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Brain Diffusion Changes in Obstructive Sleep Apnoea Syndrome

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Key Words
Sleep apnoea · Magnetic resonance imaging · Brain · Neuroradiology

Abstract
Background: Obstructive sleep apnoea syndrome (OSAS) is a disorder characterized by repeated apnoeic episodes during sleep. Neurocognitive changes secondary to OSAS are likely to occur due to hypoxia in certain brain locations. Advances in magnetic resonance imaging technology, such as diffusion-weighted imaging (DWI), enable non-invasive and accurate identification of OSAS-induced changes. ***Objective:*** We aimed to use DWI to investigate changes in the brain secondary to hypoxia in OSAS. ***Methods:*** Eighty-eight patients underwent polysomnography and were classified as non-OSAS, mild-moderate OSAS and severe OSAS sufferers. DWI was used to evaluate 14 areas of the brain, and apparent diffusion coefficients (ADCs) were calculated. We investigated whether there were differences in the ADC values in specific areas of the brain between the non-OSAS and OSAS patients. ***Results:*** We measured the ADC values of the 68 newly diagnosed OSAS patients (21 mild, 15 moderate and 32 severe) and of 20 healthy controls. There were significant increases in the ADC values in the hippocampus, amygdala and putamen in OSAS patients. Compared to the non-OSAS subjects, the ADC values of the putamen in severe OSAS patients, those of the hippocampus in moderate or severe OSAS patients and those of the amygdala in moderate OSAS patients were significantly increased. A negative correlation between the lowest oxygen saturation during sleep and the ADC values of the hippocampus and amygdala was found. ***Conclusions:*** Increased ADC levels in the hippocampus, amygdala and putamen in OSAS patients indicate hypoxia and likely cause vasogenic oedema in specific regions of the brain.

Introduction

Obstructive sleep apnoea syndrome (OSAS) is a common disorder characterized by cessation of breathing due to pharyngeal collapse during sleep [1]. Fragmented sleep leads to daytime sleepiness as well as to changes in mood and cognition [1]. Studies have shown that these changes may be due to not only sleep deprivation but also chronic hypoxia [2, 3]. Repeated hypoxia/reoxygenation and ischaemia result in failure of energy delivery to brain cells. Thus, cells become depolarized, sodium and calcium ions move into the cell and potassium ions leak into the extracellular space [4]. Water enters the cell due to

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the increased ion gradient between the intra- and extracellular compartments, resulting in cytotoxic oedema [4, 5]. Next, depolarized cells release glutamate, which is toxic to neural cells [6]. Additionally, hypoxia can lead to myelin destruction and, in chronic hypoxaemia, to demyelination, which leads to reduced tissue barriers, ion and protein leakage into the extracellular space and escalated vasogenic oedema, all of which will contribute to increased mean diffusivity values [5, 7].

Several neuroradiological studies have shown structural changes non-invasively [8]. Conventional imaging, such as magnetic resonance imaging (MRI), failed to demonstrate the expected cerebral damage due to hypoxia [9]. Advances in neuroimaging technology such as diffusion-weighted imaging (DWI) and MR spectroscopy have enabled non-invasive evaluation of brain function in vivo [3, 5, 9, 10].

DWI is used to evaluate the microstructural characteristics of water diffusion in biological tissues [3]. It provides valuable information about certain pathologies of the brain and reliably distinguishes vasogenic oedema from cytotoxic oedema. DWI provides qualitative information regarding movement of water molecules in the brain tissue. The apparent diffusion coefficient (ADC) is a quantitative measurement of the diffusion of water molecules that is altered in pathologic conditions [11]. ADC values are increased in sub-acute and chronic ischaemia [5]. A hypoxia-related decrease in the value of the ADC results from cell swelling and a reduced extracellular space volume. An increased ADC is associated with reduced cell volumes and increased extracellular space volume. Increased ADC values suggest ultrastructural changes, and therefore, reflect microstructural damage [12, 13]. The DWI can directly measure the oedema occurring secondary to hypoxia. Although several studies have demonstrated the changes secondary to hypoxia in OSAS cases, the relationship between brain diffusion changes and the severity of OSAS had not yet been investigated [10, 11]. Herein, we investigate diffusion changes in different regions of the brain in patients with mild, moderate and severe OSAS and search for an association between diffusion changes and the severity of OSAS.

