Daytime Impairment and Neurodegeneration in OSAS
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Study Objective: Controversy surrounds the pathogenesis of neurocognitive daytime dysfunction exhibited by patients with obstructive sleep apnea syndrome (OSAS). Underlying brain dysfunctions and damage have long been suspected as a cause of some of this impairment. Neuroimaging has enabled scientists to test these long-held theories. This paper is based on a comprehensive review of recent publications on neuroimaging studies in this area. It seeks to highlight results of recent research, which suggest connections between persistent neurocognitive daytime impairment of executive functions, underlying signs of cerebral metabolic impairment and neurodegeneration, considering possible cerebrovascular impairment in OSAS patients. We propose the existence of a neurodegenerative process.

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INTRODUCTION

OBSTRUCTIVE SLEEP APNEA SYNDROME (OSAS) IS A SLEEP DISORDER, INVOLVING THE REPETITIVE OCCURRENCE OF PARTIAL (HYPOPEANEA) OR COMPLETE (apnea) interruptions of airflow during sleep. The severity of OSAS is determined by the frequency of obstructive respiratory events, expressed as the apnea-hypopnea index (AHI).

OSAS patients display daytime sleepiness, mood disturbances, and cognitive impairment.1 Obstructive sleep apnea is closely associated with obesity and aging.2 OSAS has a high cardiovascular comorbidity, and some authors see a potential link between OSAS and dementia.3 Apolipoprotein E (ApoE) genotype epsilon 4 is a well-known risk factor for Alzheimer disease.4 Associations between ApoE genotype epsilon 4 subtype and vascular dementia have been demonstrated.5,6 The Wisconsin Sleep Cohort Study showed a significantly higher probability of moderate to severe (AHI≥15) sleep disordered breathing among participants with ApoE genotype epsilon 4 (12%), independent of age, sex, BMI, and ethnicity than in subjects with an AHI<15 (7%). The mean AHI among participants with ApoE genotype epsilon 4 (28% of the cohort) was significantly higher (6.5 vs. 4.8; P = .01) than in subjects without this genotype.7 In another population-based study, the presence of ApoE genotype epsilon 4 was associated with an increased odds ratio for OSAS.8

Daytime impairment in OSAS patients has long been suspected to be a consequence of underlying brain dysfunction and/or damage. This has led to increasing research, particularly using neuroimaging in OSAS patients, in order to investigate possible neurodegenerative and metabolic aspects. But we found no comprehensive review summarizing the results of neuropsychological daytime impairment and linking them to recent neuroimaging studies and research on cerebrovascular impairment in OSAS patients. Therefore we have attempted to make a contribution to filling this gap.

METHODS

This study will first look at research results relating to daytime and neurocognitive impairment in OSAS patients, analysing the nature of the impairment and showing which functions are affected. Then we outline the results of a comprehensive literature review from 1995 to 2005 using PubMed and Medline on neuroimaging studies in OSAS. Furthermore we summarize research results of cerebrovascular impairment in OSAS.

The closing discussion will consider the case for links between OSAS and cerebral metabolic dysfunctions, neurophysiological changes, and neurodegeneration including cerebrovascular factors.

Neuropsychological Functioning

Daytime sleepiness

Daytime sleepiness is defined as a heightened propensity to fall asleep while involved in activities that require alertness. Currently, the most common methods of measuring objective levels of daytime sleepiness are the Multiple Sleep Latency Test (MSLT)9 and the Maintenance of Wakefulness Test (MWT).10 Questionnaire scales like the Epworth Sleepiness Scale (ESS)11 and the Stanford Sleepiness Scale (SSS)12 are used for a subjective quantification. Patients with obstructive sleep apnea syndrome show excessive levels of both subjective and objective daytime sleepiness.13-18 Using the ESS, the Sleep Heart Health Study was able to distinguish between varying degrees of OSAS.19 Other studies demonstrated a positive correlation between the severity of OSA according to the AHI and the extent of daytime sleepiness.20-22

