Association of Hypoxia Measured by Oxygen Desaturation Index (ODI) in OSA with Delis-Kaplan Executive Function System (D-KEFS) Tests in Middle-Aged and Older Adults

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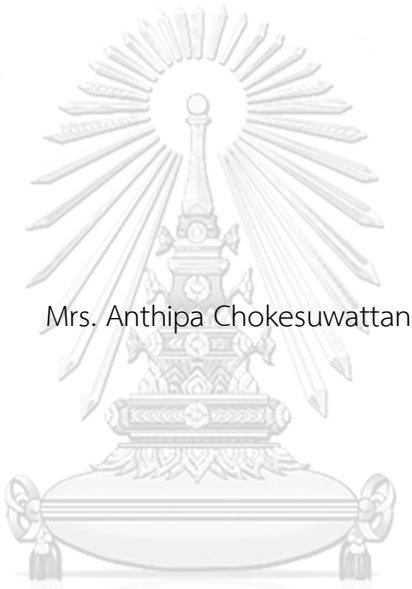

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ความสัมพันธ์ของระดับการขาดออกซิเจนซึ่งวัดโดย Oxygen Desaturation Index (ODI) ในภาวะหยุดหายใจขณะหลับจากการอุดกั้นและพุทธิปัญญาซึ่งวัดโดย Delis-Kaplan Executive Function System (D-KEFS) ในผู้ใหญ่วัยกลางคนและผู้สูงอายุ

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วัตถุประสงค์: ศึกษาความสัมพันธ์ระหว่างความผิดปกติทางพุทธิปัญญา โดยเฉพาะ ทักษะในการบริหาร วางแผน และจัดการ และการเปลี่ยนแปลงของสมอง กับการขาดออกซิเจนในภาวะหยุดหายใจขณะหลับจากการอุดกั้นในผู้ใหญ่วัยกลางคนและผู้สูงอายุ วิธีการวิจัย: ผู้เข้าร่วมวิจัยซึ่งเป็นผู้ที่เพิ่งได้รับการวินิจฉัยว่ามีภาวะหยุดหายใจขณะหลับจากการอุดกั้นขั้นปานกลางถึงรุนแรงจากโรงพยาบาลจุฬาลงกรณ์จากการตรวจการหายใจระหว่างนอนหลับ จะได้รับการตรวจความผิดปกติทางพุทธิปัญญาและตรวจภาพถ่ายคลื่นสะท้อนแม่เหล็กไฟฟ้าของสมอง ผลการศึกษา: ผู้เข้าร่วมการวิจัยทั้งหมด 17 คน เป็นผู้ชาย 8 (47%) คนและผู้หญิง 9 (53%) คน ค่าอายุมัธยฐาน คือ 57 ปี และค่า apnea-hyponea index (AHI) มัธยฐานคือ 60.6 ไม่พบความสัมพันธ์ระหว่างความผิดปกติทางพุทธิปัญญาหรือความเปลี่ยนแปลงของสมองกับระดับการขาดออกซิเจนในภาวะหยุดหายใจขณะหลับจากการอุดกั้น เมื่อแบ่งผู้เข้าร่วมวิจัยเป็นสองกลุ่มคือกลุ่มที่มีการขาดออกซิเจนรุนแรงและไม่รุนแรง โดยคำนึงว่ามีระดับการขาดออกซิเจนมากกว่าหรือน้อยกว่าค่ามัธยฐาน พบว่ากลุ่มที่มีการขาดออกซิเจนถี่กว่ามีความหนาของผิวสมองบางลงบริเวณ superior parietal ด้านขวา และกลุ่มที่มีระดับออกซิเจนต่ำกว่า พบความหนาของผิวสมองบางลง 2 บริเวณ คือ inferior frontal gyrus ด้านขวา และ inferior parietal gyrus ด้านขวา นอกจากนั้นไม่พบความแตกต่างของความผิดปกติทางพุทธิปัญญาและความผิดปกติของ white matter ระหว่างกลุ่ม สรุป: ระดับความรุนแรงของการขาดออกซิเจนในภาวะหยุดหายใจขณะหลับจากการอุดกั้นมีความสัมพันธ์กับการเปลี่ยนแปลงของ gray matter บริเวณ frontal และ parietal

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Anthipa Chokesuwattanaskul : Association of Hypoxia Measured by Oxygen Desaturation Index (ODI) in OSA with Delis-Kaplan Executive Function System (D-KEFS) Tests in Middle-Aged and Older Adults. Advisor: Yuttachai Likitjaroen, M.D., M.Sc., DR.MED Co-advisor: Assoc. Prof. NARICHA CHIRAKALWASAN, M.D.

Objective: This study aims to study the cognitive profile, in particular, executive function, and structural changes of the brain in obstructive sleep apnea (OSA) with regards to the degree of hypoxia and the characteristics of hypoxia in middle-aged and older adults. Method: Newly diagnosed moderate or severe OSA patients from King Chulalongkorn Memorial Hospital, Thailand were recruited. Respiratory parameters from the polysomnography, neuropsychological test results, and MRI brain of each participant were obtained. Results: Seventeen OSA patients were included in the study, 8 (47%) men and 9 (53%) women. The median age was 57 years and the median AHI was 60.6. There was no correlation between cognitive test scores in any domain with parameters of hypoxia. There was no correlation between cortical thickness with parameters of hypoxia. Participants were then classified as having either severe or mild hypoxia based on parameters of hypoxia. Cortical thickness analysis comparing between the severe and mild group of each hypoxic feature revealed two clusters of cortical thinning at the right inferior frontal gyrus and right inferior parietal gyrus in the severe desaturation group and a cluster of cortical thinning at the superior parietal gyrus in the high oxygen desaturation index group. There was no difference in cognitive function or white matter integrity between groups. Conclusion: A higher degree of hypoxia in OSA is associated with an early change of gray matter in the frontal and parietal regions.