Methods

Subjects

We evaluated consecutive subjects referred to our sleep laboratory with sleep-related breathing disorders. A total of 106 patients underwent polysomnography (PSG) between August 2011 and January 2012. Of these, 18 patients were excluded for the following reasons: 6 patients refused to enrol in the study, 7 had inadequate sleep quality during PSG, and 5 had coexisting central neurological diseases. Patients with cerebrovascular disease, neurological ischaemic changes, leukoaraiosis, cerebral and cerebellar atrophy, hypothyroidism, hypertension, cardiac arrhythmias, or other sleep disorders, those on medication and those who abused alcohol or drugs that could interfere with sleep or cognitive efficiency were excluded, leaving 88 patients to participate in the study. None of them were receiving continuous positive airway pressure treatment prior to MRI.

The Epworth Sleepiness Scale was used to assess subjective sleepiness [14]. Participants were divided into two groups according to the American Academy of Sleep Medicine 2007 criteria: OSAS and non-OSAS patients [15]. The OSAS group was divided into three subgroups according to the respiratory disturbance index (RDI): mild ($5 \leq RDI < 15$), moderate ($15 \leq RDI < 30$) and severe OSAS ($RDI \geq 30$) [15].

The procedures were performed in accordance with the guidelines of the Helsinki Declaration on human experimentation. Informed consent was obtained from all subjects. The study protocol was approved by the institutional ethical committee.

Polysomnographic Evaluation

A Compumedics E 3142 PSG device was used (Compumedics Inc., Melbourne, Vic., Australia). PSG findings were evaluated based on the guidelines published by the American Academy of Sleep Medicine in 2007, and OSAS was confirmed [15]. The RDI was calculated by dividing the total number of episodes of apnoea, hypopnoea and respiratory-related arousals by the total sleep time. Apnoea was defined as complete cessation of airflow for ≥10 s. Hypopnoea was defined as a reduction of >50% of three respiratory signals, airflow signal or either respiratory or abdominal signals of respiratory inductance plethysmography, with an associated decrease of ≥3% in oxygen saturation or an arousal. OSAS was defined as an apnoea-hypopnoea index ≥5 with associated symptoms (sleep attacks or excessive daytime sleepiness), unsatisfying sleep, fatigue or insomnia, or heavy snoring and/or breathing pauses reported by the subject's partner, or an apnoea-hypopnoea index ≥15 regardless of associated symptoms [15]. Patients with sleep disorders other than OSAS such as upper airway resistance syndrome, periodic leg movement syndrome or narcolepsy were excluded. The PSG data were scored by three investigators (M.E.A., M.B. and L.K.).

MRI Examination

The MRI examination consisted of routine non-contrast brain scanning, including DWI. MRI was performed on a 1.5-tesla system (Siemens, Avanto, Erlangen, Germany). Fast-spin echo T2-weighted images (TR = 4,530 ms, TE = 100 ms) were obtained in the axial and coronal planes. Subjects with normal MRI findings were included. For DWI, a single-shot spin echo-planar pulse sequence (TR = 3,216 ms, TE = 89 ms, field of view = 230 mm, matrix size = 128 × 128, number of acquisitions = 2, slice thickness = 5 mm, slice number = 25, slice orientation = axial plane, scan time = 28 s, interslice gap = 1 mm) was used in all patients with two b-values (0 and 1,000 s/mm^2). The ADC maps were reconstructed with commercially available software. In the patients and controls, 14 distinct neuroanatomical locations that

Table 1. Demographic parameters in non-OSAS and OSAS patient

Variable	Non-OSAS group (n = 20)	OSAS group		
		mild (n = 21)	moderate (n = 15)	severe (n = 32)
Age, years	44.2 (11.2)	44.5 (11.1)	53.8 (11.8)	51.6 (12.1)
Body mass index	31.7 (9.2)	34.5 (8.2)	31.1 (6.1)	37.3 (10.1)
Male gender[1], %	30.0	61.9	73.3	71.9

Data are presented as the mean, with standard deviation in parentheses.
[1] Male gender was significantly higher in mild, moderate or severe OSAS patients compared to the non-OSAS group ($p < 0.05$ for all).

have been previously suggested to be related to satiety-hunger and cognitive function were selected for the analysis [16, 17]. Regions of interest (ROIs) were drawn by experienced radiologists (R.K., A.A.) on the regions identified, and the ADC values were calculated automatically from the ADC map. The ROIs were 110–130 mm^2 in the putamen, 60–80 mm^2 in the amygdala, hippocampal gyrus and globus pallidus, 30–50 mm^2 in the genu and the splenium of the corpus callosum, optic radiation and cingulate gyrus, and 10–30 mm^2 in the cortices (parietal, insular, orbitofrontal), caudate nucleus and posterior limb of the internal capsule. We minimized partial volume effects by inspecting the slices above and below the region to avoid averaging with the cerebrospinal fluid. Similar ROIs were used for an individually selected region in all patients, which were carefully evaluated by the same radiologist, who was blinded to the condition of the subjects. The mean values of the two investigators were calculated for each region.