On the other hand there was an association of daytime sleepiness with the lowest oxygen saturation,23 and the number of dips less than 4% in oxygen saturation (hypopneas).24 Experimentally-induced sleep fragmentation resulted in increased daytime sleepiness in healthy subjects.25-26 Sleep fragmentation and other “sleep structure disturbances” are considered the main causes of daytime sleepiness in OSAS patients.13-15,22,27,28 A positive correlation between slow wave activity in the first NREM episode and the MSLT was shown by Heinzer et al (2001).29 Brzeczka (2003...
demonstrated that hypercapnic OSAS patients had a more marked sleepiness than patients without hypercapnia. 14

Another important factor in OSAS patients is the association of daytime sleepiness with elevated interleukin-6 and TNF-alpha levels, which are independent of BMI. 34 Carpagnano et al (2002) demonstrated the highest elevation of interleukin-6 levels among OSAS patients compared to obese controls and normal weight subjects. 33 A marked decrease in daytime sleepiness in OSAS patients was demonstrated after the administration of etanercept, a tumor necrosis factor-alpha antagonist, which led to diminished levels of tumor necrosis factor-alpha and interleukin-6. 32 Yokoe et al (2003) showed a decrease in interleukin-6 after CPAP treatment. 30

Hypocretin-1 (orexin A) plays an important role in regulating arousal and sleep. 35 The majority of patients with narcolepsy-cataplexy, which is associated with excessive daytime sleepiness, displayed undetectable levels of cerebrospinal fluid (CSF) hypocretin-1. 37,38 Hypocretin-1 shows normal levels in cerebrospinal fluid of untreated 39 and treated OSAS patients. 40

Treatment with CPAP improves objective daytime sleepiness, as measured by the MSLT, the MWT, and subjective daytime sleepiness (ESS). A meta-analysis of randomized controlled trials of CPAP therapy in adults with mild to severe OSAS showed that CPAP led to a significant decrease in subjective and objective daytime sleepiness values. The effect was greater in studies with participants with an AHI ≥30 (severe OSAS) and excessive daytime sleepiness (ESS score ≥11). 49

Vigilance

Simple and choice reaction time tasks are used to assess sustained attention, defined as the impairment of the ability to sustain attention for extended periods, as one part of the construct of vigilance. The psychomotor vigilance task (PVT) and Oxford Sleep Resistance Test (OSLER) are two of common tasks measuring sustained attention. Sleep-restricted healthy adults show vigilance impairment in the PVT parameters. Both decreased sustained attention and decreased divided attention contribute to the impairment of daytime functioning in OSAS patients. The decline in vigilance measured by simple and choice reaction time tasks appears also closely linked to nighttime sleep disruption in OSAS. Montplaisir et al (1992) and Bedard et al (1991) demonstrated that vigilance was affected by sleep fragmentation in subjects with obstructive sleep apnea. Cheshire et al (1992) found the strongest correlation between the AHI and hypoxemia to vigilance measures. Contrary to these findings, Sauter et al (2000) could not show any differences of vigilance impairment between OSAS patients with AHI ≥40 and AHI <40. Furthermore patients with high intelligence showed no difference in vigilance levels compared to highly intelligent controls, but OSAS patients of normal intelligence exhibited a significantly worse performance in sustained attention compared to normal intelligent controls.

OSAS patients have increased incidents of automobile accidents compared to controls. 63-69 “Steer Clear” is a common driving simulation task, where patients with severe OSAS showed a reduced driving simulation performance. In other driving simulation tasks, a reduction in performance was also found in moderately affected OSAS patients.

After CPAP treatment, a decrease in vigilance impairment and an improvement in driving performance were recorded in subjects with obstructive sleep apnea syndrome.

Cognitive Dysfunction

Daytime impairment of OSAS patients is complex. At present, there is no agreement on the pathogenesis or the pattern of neuro-psychological and neurocognitive dysfunctions. One problem is the lack of common standards, with researchers using a variety of different study designs and test batteries. Even a single task measurement for example in the field of alertness and attention is subject to differing interpretations. 60,74 There are different theoretical assumptions in sub-summarizing psychological functions under the construct of executive functions. Psychologists define this construct as the ability to develop and sustain an organized, future-orientated, and flexible approach to problem situations. In sleep literature there are different approaches. Beebe and Gozal propose the following construct of the executive functions: behavioral inhibition, set-shifting, self-regulation of affect and arousal, working memory, analysis/synthesis, and contextual memory based on the theoretical models by Barkley, Pennington, and Fuster. The construct of executive functions used by Fulda and Schulz (2003) and Decary et al (2000) according to Lezak is more restricted including concept formation, reasoning and executive functions: volition, planning, purposive action, and effective performance.