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Student's Signature .....
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ขอบพระคุณเจ้าหน้าที่และพยาบาลศูนย์นิทราเวช โรงพยาบาลจุฬาลงกรณ์ คุณยุทธชัย ศรุติเกรียงไกร และคุณ นักจิตวิทยา สาขาประสาทวิทยา โรงพยาบาลจุฬาลงกรณ์ และเจ้าหน้าที่ภาควิชารังสีวิทยา ที่ให้ความร่วมมือในการเก็บข้อมูลและทำการทดสอบทางจิตวิทยา ขอบพระคุณผู้ป่วยและผู้ดูแลทุกท่านที่เสียสละเวลาอันมีค่าในการเข้าร่วมโครงการนี้

ผู้วิจัยรู้สึกซาบซึ้งในความกรุณาของทุกท่านที่กล่าวมาตลอดจนผู้ที่ไม่ได้กล่าวนามในที่นี้ซึ่งมีส่วนให้งานวิจัยสำเร็จลุล่วงไปได้ด้วยดี

สุดท้ายนี้ กราบของพระคุณ ครอบครัวที่ให้ความช่วยเหลือและเป็นกำลังใจตลอดมา

นอกจากนี้ งานวิจัยนี้สำเร็จลุล่วงได้รับทุนสนับนุนจาก ทุนวิจัยรัชดาภิเษกสมโภช คณะแพทยศาสตร์ สัญญาทุนเลขที่ RA 62/065

Anthipa Chokesuwattanaskul

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Chapter 1 Introduction

1.1 Background and Rationale

Obstructive sleep apnea (OSA) is one of the most common sleep-related breathing disorder which is characterized by repeated complete or partial collapse of the upper airway despite an effort to breath during sleep (1). Symptoms of OSA vary ranging from excessive daytime sleepiness (EDS), fatigue, insomnia, snoring, observed apnea and headache. Some studies have also found OSA was associated with several diseases such as hypertension, diabetes, coronary artery disease, cardiac arrhythmia, congestive heart failure, cerebrovascular disease, cognitive disorder, and mood disorder (2-4). The standard diagnostic test is polysomnography where the presence of symptoms of OSA are accompanied by five or more predominantly obstructive respiratory events (obstructive or mixed apneas, hyponeas or respiratory effort-related arousals) per hour of sleep or in the absence of symptoms, fifteen or more obstructive respiratory events per hour of sleep must be present in order to meet the diagnostic criteria for OSA (5).

Some studies have reported up to 60% of the elderly have mild OSA and 17% of elderly men and 9% of elderly woman have moderate to severe OSA (6, 7). These data represented that the risk factors of OSA may increase with age. Many studies found the correlation between age and the collapsibility of the upper airway as well as the upper airway narrowing regardless of sex or obesity, which is the main mechanism contributing to the development of OSA (8-11). In addition, the fluid shifting from the periphery to the trunk and neck during sleep causes narrowing of the upper airway dimension also increases with age (12). Other non-anatomical phenotypes that contribute to the development of OSA include poor upper airway responsiveness, unstable respiratory control system (loop gain), and low respiratory arousal threshold. Evidences supporting the role of non-anatomical phenotypes in older adults are still inconclusive. Some studies suggested that factors including respiratory control system, respiratory arousal threshold, and upper airway responsiveness contributes less to the development of OSA in older adults (10, 11, 13-16).

Other conditions that have been claimed to be associated with OSA are cognitive disorders. However, the evidence regarding this association is inconsistent due

to the differences in research questions and research methodologies (17-23). As the elderly population is increasing globally, OSA-associated cognitive decline has become a great concern. Cognitive impairment is one of the factors that prevents older adults from living independently. The condition not only incapacitate the elderly, but also bring both economic and psychologic burden to their families. As a treatable condition that could help prevent or reverse cognitive impairment, a robust evidence supporting the association of OSA with cognitive impairment is needed.

According to previous studies of the association between OSA and cognitive functions, the common affected cognitive domains are attention or vigilance, executive function, and memory. There are also some reports of involvement in the processing speed and visuospatial or constructional ability but language is often spared (19-21, 23-27). OSA also increases the risk as well as accelerates the onset of mild cognitive impairment or dementia. Furthermore, several longitudinal studies have demonstrated a decrease in global cognition in OSA compared to control after the OSA patient had been followed for several years in both cognitively normal individual and those with mild cognitive impairment (28-31).

The two main effects of OSA are hypoxia and sleep fragmentation (3). Some proposed that both hypoxia and sleep fragmentation contribute to cognitive impairment. Several studies that tried to determine the effect of each individual components have provided conflicting results (18, 32, 33). While some studies found that higher degree of hypoxia correlates to decreased attention/vigilance, memory, executive function, and global cognition, others found no association between hypoxia and the decline cognitive function in any domain (18, 19, 23, 25, 27, 34). Some studies found that only the severity of hypoxia is associated with higher risk of mild cognitive impairment or dementia while sleep fragmentation did not (20, 21, 23, 35). Although there have been more evidence pointing toward hypoxia as the main culprit, some argued that sleepiness associated with sleep fragmentation caused attention impairment which contributed the underperformance of all other cognitive domains (18, 23). However, evidence have emerged against the later argument as improvement in sleepiness did not always correlate with improvement in cognitive function. Of note, in studies where treatment for OSA alleviated symptoms of sleepiness, cognitive

functions were not fully reversed (19). Future studies that could characterize the extent that these two factors affect the functions and structures of the brain is needed.

Hypoxia and sleep fragmentation were alleged to cause both direct and indirect adverse effects to the brain. The direct effects of hypoxia include the hypoxic injury and reoxygenation injury. The most susceptible brain areas to those effects are the prefrontal, frontal, hippocampus, and basal ganglia. This process causes endothelial dysfunction, decreased level of nitric oxide, disruption of synapses and neurotransmission, as well as, increased oxidative stress, neuroinflammation, and increased beta-amyloid burden, accumulation of amyloid plaque and phosphorylation of tau, all of which lead to neuronal loss (21-23). In addition, chronic intermittent hypoxia observed in long-standing OSA leads to vasculopathy and hypertension through increased sympathetic activation and activation of the renin-angiotensin-aldosterone system, which results in cerebral small vessel disease and increased risk of stroke (20, 23). Apart from sleepiness, sleep fragmentation also plays a role in disrupting the process of memory consolidation and synaptic plasticity causing poor

memory consolidation, increased amyloid beta burden and subsequent neuronal loss (21).