Statistical Analysis

All statistical analyses were performed using the commercially available SPSS version 16.0 software package (SPSS, Inc., Chicago, Ill., USA). The results are presented as means ± standard deviation. The Kruskal-Wallis test was used to assess differences in the ADC values of each brain location between non-OSAS and mild OSAS patients, or the moderate and severe OSAS patients. Significance was assigned for $p < 0.017$, after Bonferroni correction for multiple comparisons. Spearman's test was used for correlation analysis.

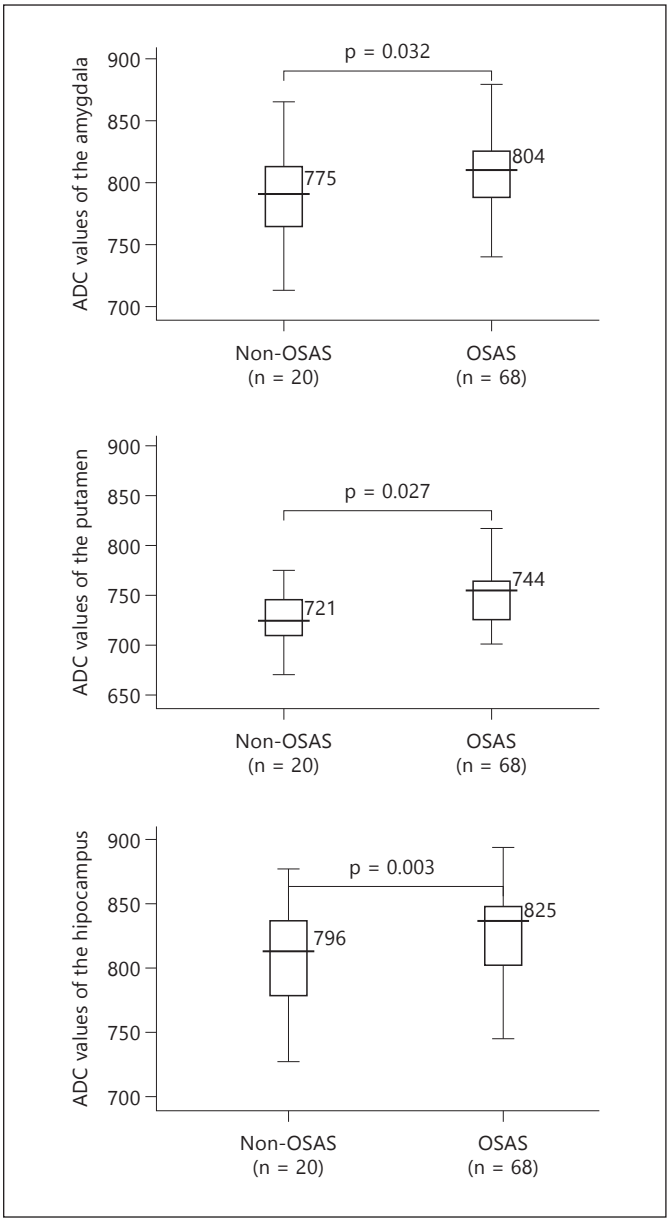

Fig. 1. Box plots of ADC values of specific brain regions in non-OSAS and OSAS subjects. Dark lines within boxes = median values; boxes = interquartile ranges (25–75%); bars = 25% of values outside of the interquartile range.

Results

There were no significant differences in age or body mass index between the OSAS and non-OSAS groups. Male gender was significantly higher in mild, moderate or severe OSAS patients compared to the non-OSAS group ($p < 0.05$ for all; table 1). The ADC values of the hippocampal gyrus ($p = 0.003$), amygdala ($p = 0.032$) and putamen ($p = 0.027$) were significantly higher in the OSA groups (n = 68) compared to the non-OSAS group (n = 20; fig. 1). After Bonferroni correction, there were significant differences between ADC values of the amygdala of non-OSAS and moderate OSAS patients ($p = 0.013$), from the putamen of non-OSAS and severe OSAS patients ($p = 0.012$), and from the hippocampus

of non-OSAS patients and moderate (p = 0.004) or severe OSAS patients (p = 0.011; fig. 2). The mean ADC levels of other brain regions are shown in table 2.