Decary et al (2000) summarized the main impaired cognitive functions in OSAS as impaired general intellectual functioning, deficits in attentional functioning, memory and learning deficits, the impairment of executive functions, and decreased motor performance. Engleman et al (2000) performed a meta-analysis of case-control studies and provided effect sizes integrating results across studies statistically. They showed that cognitive deficits broadly worsen with disease severity. Large average values for attentional (effect size =1.0) and executive cognitive scores (effect size =0.9) were demonstrated. Memory related performance scores had moderate values (effect size =0.6). A meta-analysis of norm-referenced and case-controlled data by Beebe et al (2003) showed impairments in vigilance, executive functioning, and motor coordination in OSAS patients. Another meta-analysis by Fulda and Schulz (2003) reviewed 55 studies (including case-control and norm-referenced studies) but omitted computer-assisted tasks for methodological reasons. They found moderate to large reduction in visual delayed retrieval, mental flexibility, and driving simulation in sleep related breathing disorder patients. Only small to moderate reductions were shown in focused attention, sustained attention, verbal delayed memory retrieval, verbal fluency, and composite measures of general intellectual functioning.

Patients with sleep related breathing disorders have been examined in population-based studies. The Wisconsin Sleep Cohort Study (median AHI=1.24, range: 0-94, 199 participants with AHI ≥5,642 participants with AHI <5) showed a significant negative correlation between logarithmically transformed AHI (log AHI) and the psychomotor efficiency score independent of age, gender, and educational status (P =.017). This relationship was not explained by self-reported sleepiness. The memory score did not reveal any correlation with logAHI. Patients with milder forms of sleep related breathing disorders did not show any signs of cognitive impairment as measured by the Delayed Word Recall
Some studies demonstrated a persistent impairment in executive functions after CPAP treatment.43,80-83 OSAS patients with cognitive dysfunctions but without vigilance impairment before treatment displayed only partial reversibility of the cognitive dysfunction after CPAP.52 When compared to a sham-CPAP OSAS group, patients without subjective (ESS) and objective (MSLT) daytime sleepiness did not show any improvement in cognitive tasks.84 Jones and Harrison (2001) state that executive impairment in OSAS patients appears to be more closely related to hypoxic events rather than daytime sleepiness.85 Cognitive impairments in attention/vigilance (sustained attention), and memory functioning were attributed by some authors to extensive daytime sleepiness.77,54,55

Mood

Restricting sleep to 4-5 hours for a week led to mood disturbances in healthy adults in research by Dinges et al (1997).52 Depressive symptoms have also been reported in OSAS patients.73,86-92 Bardwell et al (1999) demonstrated an association between anger and vigor and sleep variables in OSAS.99 Unlike OSAS patients without depression, those who were depressed exhibited negative correlation between the MSLT and MWT scores and disturbed sleep, with decrease in total sleep time, decrease in stage 3 sleep, and an increase in stage 1 sleep.90

An improvement of mood after CPAP has been reported.72,88,91,92 However, Munoz et al (2000) could not show any improvement in depression and anxiety after CPAP treatment.47

Neurodegeneration in OSAS

Brain Morphology and Function

Neurophysiological studies found prolonged N2 and P3 latencies of event-related evoked potentials in OSAS patients.82,93-96 Subcortical structures, like the limbic system and the prefrontal cortex, are involved in the generation of these potentials.95,97 After CPAP treatment, although the impaired N2 and P3 latencies showed improvement, they did not return to normal levels.82,94,95