This study aimed to study the association of hypoxia in OSA with cognitive impairment in the executive function domain in older adults.

1.2 Research Questions

Primary Research Question

- Does hypoxia indicating by oxygen desaturation index (ODI) from polysomnography study negatively correlate, correlation coefficient of - 0.5 or more, with score from D-KEFS Tower Test in middle-aged and older adults with moderate to severe OSA?

Secondary Research Questions

- Does hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study has a significant effect on the composite measurement of executive function tests, regression coefficient not equal to zero, in middle-aged and older adults with moderate to severe OSA?

- Does hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study has a significant effect on the composite measurement of memory tests, regression coefficient not equal to zero, in middle-aged and older adults with moderate to severe OSA?
- Does hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study has a significant effect on the composite measurement of attention tests, regression coefficient not equal to zero, in middle-aged and older adults with moderate to severe OSA?
- Does hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study has a significant effect on the composite measurement of processing speed tests, regression coefficient not equal to zero, in middle-aged and older adults with moderate to severe OSA?
- Does hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study has a significant effect on the cortical thickness measurement from magnetic resonance imaging of the brain in the prefrontal area, regression coefficient not equal to zero?

- Does hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study has a significant effect on the fractional anisotropy (FA) values from diffusion tensor imaging study of the brain in the subcortical frontal area, regression coefficient not equal to zero?

- Does hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study has a significant effect on the resting state functional connectivity (rsFC) from functional magnetic resonance imaging study of the brain in the prefrontal area, regression coefficient not equal to zero?

1.3 Objective

- To study the correlation between hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography with score from D-KEFS Tower Test in middle-aged and older adults with moderate to severe OSA.

- To study the relationship between hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography with the composite measurement of executive function tests in middle-aged and older adults with moderate to severe OSA.

- To study the relationship between hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography with the composite measurement of memory tests in middle-aged and older adults with moderate to severe OSA.
- To study the relationship between hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography with the composite measurement of attention tests in middle-aged and older adults with moderate to severe OSA.
- To study the relationship between hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography with the composite measurement of processing speed tests in middle-aged and older adults with moderate to severe OSA.

- To study the relationship between hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study with cortical thickness measurement from magnetic resonance imaging of the brain in the prefrontal area.
- To study the relationship between hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study with fractional anisotropy (FA)

values from diffusion tensor imaging study of the brain in the subcortical frontal area.

- To study the relationship between hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study with resting state functional connectivity (rsFC) from functional magnetic resonance imaging study of the brain in the prefrontal area.

1.4 Hypothesis

Null hypothesis

- Hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study negatively correlate, correlation coefficient of less than -0.5, with score from D-KEFS Tower Test in middle-aged and older adults with moderate to severe OSA.

- Hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study does not have a significant effect on the composite measurement of executive function tests, regression coefficient equal to zero, in middle-aged and older adults with moderate to severe OSA.

- Hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study does not have significant effect on the composite measurement of memory tests, regression coefficient equal to zero, in middle-aged and older adults with moderate to severe OSA.
- Hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study does not have significant effect on the composite measurement of attention tests, regression coefficient equal to zero, in middle-aged and older adults with moderate to severe OSA.
- Hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study does not have significant effect on the composite measurement of processing speed tests, regression coefficient equal to zero, in middle-aged and older adults with moderate to severe OSA.
- Hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study does not have significant effect on the cortical thickness measurement from magnetic resonance imaging of the brain in the prefrontal area, regression coefficient equal to zero.

- Hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study does not have significant effect on the fractional anisotropy (FA) values from diffusion tensor imaging study of the brain in the subcortical frontal area, regression coefficient equal to zero.

- Hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study does not have significant effect on the resting state functional connectivity (rsFC) from functional magnetic resonance imaging study of the brain in the prefrontal area, regression coefficient equal to zero.

Alternative hypothesis

- Hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study negatively correlate, correlation coefficient of -0.5 or more, with score from D-KEFS Tower Test in middle-aged and older adults with moderate to severe OSA.

- Hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study has a significant effect on the composite measurement

of executive function tests, regression coefficient not equal to zero, in middle-aged and older adults with moderate to severe OSA.

- Hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study has a significant effect on the composite measurement of memory tests, regression coefficient not equal to zero, in middle-aged and older adults with moderate to severe OSA.
- Hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study has a significant effect on the composite measurement of attention tests, regression coefficient not equal to zero, in middle-aged and older adults with moderate to severe OSA.

- Hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study has a significant effect on the composite measurement of processing speed tests, regression coefficient not equal to zero, in middle-aged and older adults with moderate to severe OSA.
- Hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study has a significant effect on the cortical thickness

measurement from magnetic resonance imaging of the brain in the prefrontal area, regression coefficient not equal to zero.

- Hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study has a significant effect on the fractional anisotropy (FA) values from diffusion tensor imaging study of the brain in the subcortical frontal area, regression coefficient not equal to zero.
- Hypoxia during sleep indicating by oxygen desaturation index (ODI) from polysomnography study has a significant effect on the resting state functional connectivity (rsFC) from functional magnetic resonance imaging study of the brain in the prefrontal area, regression coefficient not equal to zero.

