users. This pattern was evident in the dentate gyrus, CA1, and EC, even though some layers of the EC showed no significant relationship for the whole sample (Figure 6, b and c). This finding suggests that more substantial atrophy occurs in CPAP nonusers/unconfirmed, and that users of CPAP may be associated with less cortical atrophy. If this observation can be confirmed in future studies, then our finding implies that CPAP may be able to protect against hippocampal atrophy and memory impairment. This association is already supported by MRI studies which have found that people with OSA with decreased hippocampal volume experience a subsequent increase in hippocampal volume after as little as 3 months of CPAP treatment [1, 11]. Furthermore, Canessa et al. found parallel improvements in short- and long-term memory after 3 months of treatment [1].

Conversely, CPAP use does not seem to consistently protect against myelin loss. Compared with the whole sample, CPAP nonusers/unconfirmed had stronger relationships between ODI and myelin staining in the EC layers 6 and the deep WM. However, CPAP users also had stronger relationships in the EC layer 6, whereas a slightly weaker relationship was seen in the deep WM (Figure 6, b and c). This inconsistency suggests that CPAP is ineffective at protecting against myelin loss. A previous MRI study reported that 3 months of CPAP treatment provided little improvement in WM integrity for people with OSA, whereas more significant improvements in WM integrity were seen after 12 months of treatment [40]. The duration of CPAP treatment use in the current study was on average 7.1 ± 6.2 years, and yet no improvement in myelination was found. It is possible that WM integrity improves in some brain regions but not in the hippocampus; indeed, Castronovo et al. did not report improvements in the hippocampus [40]. Early intervention may be required to protect against hippocampal WM damage.

The patterns of cortical atrophy and demyelination seen in the present study are similar to changes seen in the hippocampus in mild cognitive impairment (MCI) and AD. Thinning of the CA1 and WM damage are commonly seen in the AD brain [31, 59, 60]. Evidence suggests that WM deteriorates early in the pathological process of AD [61, 62]. Indeed, damage to WM is present in the brains of people with MCI, who have no discernible neuronal loss [29]. Neuronal loss is evident in AD in the CA1, CA2, CA3, CA4, and layer 2 of the EC [22, 25, 26]. Conversely, people with preclinical AD who had Aβ plaques and/or NFTs but no clinical symptoms had no neuronal loss in the CA1 or layer 2 of the EC [63], which is similar to the pattern seen in the present study. In cognitively normal elderly people, atrophy of the CA1 predicts those who will develop MCI and

then AD at follow-up [64]. This trend has implications for OSA, as CA1 atrophy may be a useful biomarker for predicting those people with OSA who are at increased risk of MCI/AD. Improvements in the spatial resolution of MRI may enable this parameter to be used in living patients. Additionally, CPAP treatment could be targeted to these individuals to potentially delay or prevent further neurodegeneration.

There are limitations of the present study that could be improved in future studies, including a larger sample size which would allow potentially confounding variables such as age and disease duration to be controlled for, and the recording of detailed information regarding compliance with CPAP use across the lifespan. An additional limitation of the present study is that the scarcity of tissue restricted the number of hippocampal sections that could be obtained and consequently prevented stereological cell counts, which are often performed in animal brains to obtain estimates of neuronal number. Despite these limitations, the present study has, for the first time, shown that cortical thinning and demyelination occur in specific regions of the hippocampus and EC of people with OSA, and that CPAP use may be protective against cortical thinning but not demyelination.

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