Using magnetic resonance imaging Davies et al (2001) found subclinical cerebrovascular disease in OSAS patients and matched controls but did not uncover any differences between these groups.88 High-resolution T1-weighted magnetic resonance imaging showed brain morphology changes in OSAS patients. Macey et al (2002) found loss of gray matter, which often occurred unilaterally (right) in areas including the frontal and parietal lobe, anterior cingulate, hippocampus, and cerebellum.98 Morrell et al (2003) found significantly lower gray matter concentration in the right hippocampus of OSAS patients compared to controls.100 However an optimized voxel-based measurement could not demonstrate proof of any differences in total gray matter volume between OSAS patients (AHI>30) without comorbidities and age-matched controls.100 Single Photon Emission Computed Tomography (SPECT) study was performed in OSAS patients, with tracer administration between 2 am and 4 am, during sleep stage 2.102 Five of 14 OSAS patients examined showed hyperperfusion. Semiquantitative analysis of the regional perfusion indices showed hyperperfusion of the left parietal region. Both effects were reversible after CPAP treatment.102 Functional imaging of working memory in patients with obstructive sleep disordered breathing and controls showed significantly slower working memory speed in OSAS patients than controls. There was absence of dorsolateral prefrontal activation, regardless of nocturnal hypoxemia in OSAS subjects. There was no significant change in behavioral performance and persistent lack of prefrontal activation after 8 weeks of CPAP administration.103

Using the magnetic resonance spectroscopy an impairment of cerebral metabolism in OSAS was found. A significantly lower N-acetylaspartate/choline (NAA/choline) ratio in the cerebral white matter of moderate to severe sleep apnea patients compared with mild sleep apnea patients and healthy subjects was demonstrated by Kamba et al (1997).106 Alchanatis et al (2004) demonstrated significantly reduced N-acetylaspartate/creatine and choline/creatine ratios and significantly lower absolute concentrations of N-acetylaspartate and choline in frontal white matter of OSAS patients without cardiovascular disease compared to healthy controls.105 Furthermore a significant correlation between the AHI and the NAA/choline ratio for cerebral white matter was shown in OSAS.106 On the other hand Bartlett et al (2004) demonstrated lower levels of hippocampal creatine-containing compounds in OSAS patients in comparison to controls.107

In Positron Emission Tomography studies (PET), the most active brain regions in wakefulness were located in the prefrontal and anterior cingulate cortex.108 After 24 hours of sleep deprivation, healthy subjects displayed significant decreases in the regional cerebral metabolic rate of glucose as measured by PET, predominantly in the thalamus, the prefrontal, and posterior parietal cortices. These deactivations were associated with impairment in alertness and cognitive performance.109 During normal REM sleep deactivation of the dorsolateral prefrontal cortex has been found in PET and quantitative EEG studies.10 Low-resolution brain electromagnetic tomography showed enhanced delta activity in the medial prefrontal cortex, which spread into the anterior cingulate and the orbitofrontal cortex during sleep stage 4 in normal sleepers.111

Tables 1 and 2 summarize the mentioned neuroimaging studies in OSAS patients.

Cerebral Blood Flow and Oxygenation

Studies on sleep apnea and cerebrovascular dysfunction were performed with the noninvasive Doppler technique. There was a gradual increase of the cerebral blood flow velocity with a steep rise at the end of apnea and a rapid decrease after apnea termination and at the onset of ventilation during obstructive apneas.112-116 Transcranial measurement of cerebral blood flow velocity of the middle cerebral artery found decreased intracranial hemodynamics before sleep, during sleep, and upon awakening in patients with OSAS compared to controls.117 Cerebral vascular reactivity to hypercapnia showed impairment in OSAS patients.113,118 Near-infrared spectroscopy showed consistent decrease in oxyhemoglobin and increases in deoxyhemoglobin and total hemoglobin in cerebral tissue during obstructive apneas at every sleep stage. These results were significantly (P<.001) higher in REM sleep than in NREM sleep.12 Near-infrared spectroscopy also revealed reduced cerebral tissue oxygenation, which was associated with changes in the intracellular cytochrome-oxidase oxidation state during obstructive sleep apnea.121

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Association With Cerebrovascular Disease

There is no clear evidence that obstructive sleep apnea is an independent risk factor for strokes, but there are some potential mechanisms connecting the two. OSAS patients display many risk factors such as obesity, metabolic disturbances, hypertension, cardiovascular disease, alterations in coagulation parameters, and higher blood viscosity. The elevation of inflammatory cytokines in OSAS contributes to increased coagulation. These factors can increase cerebrovascular risk in OSAS patients. Several retrospective studies have reported an association between snoring and the development of strokes. Prospective studies, however, did not show any independent association between sleep-disturbed breathing and strokes.