1.5 Conceptual Framework

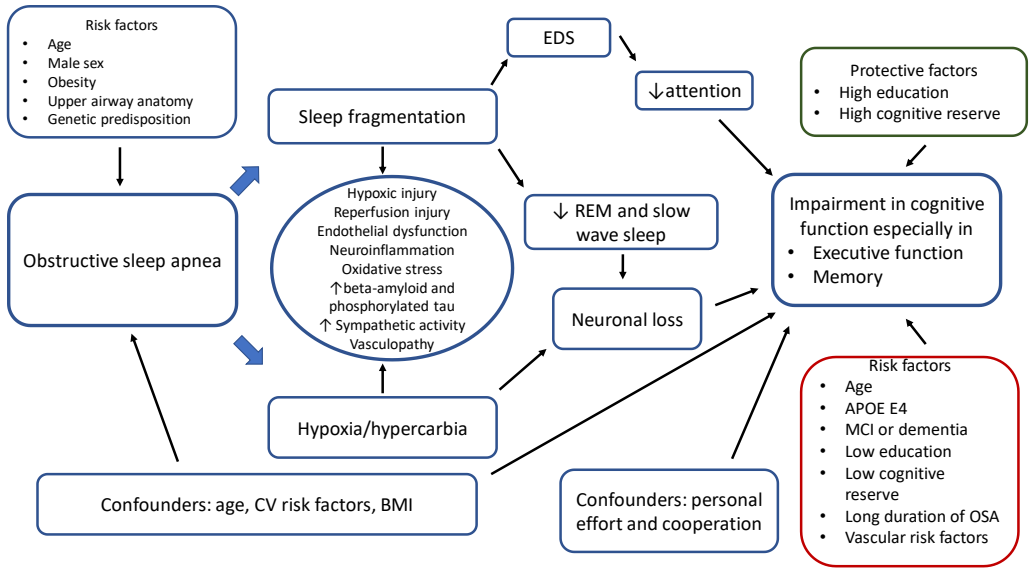


Figure 1 Conceptual framework

1.6 Assumption

All participants are diagnosed with moderate to severe OSA based on a split-night polysomnography according to the International Classification of Sleep Disorders – third edition(5). Cognitive functions are measured using a standardized neurocognitive test administered by a certified psychologist, all tests will be administered in Thai language.

1.7 Key Words

Obstructive sleep apnea

Cognitive impairment

Memory

Executive function

Elderly

Magnetic resonance imaging

1.8 Operational Definition

Obstructive sleep apnea (5)

1. Signs or symptoms of OSA or associated medical or psychiatric disorder coupled with five or more predominantly obstructive respiratory events per hour of sleep during PSG *or*
2. In the absence of associated symptoms or disorders, fifteen or more predominantly obstructive respiratory events per hour of sleep during PSG

Apnea (36)

1. There is a drop in the peak signal excursion of airflow by ≥ 90 % of pre-event baseline *and*
2. The duration of the ≥ 90% drop in airflow is ≥ 10 seconds

Hypopnea (36)

1. The peak signal excursions of airflow drop by ≥ 30% of pre-event baseline *and*
2. The duration of the ≥ 30% drop in airflow signal excursion is ≥ 10 seconds *and*
3. There is a ≥ 3% oxygen desaturation from the pre-event baseline or the event is associated with an arousal

Severity of OSA (37)

1. moderate OSA = AHI 15-30
2. severe OSA = AHI > 30

1.9 Ethical Considerations

Respect for person

All participants were fully informed on the objective and research process. Participants were admitted to the research at their own will and were permitted to withdraw from the study at any time, their decision does not cause any change to their plan of treatment.

Beneficence/Non-malificence

Participants would benefit from a through neuropsychological assessment and neuroimaging of the brain by knowing the current status of their own cognitive impairment and brain structural changes, as well as other deficits that may be found by the test. Abnormalities were thoroughly investigated, treated to reverse or prevent further decline of function. Aside from stress and fatigue, there is no harm from neuropsychological assessment or magnetic resonance imaging of the brain.

Confidentiality

All participant's information in the research were kept confidential, no information is to be disclosed to other party without the participant's consent. Name and hospital number of participants were collected for data collection and analysis during the study period.

Justice

Participants were selected by inclusion and exclusion criteria on a consecutive case basis.

1.10 Limitations

As a cross-sectional study, causality cannot be claimed of any associations.

Subjects were recruited from the Excellence Center for Sleep Disorders at King Chulalongkorn Memorial Hospital which is a tertiary care center, therefore, the results might not represent the general population. Moreover, most subjects in this study had sleep-related problems which led them to undergo polysomnography and therefore might not address the whole spectrum of cases with OSA that manifests without sleep-related symptoms. Obtaining duration of OSA might not be accurate due to the recall bias of the onset. Differences in the duration of symptoms is thought to be one of the key factors affecting cognition, therefore, a longitudinal study design of several years would be more informative.

Although patients included in this study have moderate to severe OSA, there is a night to night variability in the degree of hypoxia and arousal. Implying that the measured parameters from polysomnography might be more or less severe than their average nights. The proportion that participants spend in the supine position is one of the factors that determine the severity of OSA in that night, sleeping in the supine position leads to more apnea or hypopnea than in other positions.

Measures from polysomnography of hypoxia and sleep fragmentation also might not fully reflect the true severity of each features. Hypoxia is measured using the oxygen desaturation index (ODI) and T90, thereby, assigning equal severity to every single desaturation event and treating desaturation below SpO2 90% equal to desaturation below SpO2 of 80% or 70%. Likewise, sleep fragmentations are counted as time per hour. A more accurate measurement of each feature could better represent the true degree of hypoxia and sleep fragmentation.

Performance on neuropsychological tests largely depends on the participant's cooperation. Limiting the neuropsychological tests duration to less than two hours and allowing breaks in between help prevent fatigue but does limit the number of tests applied. Some of the tests still lack normative data in Thai population.

Regarding neuroimaging studies, each technique has its own limitations. Voxel-based morphometry is one of the most widely used analysis, however, the technique varies between laboratories. Cortical thickness measurement is quite consistent, but the measurement does not take into account subcortical areas. While functional connectivity in resting state functional MRI varies less than task functional MRI, there is

still some variability depending on the subject's state, for example, excited, sleepy, or tired, etc.