A negative correlation was detected between lowest oxygen saturation and the ADC values of the amygdala (p = 0.025; r = –0.209; fig. 3a) and the hippocampus (p = 0.038; r = –0.190; fig. 3b). A positive correlation was detected between the rapid eye movement (REM), RDI and ADC values of the globus pallidus (p = 0.031; r = 0.231; fig. 3c). The apnoea index was positively correlated with the ADC values of the putamen (p = 0.012; r = 0.266; fig. 3d).

Discussion

We used neurological structural changes using MRI in patients with OSAS. The findings were mainly localized to the hippocampus, putamen and amygdala, which are near neuronal axon connections and are part of the limbic system. In our study, ADC values of the hippocampus, amygdala and putamen were higher in the OSAS group than in the non-OSAS group. These findings could be related to vasogenic oedema with/without neuronal cell damage, and also indicated that OSAS is associated with an altered extracellular/intracellular fluid ratio in these centres. These microstructural changes in OSAS patients could be related to hypoxia.

Few studies have investigated the neurological changes in patients with OSAS [5, 10]. Algin et al. [10] found no differences in DWI measurements of limited brain regions, including the thalamus, hippocampus and frontal lobes between OSAS patients and the control group. Following this study, Kumar et al. [5], using DWI, discovered that OSAS patients had decreased whole brain main diffusions compared to the non-OSAS group. Our study was unique in that it showed increased ADC levels in 14 specific brain regions associated with cognitive, motor function and learning and cardiovascular regulation centres.

There was a significant correlation between the incidence of apnoea per hour during sleep and the putamen ADC values in our study. The putamen has many functions, including control of motor learning, motor performance and tasks, motor preparation, specifying amplitudes of movement, and controlling movement sequences [18–21].

Oxidative stress in OSAS patients can cause cardiovascular complications due to microvascular endothelial dysfunction [22]. In addition to the anterior cingulate