The reported prevalence of sleep apnea following strokes varies between 44% and 94%. Nighttime stroke events seem to have a higher prevalence in patients with sleep disordered breathing. Some studies could not find any correlations between neurologically topography and the presence or type of sleep related breathing disturbances. However, patients with lacunar strokes had worse sleep disordered breathing than subjects with anterior circulation cortical strokes. No changes in the frequency of obstructive apneas 3 months after strokes, but a significant decrease in central apneas was shown by Parra et al (2000). On the other hand, Harbison et al (2002) found an improvement of the AHI in the 6-9 weeks follow up.

DISCUSSION

OSAS patients show a broad pattern of daytime impairment including excessive daytime sleepiness, decreased vigilance and attention capacity, reduced performance in visual and verbal delayed retrieval, the impairment of executive functioning, decrease in motor performance, and depressive symptoms. A variety of concomitant factors contribute to daytime sleepiness in OSAS patients including hypoxia, the level of severity of AHI, sleep fragmentation with consecutively elevated inflammatory cytokines, and a loss of slow wave activity. The exact pattern of the pathogenesis of daytime sleepiness differs from individual to individual depending on the degree of OSAS, concomitant sleep variables, anatomical differences, and risk profiles. Some studies attributed the cognitive impairment in attention/vigilance (sustained attention), and memory functioning to extensive sleep fragmentation with consecutively elevated inflammatory cytokines, and a loss of slow wave activity. The exact pattern of the pathogenesis of daytime sleepiness differs from individual to individual depending on the degree of OSAS, concomitant sleep variables, anatomical differences, and risk profiles. Some studies attributed the cognitive impairment in attention/vigilance (sustained attention), and memory functioning to extensive sleep fragmentation with consecutively elevated inflammatory cytokines, and a loss of slow wave activity.
Several studies have attempted to locate the area of cerebral impairment, which leads to impairment of executive functions. According to Kane and Engle (2002) the prefrontal cortex (PFC) has a unique executive attention role in actively maintaining access to stimulus representations and goals in interference-rich contexts. Sleep deprivation associated with disease-related sleep fragmentation produces neurocognitive performance decrements similar to those associated with sleep restriction according to Durmer and Dinges (2005). In their focus on the impairment of executive functions, Jones and Harrison found that after sleep restriction and sleep deprivation, normal sleepers showed striking similarities to OSAS patients in cognitive impairment. For example, there was a decline in short-term recall, working memory performances, and reduced cognitive task learning after sleep restriction in normal sleepers. During a working memory task, an absence of prefrontal activation was demonstrated in OSAS patients. Furthermore, there was no significant change in performance and a persistent lack of prefrontal activation after 8 weeks of CPAP treatment. According to Thomas et al (2005) the persistence of prefrontal perfusion absence after therapy suggests underlying permanent neuronal degeneration in this region. These findings may show a link to the cognitive daytime impairment of executive functions in OSAS patients.

The fact that prefrontal areas, which control executive functions, are especially vulnerable to sleep restriction and need sleep-related recovery, is highly significant for OSAS patients. Ficker et al (1997) showed hyperperfusion of the prefrontal regions of OSAS subjects in sleep, which indicates that the normal restorative function of sleep is disrupted by these changes. Proton magnetic resonance spectroscopy showed lower n-acetylaspartate/choline ratio for cerebral white matter in OSAS patients than in normal sleepers, indicating signs of axonal injury or glyosis. Alchanatis et al (2004) showed metabolic changes in the frontal white matter of OSAS patients with a decrement of choline. They hypothesize that OSAS induces brain metabolic impairment through a unique combination of fluctuating hemodynamic impairment, sleep fragmentation, and intermittent hypoxia.