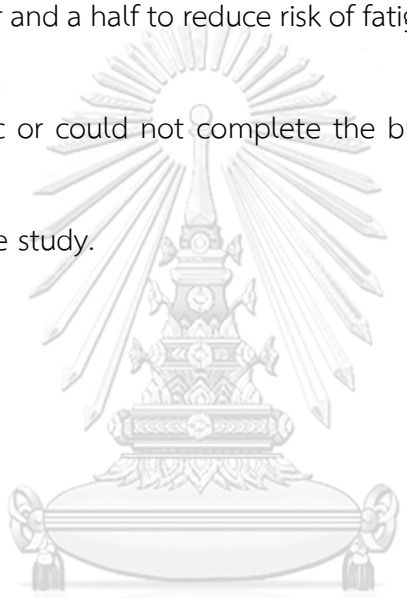
1.11 Expected Benefits and Applications

OSA has been regarded as one of the reversible causes of cognitive impairment, but the association between each effect of sleep and cognitive domain is still unclear. Besides demonstrating the association between hypoxia in OSA and impairment in executive functions in older adults, this study also provides further understanding of the pathophysiological effect of hypoxia in OSA on the brain. As both functional and structural imaging are used, brain structural changes as a result of hypoxia could be detected earlier and might even be reversible.

The result may provide patients with more compelling resolution to seek and adhere to treatment of OSA to reverse or stabilize certain cognitive impairment as well as be able to provide a fair expectation of certain cognitive impairment, which is remediable and that which is unresponsive to treatment.

1.12 Obstacles and Strategies to Solve the Problems

Some neuropsychological tests might be stressful to participants and the participants might not fully cooperate on some tests. To minimize the stress, psychologists administering the test should not put pressure on subjects and also take note of subject cooperation during each test. Furthermore, the assessment duration was limited to one hour and a half to reduce risk of fatigue on participants. Participants who are claustrophobic or could not complete the brain MR imaging by any means were excluded from the study.



Chapter 2 Review of Related Literatures

Studies of the relationship between OSA and cognitive impairment in older adults have provided mixed results in many aspects such as the cognitive domain affected, association of the degree of OSA to the degree of cognitive impairment, association of OSA to the risk of developing mild cognitive impairment or dementia, cognitive outcome after treatment with CPAP, and imaging findings in OSA. However, some prominent trends could be inferred from these past studies. Review of evidences and hypothesis for each aspects of the association between OSA and cognitive function will be presented below.

2.1 The relationship between OSA and cognitive impairment

Not all OSA patients develop cognitive impairment. Several factors were alleged to predispose an individual to the negative effect of OSA on cognition, namely, pre-existing mild cognitive impairment or dementia and APOE E4 positive status (38-40). On the other hand, those with higher cognitive reserve or higher education are more resilient (41). The severity of OSA also should be considered, some community-based

studies that included only mild to moderate OSA found no relationship between measurements of the severity of OSA (number of apnea or hypopnea events per hour, hypoxia, or sleep fragmentation) and cognition (20, 42-45). While some studies reported that the severity of OSA or hypoxia correlates to the degree of global cognitive impairment and impairment in certain cognitive domains, thus suggesting that there may be a threshold effect of OSA severity on cognition (17, 40).

The proposed mechanisms are consistent with brain imaging findings in OSA patients where structural changes in both white matter and gray matter represent permanent damage caused by OSA that could not be fully reversed with treatment. Another finding in OSA patients compared to controls were the increase of brain white matter lesions especially in the frontal lobe and decreased grey matter volume in several areas mostly associated with memory and executive functions, for example, hippocampus, caudate, frontal lobe, etc (18, 21-23, 46-54). Brain functional imaging also portrayed a similar picture showing hypometabolism in the prefrontal, pareito-temporal, hippocampus, cingulate, cuneus, and precuneus areas (55).

Currently, continuous positive airway pressure (CPAP) is the first-line treatment in most patients. There are reports that treatment with CPAP improves cognitive function and delays the onset of mild cognitive impairment but the improvements are mostly partial and only seen in some certain cognitive domains. The lack of efficacy of the treatment could in part be confounded by the poor compliance with CPAP in many studies, reports have found that around half of patients prescribed CPAP did not use it or used it less than four hours per night (11). Also, the aforementioned structural changes in certain areas might not be fully reversible with treatment.

Studies of the association between cognitive function and OSA have been carried-out in all populations, both adults and children, but few focused only on older adults. Most studies included middle-aged patients more than older adults with mean ages ranging from 50s-60s and the maximum mean age amongst studies belongs to Ju et al. (56) with a mean age of 68 years. Other studies that focused on elderly populations were community-based (25, 35, 40, 45), which the participants comprised mostly of mild to moderate OSA and home polysomnography or portable polysomnography were used instead of laboratory polysomnography used in sleep

clinic setting for measurements and diagnosis of OSA. It was hypothesized that OSA effects cognitive function in the older adults differently from other populations as some studies found that older adults cognitive function were more vulnerable to the negative effect of OSA than their younger counterparts, thus studies that focus on older adults are needed (21). Moreover, failure to include all severities of OSA especially the most severe ones could provide a biased result due to the threshold effect of OSA severity on cognition. While home polysomnography provides a fair alternative to laboratory polysomnography some studies have found that measures from home with portable polysomnography differed significantly from laboratory polysomnography, especially in those with severe OSA (43).

Results on cognitive impairment associated with OSA also varies in part due to the difference in cognitive domain assessed and adoption of different neuropsychological assessment tools for each cognitive domain across the studies with some studies using only a single global cognition test. Also, commonly found in most studies is the fact that each cognitive domain was not equally vulnerable to the effect of hypoxia/hypercarbia and sleep fragmentation. To understand more about how each

cognitive domain is affected, the incorporation of neuroimaging studies which can demonstrate the injuries or structural changes in associated brain areas correlating to the cognitive impairment observed could provide further evidence of the effect of OSA on each region of the brain (54, 57, 58).

Regarding the neuropsychological assessment, cognitive domains that have been assessed and showed impairment across most studies were attention, executive function, and memory with some also providing neuroimaging correlates (45, 53, 54, 56-62). Tests for measurement of functions of each cognitive domain should take into account subject's performance in global cognition and attention as well as provide a comprehensive assessment of all subdomains of executive function (63). Subsequently, a standardized score should be obtained to account for confounding factors, such as age, sex, education, race, etc., then a common distribution-based scales calculated to equate units across different tests for comparison (64).