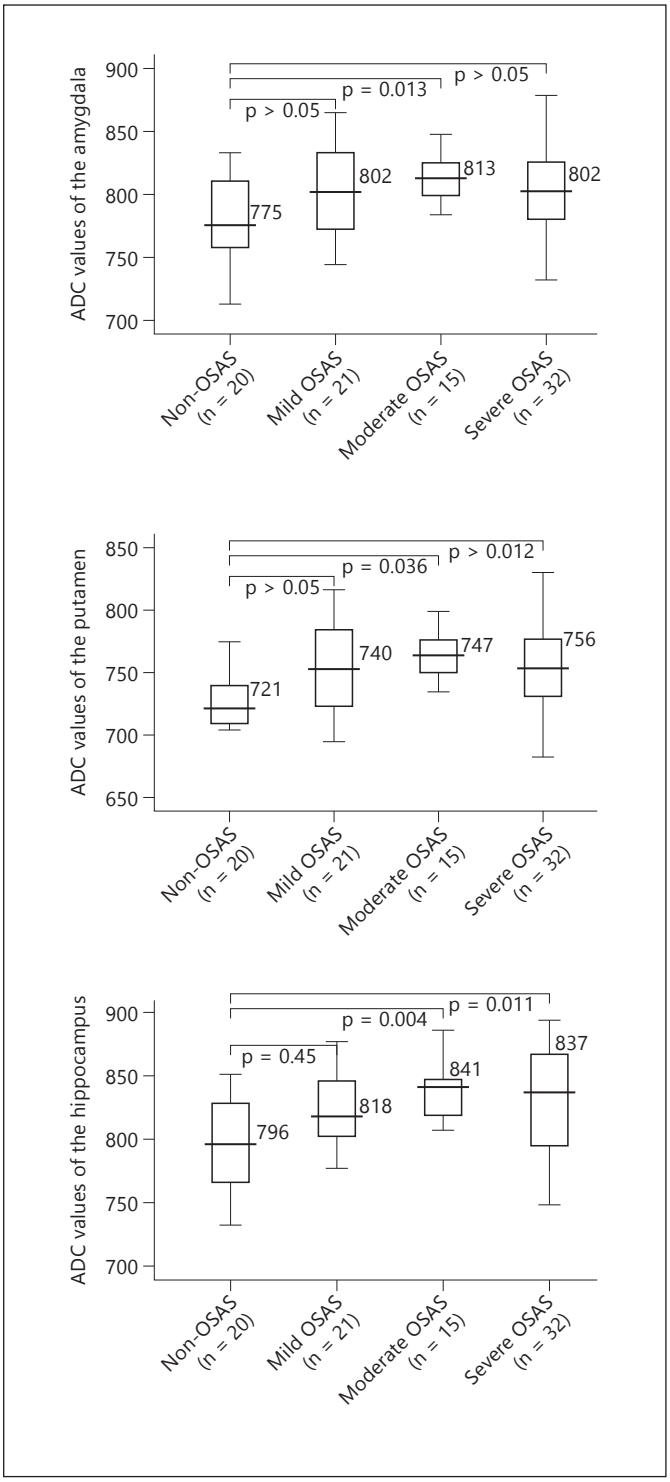

Fig. 2. Box plots of ADC values of specific brain regions according to OSAS severity. Dark lines within boxes = median values; boxes = interquartile ranges (25–75%); bars = 25% of values outside of the interquartile range.

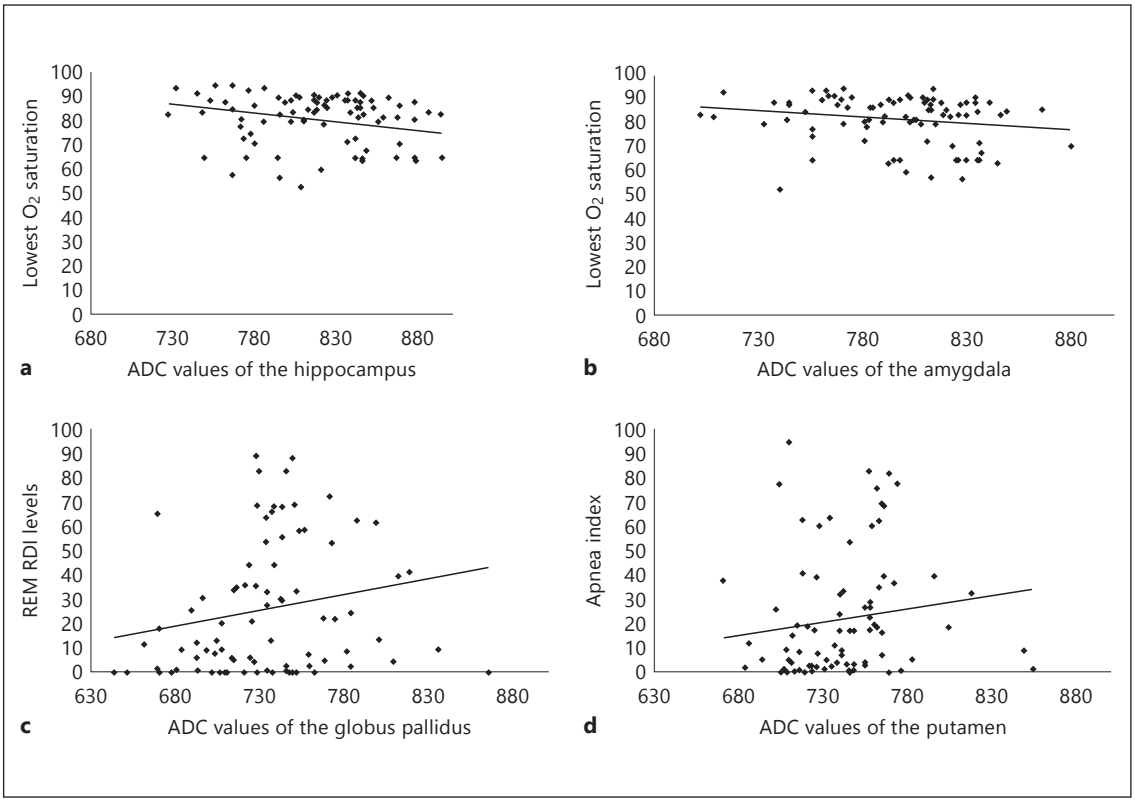

Fig. 3. a Correlation between lowest O_2 saturation and ADC values of the hippocampus ($p = 0.025$; $r = -0.209$). **b** Correlation between lowest O_2 saturation and ADC values of the amygdala ($p = 0.038$; $r = -0.190$). **c** Correlation between REM RDI levels and ADC values of the globus pallidus ($p = 0.031$; $r = 0.231$). **d** Correlation between the apnoea index and ADC ($p = 0.012$; $r = 0.266$).