Table 2 — MRT* Studies in OSAS Patients

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Technique</th>
<th>Participants</th>
<th>Results</th>
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<tbody>
<tr>
<td>Davies et al. 2001</td>
<td>MRTv</td>
<td>45 OSAS male patients AHI&gt;5, mean: AHI 29.1 (SD 13.4), age 51.7 (SD 10.4), BMI 30.9 (SD 2.8)</td>
<td>abnormalities on cerebral MRT were common in both groups</td>
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<td></td>
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<td>45 controls, mean: AHI 1.7 (SD 1.6), age 52.2 (SD 10.4), BMI 30.5 (SD 2.4)</td>
<td>increase in blood pressure in OSAS</td>
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<tr>
<td>Macey et al. 2002</td>
<td>hr-MRT*, T1-weighted VBM**</td>
<td>21 male OSAS patients, mean: AHI 34 (SD 20), BMI 30 (SD 4), age 49 (SD 11)</td>
<td>no increase in MRT evident subclinical cerebrovascular disease in OSAS patients compared to matched controls</td>
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<td></td>
<td></td>
<td>21 controls, mean: BMI 27 (SD 4), age 47 (SD 11)</td>
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<tr>
<td>Morrell et al. 2003</td>
<td>hr-MRT*, T1-weighted VBM**</td>
<td>7 right handed male OSAS patients, median: age 50 (range 28-65), AHI 28 (range 25-40)</td>
<td>gray matter loss in OSAS: often unilateral (right)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 healthy controls matched for handedness and weight</td>
<td>Frontal, parietal cortex; temporal lobe; anterior cingulate; right hippocampus; cerebellum</td>
</tr>
<tr>
<td>O'Donoghue et al. 2005</td>
<td>hr-MRT*, T1-weighted VBM** optimized version</td>
<td>27 male OSAS patients AHI&gt;30, mean: AHI 71.1 (SD 17), BMI 33.2 (SD 4.7), age 45.7 (SD 10.1)</td>
<td>extent of gray matter loss increased with severity of OSAS</td>
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<td>24 controls, mean: AHI 5.9 (SD 4.7), BMI 25.3 (SD 2.8), age 43.3 (SD 9.4)</td>
<td>significantly lower (p=0.004) gray matter concentration in OSAS patients within the right hippocampus</td>
</tr>
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<td></td>
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<td>7 right handed male OSAS patients, mean: age 50 (range 28-65), AHI 28 (range 25-40)</td>
<td>no further focal gray matter differences</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 healthy controls matched for handedness and weight</td>
<td>no difference in total gray matter volume between patients and controls</td>
</tr>
<tr>
<td>Thomas et al. 2005</td>
<td>functional MRTv</td>
<td>15 male, 1 female OSAS patients, AHI&gt;30, mean: age 40.3 (SD 7.3), BMI 26.2 (SD 1.8)</td>
<td>working memory speed in OSAS patients was significantly slower than in controls</td>
</tr>
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<td>11 male 5 female controls, mean: age 37.6 (SD 6.3), BMI 23.9 (SD 0.8)</td>
<td>absence of dorsolateral prefrontal activation during the working memory task in OSAS</td>
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<td></td>
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<td>after CPAP persistence of the lack of dorsolateral prefrontal activation</td>
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5magnet resonance tomography, 6apnea-hypopnea index (number of apneas and hypopneas per hour), 7body mass index (in kg/m²), *high-resolution magnet resonance tomography, **voxel-based measurement

According to Thomas et al (2005) the persistence of prefrontal perfusion absence after therapy suggests underlying permanent neuronal degeneration in this region. These findings may show a link to the cognitive daytime impairment of executive functions in OSAS patients. The fact that prefrontal areas, which control executive functions, are especially vulnerable to sleep restriction and need sleep-related recovery, is highly significant for OSAS patients. Ficker et al (1997) showed hyperperfusion of the prefrontal regions of OSAS subjects in sleep, which indicates that the normal restorative function of sleep is disrupted by these changes. Proton magnetic resonance spectroscopy showed lower n-acetylaspartate/choline ratio for cerebral white matter in OSAS patients than in normal sleepers, indicating signs of axonal injury or glyosis. Alchanatis et al (2004) showed metabolic changes in the frontal white matter of OSAS patients with a decrement of choline. They hypothesize that OSAS induces brain metabolic impairment through a unique combination of fluctuating hemodynamic impairment, sleep fragmentation, and intermittent hypoxia. These
findings are another link between executive impairment in OSAS and possible underlying brain impairment in frontal areas.108 This impairment of frontal white matter could also contribute to persistent depressive symptoms in OSAS patients.