2.2 The association of hypoxia in OSA and cognitive impairment

As one of the main mechanisms hypothesized to cause end organ damage by OSA, few studies have investigated its relationship to cognitive impairment. The studies

are listed in table 1. There are five community setting studies and five sleep clinic setting studies. Among the respiratory parameters from polysomnography, mean oxygen saturation, nadir oxygen saturation, ODI, and T90 were commonly used as representatives of hypoxia. Neuropsychological test employed to measure cognitive functions also varies between the studies. Trail making test, phonemic fluency, Wisconsin card sorting test, and Stroop test were examples of test used to measure executive function. Delayed word recall test was used to measure memory function. Digit symbol substitution, Paced Auditory Serial Addition Test (PASAT), and letter number sequencing were used to assess the cognitive processing speed. Two sleep clinic studies and one community study found an association between hypoxia parameters and performance on executive function tests. A study by Ju et al. (56) found that subjects with more severe hypoxia performed worse on memory function test. Another study by Quan et al. (65) reported that subject with higher degree of hypoxia had lower cognitive processing speed.

2.3 The association of hypoxia in OSA and brain structural change

There are two studies exploring the effect of hypoxia in OSA and brain cortical gray matter change. The first study by Baril et al. found an increased in cortical thickness at the frontal, parietal, and cingulate regions in relation to severity of hypoxia measured by T90 and nadir oxygen saturation. While the second study by Cross et al. found a decreased in cortical thickness at the temporal pole and fusiform gyrus in relation to the severity of the desaturation. Other studies comparing cortical thickness between OSA patients and controls found a decreased in cortical thickness in several regions in OSA patients. In addition, a study by Dalmases et al. comparing the cortical thickness of OSA patients before and after 3 months of CPAP treatment found an increased in cortical thickness at the frontal and parietal regions after treatment. The details of the studies are listed in Table 2.

2.4 The association of OSA and white matter integrity

Diffusion tensor imaging analysis has been used to explore the changes of the white matter integrity in many conditions. Parameters from the diffusion tensor imaging analysis includes fractional anisotropy (FA), median diffusivity (MD), axial diffusivity, and radial diffusivity. FA represents the directions of the water molecule diffusion in brain

parenchyma where a value of 0 represents isotropic diffusion and 1 represents anisotropic diffusion. The decrease of FA indicates the low integrity which may be associated with brain parenchymal injury. MD is the mean of water molecules diffusivity in 3-dimensional space. In contrast, high MD values are associated with low white matter integrity. Axial diffusivity represents the diffusion along the major axis and radial diffusivity represents the average diffusion in the minor axes perpendicular to the major axis (66). Typically, axonal damage without myelin injury would result in a decreased in both FA and axial diffusivity with an increased in radial diffusivity and normal MD value. On the other hand, demyelination without axonal damage would result in an increased in radial diffusivity without any change in axial diffusivity (67).

We found 4 studies comparing diffusion tensor imaging parameters between OSA patients and controls. None of the studies specifically assessed the effect of hypoxia in OSA. Findings included reduce in FA with an increase in MD, radial diffusivity, and axial diffusivity which indicates an injury in the acute stage to the white matter of the brain in OSA group. The details of the studies are listed in Table 3.

2.5 The association of OSA and functional changes of the brain

Listed in Table 4 are studies using functional MRI to investigate the functional changes in OSA patients. The technique used varies from study to study. Examples include seed-based functional connectivity, independent component analysis (ICA), graph theory analysis, Regional homogeneity analysis (ReHo), and amplitude of low-frequency fluctuations analysis (ALFF). Most reported decreased or aberrant functional connectivity from region to region and decreased of both regional and global functional connectivity. Connectivity in large brain networks such as default mode network (DMN), salience network (SN), central executive network (CEN), and sensorimotor network (SMN) was also reported to be compromised in OSA patients.

Table 1 Literature review of the association between hypoxia in obstructive sleep apnea and cognitive functions in older adults

Author/ Year	Country/ setting	Study design	Total No. (patients/ controls)	Mean age (SD) (years)	Mean AHI/RDI	Exposure Measuremer	Outcome	Confounder Adjusted
Blackwell, 2015 (68)	USA/ community	Cohort	2,636	76	12.4	Home PSG – ODI, T90	ODI ≥ 15 - Decline in TMT-B OR = 1.05 (0.78-1.43) T90 ≥1% - Decline in TMT-B OR 0.93 (0.68-1.27)	Age, site, race, BMI, education, DM, stroke, CHD, PD, BZD, depression, SSRI, alcohol, smol impaired iADL, physical activity
Boland, 2002 (42)	USA/ community	Cross-sectional	1760	62.3	4.2	Home PSG · T90	No association between T90 and DWR, DSS, WF scores	Age, education, occupation, DM HT, BMI, CNS meds, alcohol
Ferini-Strambi, 2003 (59)	Italy/ sleep clinic	Cross-sectional	23 OSA 23 control	56.52	54.95	Lab PSG – T90	T90 and phonemic fluency (r = -0.512, p = 0.018)	-
Hoth,	USA/	Cross-	40 OSA	54.55	37.8	Lab PSG –	High (T 90 ≥20%) vs.	-

Author/ Year	Country/ setting	Study design	Total No. (patients/ controls)	Mean age (SD) (years)	Mean AHI/RDI	Exposure Measuremer	Outcome	Confounder Adjusted
2013 (69)	sleep clinic	sectional				T90	Low (T 90 ≤ 6%) hypoxemia: no difference in COWAT, PASAT, TMT-A, TMT-B, Letter-Number Sequencing	
Ju, 2012 (56)	Korea/ sleep clinic	Cross-sectional	42 OSA 21 control	68	36.61	Lab PSG - ODI	WLRT (β = -0.37, p = 0.003)	Education, AHI
Mathieu, 2008 (>50 yrs) (70)	Canada/ sleep clinic	Cross-sectional	14 OSA 18 control	62.3	42.5	Lab PSG – Mean O2, T90, nadir SpO2	No association between any Measurement of hypoxia with TMT-B and Wisconsin Card Sorting Test	-
Quan, 2006 (65)	USA/ community	Cross-sectional	67 OSA	59.4	22.4	Home PSG - T85	T85 contributes to processing speed (R^2 = 0.122, p < 0.001)	Age, gender, education, ESS
Sforza, 2010 (45)	France/ community	Cross-sectional	827	68	20.4	Home PSG - ODI	Stroop test - color (r = -0.083, p = 0.02) - word (r = - 0.12, p = 0.001)	Gender, BMI, BP, DM, HT, ESS, anxiety, depression, self-reported sleep time