Table 2. ADC values ($\times 10^{-6}$ mm^2/s) of 11 brain regions of non-OSAS, mild, moderate or severe OSAS patients excluding the putamen, hippocampus and amygdala

	Non-OSAS group (n = 20)	OSAS group		
		mild (n = 21)	moderate (n = 15)	severe (n = 32)
Insular cortex	806 (753–833)	822 (869–847)	788 (747–814)	810 (791–822)
Parietal cortex	758 (732–772)	768 (727–788)	765 (738–781)	740 (757–779)
Orbitofrontal cortex	762 (732–786)	760 (749–787)	763 (748–803)	774 (744–815)
Cingulate gyrus	794 (769–815)	778 (761–794)	786 (766–812)	794 (766–818)
Posterior limb of internal capsula	692 (673–720)	711 (687–738)	687 (675–723)	706 (689–721)
Caudate nucleus	731 (712–745)	709 (694–750)	715 (703–741)	729 (694–752)
Globus pallidus	739 (698–759)	724 (701–751)	733 (704–758)	736 (726–749)
Optic radiation	761 (753–793)	778 (760–782)	761 (746–779)	773 (751–808)
Genu of corpus callosum	797 (748–846)	776 (735–799)	785 (764–807)	782 (746–802)
Splenium of corpus callosum	752 (714–808)	748 (728–795)	723 (710–752)	761 (712–796)
Frontal white matter	777 (757–792)	759 (734–771)	758 (733–788)	759 (739–792)

Data are presented as the median, with the 5th to 95th percentile range in parentheses. No significant difference was present for each ADC value of brain regions listed above in the Kruskal-Wallis test.

cortex and the medial prefrontal cortex, the hippocampus and amygdala also regulate blood pressure [23, 24]. The high ADC levels in the hippocampus and amygdala in the present study may indicate early hypertension, which can lead to cerebral ischaemia via microvascular damage [9, 25]. To avoid the confounding effect of hypertension, we excluded patients with co-existing hypertension from this study.

Additionally, there was a negative correlation between the ADC values of the amygdala and hippocampus and the lowest oxygen saturation levels measured by PSG. These findings suggest that vasogenic oedema in the amygdala and hippocampus increase as hypoxia deepens during sleep. When OSAS severity is classi-fied based on RDI, its impact is observed in similar regions. While this finding does not demonstrate a clear causality, it indicates that the neurologic oedema observed in OSAS patients may be associated with hypoxic interference.

As the RDI values measured during REM sleep increased, the ADC values of the globus pallidus also increased. Increased respiratory disturbances during REM sleep are associated with increased complications related to sleep deprivation, such as hypertension, memory disturbances, concentration problems and impaired motor coordination. Of the 14 brain regions measured, only the ADC value of the globus pallidus was positively correlated with the REM and RDI values. Considering that the main role of the globus pallidus is control of motor functions, we can speculate that the increased ADC values of this region could account for the motor coordination difficulties of OSAS patients. Tests to evaluate the motor and cognitive dysfunctions in OSAS patients, which were absent from our current study, are important for identifying associations between the pathological findings and their clinical implications. This issue is likely to be the topic of future studies.

We did not find any correlation between Epworth Sleepiness Scale and ADC values in any brain region. The non-OSAS group comprised subjects referred to the sleep laboratory complaining of sleepiness and snoring. As a limitation of this study, we did not find a significant difference between ADC values obtained from the amygdala of non- and severe OSAS patients, although we did find significance between non- and moderate OSAS patients. The association between RDI and hypoxia was indirect. There was a negative correlation between the lowest oxygen saturation and the ADC values of the amygdala. It is likely that the significance between the ADC values of the amygdala of non- and severe OSAS patients will be demonstrated in a study performed with a greater number of patients.

The ADC values increased not only in the severe OSAS subgroup but also in the mild OSAS subgroup in the hippocampus. These findings suggest vasogenic oedema also in the brain tissue of patients in the mild OSAS subgroup. However, due to the lack of detailed information regarding the clinical implications of these radiological changes, further interpretation was regrettably not possible. These radiological changes, their clinical significance and their impact on treatment options should be investigated in further studies. Interestingly, we noticed increased ADC values in the putamen, hippocampus and amygdala of newly diagnosed OSAS patients, the clinical significance of which is as yet unknown.

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