Initial results using high-resolution MRT showed gray matter loss in severe OSAS unilaterally (right) in the frontal and parietal lobes, anterior cingulate, hippocampus, and cerebellum.49 Another study also demonstrated gray matter loss in the right hippocampus in OSAS patients.109 This finding underlines possible impairment of memory functions. But there are also contradictory findings. O’Donoghue et al (2005) could not find any gray matter changes in OSAS patients without comorbidities compared to age-matched controls using optimized voxel-based measurement.109 Yet neuropsychological studies showed prolonged N2 and P3 latencies of event-related evoked potentials even after CPAP treatment in OSAS patients.82,93-96 Although there was an improvement after CPAP treatment of the impaired N2 and P3 latencies, there was no return to normal latencies.82,93-95 These potentials have been shown to reflect cognitive processing in a large number of studies on normal adults. Subcortical structures, like the limbic system and the prefrontal cortex, are involved in the generation of these potentials.85,97 Probable underlying hypoxic brain damage in these regions in OSAS patients has been suggested as an explanation of these pathological findings.82

Cerebrovascular dysfunction has been demonstrated in OSAS patients.116-119 Near-infrared spectroscopy showed decreases in oxyhemoglobin and increases in deoxyhemoglobin in cerebral tissue during apneas in OSAS.120 There was reduced oxygenation of cerebral tissue in this patient group.121 These results show possible pathogenetic factors contributing to hypoxic brain damage during apneas.

Associations of OSAS with cerebrovascular disease and vascular dementia are possible, but there is still no clear research evidence. Antonelli Incalzi et al (2004) found some analogy in the neuropsychological dysfunction in OSAS patients and the cognitive pattern in multi-infarct dementia. They hypothesize the sharing of mainly subcortical damage by these groups, but with differences in location and severity, and thus clinical effects.167 The risk profiles of OSAS patients (obesity, metabolic changes, hypertension, increase in coagulability, elevated inflammatory cytokine levels) and the high prevalence of sleep disordered breathing after strokes suggest a possible correlation of cerebrovascular impairments with hypoxic brain damage in OSAS patients. Harbison et al (2003) showed an association between pre-stroke white matter disease severity and AHI. White matter disease in frontal and basal ganglia areas had the strongest association with AHI.168 These findings underline the possible connection between the impairment of executive functions and possible cerebrovascular impairment in frontal cerebral areas. Jones and Harrison (2001) have already shown there is an association between hypoxemia and the level of executive impairment.80 Other studies could not show any correlation between neurological topography and the presence or type of sleep related breathing disturbances.162,163 On the other hand, some investigations demonstrated that patients with lacunar strokes show worse sleep disordered breathing than subjects with anterior circulation cortical strokes.158,164 More research is needed to explain these findings.

So far we have some hints and possible correlations between the neurocognitive daytime impairment especially of the executive function and neuroimaging and neurophysiological findings in OSAS patients. But there are still contradictory results concerning neurodegenerative changes and neurocognitive impairment in OSAS. In part, this confusing situation is due to different concepts and neuropsychological definitions of the executive functions. Agreement is needed on the memory functions and their relationship to the construct of executive functions. But there are also discrepancies and inconsistencies in task classification and the absence of any unifying clarification of neurocognitive dysfunction and deficits in OSAS. As Decary et al (2000) proposed, a test battery is needed for OSAS patients.100

Research into the neurodegenerative mechanisms in OSAS is in its infancy. Further studies especially using optimized neuroimaging techniques during the performance of special cognitive tasks and anatomical neuroimaging studies in OSAS are required in order to clarify the current, sometimes contradictory, findings. More attention should also be paid to the divergence of OSAS patient groups regarding comorbidities, severity and duration of the illness, age subgroups, possible risk factors (positive cardio- and cerebrovascular profiles), protective factors, and familial aggregation. These factors can have an important impact on research results. Thus, further research must take into account the impact of these factors on neurocognitive dysfunction and neurodegenerative processes. Based on current research results, we suggest a neurodegenerative process, which depends in its degree on the severity, duration and comorbidities in OSAS. This process, which begins with hypoxia in cerebral tissue during apneas, can be halted by treatment with CPAP, but some irreversible dysfunctions may persist even after treatment.

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