Author/ Year	Country/ setting	Study design	Total No. (patients/ controls)	Mean age (SD) (years)	Mean AHI/RDI	Exposure Measuremer	Outcome	Confounder Adjusted
Sharma, 2010 (71)	India/ sleep clinic	Cross-Sectional	50	43	54.2	Lab PSG – T90	Stroop error (r = 0.64, p <0.03) Wisconsin Card Sorting Test - no. of trials (r = 0.05, p < 0.02) - perseverative errors (r = 0.36, p < 0.02)	-
Spira, 2008 (40)	USA/ community	Cross-sectional	448	82.8	15.5	Home PSG – Nadir O2 < 80%	OR MMSE 2.7 (1.1-6.6) OR TMT-B 1.2 (0.5-3.2)	Age, education, SSRI use

Abbreviation: AHI, apnea-hypopnea index. BMI, body mass index. BP, blood pressure. BZD, benzodiazepine. CHD, congestive heart disease. CNS, central nervous system. COWAT, Controlled Oral Word Association Test. DM, diabetes mellitus. DSS, digit symbol substitution. DWR, delayed word recall. ESS, Epworth Sleepiness Scale. HT, hypertension. iADL, instrumental activities of daily living. MMSE, Mini-Mental State Examination. O2, oxygen. ODI, oxygen desaturation index. OR, odds ratio. OSA, obstructive sleep apnea. PASAT, Paced Auditory Serial Addition Test. PD, Parkinson disease. PSG, polysomnography. r, Pearson's correlation coefficient. SSRI, selective serotonin reuptake inhibitor. T90, %time spent below 90% oxygen saturation. TMT, trail making test. WF, word fluency. WLRT, word-list recall test.

Table 2 Review of literature of structural MRI studies in OSA

Author/Year	Country/ Setting	Total No. (Patients/Controls)	Mean age (SD) (years)	Imaging analysis	Outcome
Joo et al. 2013 (72)	Korea/ Sleep clinic	43/ 36	43.7 ± 6.4	Cortical thickness: OSA compared to controls (adjusted for age and brain volume)	Cortical thinning at bilateral frontal regions, pre- and post-central gyrus, anterior cingulate, insula, inferior parietal lobule supramarginal gyrus, precuneus, uncus, parahippocampal, fusiform gyrus, superior, middle, inferior temporal gyrus
Joo et al. 2013 (72)	Korea/ Sleep clinic		43.7 ± 6.4	Cortical thickness: negative correlation to maximum apnea duration	Thickness of left middle frontal gyrus and right inferior frontal gyrus
Dalmases et al. 2015 (73)	Finland/ Sleep clinic	17/16 OSA assigned to CPAP or conservative treatment	71.3 ± 5.51	Cortical thickness after 3-month CPAP treatment	Increased thinning compared to baseline in control group: right frontal and parietal (pars opercularis, paracentral, inferior parietal, postcentral, precuneus); left middle frontal and lingual gyrus
Baril et al. 2017 (74)	Canada/ Sleep clinic	59/12		Cortical thickness relation to hypoxemia (nadir O2 and T90)	Increased thickness of left middle frontal gyrus, right frontal pole, right superior and inferior parietal lobule, left posterior cingulate
Macey et al. 2018 (75)	USA/Sleep clinic	48/62		Cortical thickness (adjusted for sex)	Decreased cortical thickness at left precentral gyrus, left superior temporal gyrus, insular cortex, right postcentral gyrus

Author/Year	Country/ Setting	Total No. (Patients/Controls)	Mean age (SD) (years)	Imaging analysis	Outcome
Cross et al. 2018 (76)	Australia/ Community setting	90	67.4 ± 7.5	Cortical thickness: relation to severity of desaturation (adjusted for age, sex, education, MCI, BMI, ESS, HT, DM, CVD, depression	Decreased cortical thickness at left temporal pole, right fusiform gyrus

Abbreviation: BMI, body mass index. CPAP, continuous positive airway pressure. CVD, cerebrovascular disease. DM, diabetes mellitus. ESS, Epworth Sleepiness Scale. HT, hypertension. MCI, mild cognitive impairment. O2, oxygen. OSA, obstructive sleep apnea. SD, standard deviation. T90, %time spent below 90% oxygen saturation.

Table 3 Review of literature of DTI studies in OSA

Author/Year	Country/ Setting	Total No. (Patients/Controls)	Mean age (SD) (years)	Imaging modality	Outcome
Castronovo et al. 2014 (57)	Italy/ Sleep clinic	13/15	43.23 (7.63)	DTI	Lower FA: bilateral superior parietal (sup longitudinal fascicle), left inferior frontal (uncinate), left optic radiation, right transcallosal connection, right corticospinal tract Lower MD: bilateral superior parietal (sup longitudinal fascicle), right mesial posterior frontal WM
Kumar et al. 2012 (77)	USA/ sleep clinic	23/23		DTI (controlled for age)	Reduced MD: dorsal, ventral, ventrolateral medulla, bilateral cerebellum, temporal lobe, bilateral hippocampus, bilateral putamen and thalamus, right insula, left caudate, anterior corpus callosum, bilateral frontal and occipital, left prefrontal, right posterior cingulate, corona radiata

Author/Year	Country/ Setting	Total No. (Patients/Controls)	Mean age (SD) (years)	Imaging modality	Outcome
Kumar et al. 2014 (78)	USA/ Sleep clinic	23/23	44.4 ± 9.3	DTI: Axial and radial diffusivity	Reduced radial diffusivity in OSA at medulla, corpus callosum, corona radiata, frontal white matter, insula, hippocampus, occipital, internal capsule, amygdala, cerebellum, thalamus, putamen, temporal white matter Reduced axial diffusivity in OSA at corona radiata, frontal white matter, globus pallidus, hippocampus, thalamus, medulla, temporal white matter, putamen, cingulate, corpus callosum, external capsule, cerebellum
Macey et al. 2008 (79)	USA/ Sleep clinic	41/ 69	35.7 ± 18.1	DTI: FA	Lower FA in OSA compared to controls at cerebellum, pons, thalamus, right fornix, cingulate, insula, internal capsule, prefrontal cortex, parietal, and temporal white matter

Abbreviation: DTI, diffusion tensor imaging. FA, fractional anisotropy. MD, mean diffusivity. OSA, obstructive sleep apnea. SD, standard deviation.

Table 4 Review of literature of fMRI studies in OSA

Author/Year	Country/ Setting	Total No. (Patients/Controls)	Mean age (SD) (years)	Imaging modality	Outcome
Chen et al. 2018a (80)	China/ Sleep clinic	46/46		Seed-based, global and regional connectivity (graph analysis)	Altered FC within DMN, global network measure and regional network measures with correlation to MoCA
Chen et al. 2018b (81)	China/ Sleep clinic	45/45	37.56 8.86	Global and regional connection	Impaired global and regional functional connection in DMN, SN and CEN, correlate to MoCA and PSG
Huang et al. 2019 (82)	China/ Sleep clinic	29/26	39.62 9.95	Graph theory small-world parameters	Changes in small-world network property in OSA, no correlation to MMSE
Li et al. 2015 (83)	China/ Sleep clinic	25/25	39.4 1.7	Spontaneous brain activity by ALFF	Lower ALFF in OSA in PC, PCC, higher in IFG; low ALFF correlate to nadir O2 and MoCA
Li et al. 2016 (84)	China/ Sleep clinic	40/40	38.6 8.1	Seed-based selected ROI in DMN	Altered rsFC between regions of DMN compared to control, some correlation to np tests
Park et al. 2016a (85)	USA/ Sleep clinic	67/75	48 9.2	Seed-based drawn ROI at right and left insular	complex aberrant FC between the insular cortices and several other brain regions regulating autonomic, affective, sensorimotor, and cognitive functions.

Author/Year	Country/ Setting	Total No. (Patients/Controls)	Mean age (SD) (years)	Imaging modality	Outcome
Park et al. 2016b (86)	USA/ Sleep clinic	69/82	48.3 9.2	Whole brain connectome, graph theory for global and regional connectivity	Altered connections between areas regulating autonomic, affective, sensorimotor and cognitive functions. Reduced global efficiency (specialization and integration) and trend towards decreased local efficiency
Peng et al. 2014 (87)	China/ Sleep clinic	25/25	39.4 1.7	ReHo	Altered ReHo in several regions (MFG, SFG, PC, angular, SP, cerebellum, cingulate, lentiform, putamen, insula), some correlation to sleep stages
Santarnecchi et al. 2012 (88)	Italian/ Sleep clinic	19/19	43.2 8	ReHo	ReHo abnormality in regions (thalamus, frontal, somatosensory)
Song et al. 2018 (89)	USA/ Sleep clinic	70/89	48.3 9.2	Seed-based ROI (hippocampus and caudate)	Impaired FC of hippocampus and caudate to cortical regions.
Yu et al. 2019 (90)	China/ Sleep clinic	40/40	37.03 8.74	Seed-based ROI in amygdala	Aberrant connection between amygdala and cerebellum, PFC, IFG, STG
Zhang et al. 2013 (91)	China/ Sleep clinic	24/21	44.6 7.4	ICA	Altered rsFC in cognitive and sensorimotor networks

Author/Year	Country/ Setting	Total No. (Patients/Controls)	Mean age (SD) (years)	Imaging modality	Outcome
Zhang et al. 2015 (92)	China/ Sleep clinic	24/21	44.6 7.4	Seed-based ROI at right anterior insula	Reduced functional connectivity between AI and DMN but not CEN nodes

Abbreviation: AI, arousal index. ALFF, amplitude of low frequency fluctuations. CEN, central executive network. DMN, default mode network. FC, functional connectivity. ICA, independent component analysis. IFG, inferior frontal gyrus. MGF, middle frontal gyrus. MMSE, Mini-Mental State Examination. MoCA, Montreal Cognitive Assessment. O2, oxygen. OSA, obstructive sleep apnea. PC, precuneus. PCC, posterior cingulate cortex. PFC, prefrontal cortex. ROI, region of interest. ReHo, regional homogeneity. rsFC, resting-state functional connectivity. SFG, superior frontal gyrus. SN, salience network. SP, superior parietal. STG, superior temporal gyrus.

Chapter 3 Research Methodology

3.1 Research design

Cross-sectional, descriptive study

3.2 Research Methodology

Study population

- **Target Population**

Newly-diagnosed moderate to severe OSA by a split-night laboratory polysomnography, AHI ≥ 15, from the Excellence Center for Sleep Disorders, King Chulalongkorn Memorial Hospital.

- **Inclusion criteria**

1. Newly diagnosed with moderate to severe OSA by a split-night laboratory polysomnography, AHI ≥ 15, according to the International Classification of Sleep Disorders – third edition.
2. Age ≥ 50 years

- **Exclusion criteria**

1. Severe systemic diseases: cirrhosis (Child-Pugh score B or C), chronic kidney disease stage 3 or more, pulmonary disease with chronic hypoxia or hypercarbia, heart failure NYHA II or more
2. Psychiatric illness
3. Neurological diseases: brain tumor, stroke, epilepsy, coma, history loss of consciousness of more than 30 mins after head trauma, encephalitis
4. Use of psychotropic medications
5. Alcohol or illicit drug abuse
6. Prior therapy for OSA
7. Sleep disorders other than OSA including central sleep apnea, insomnia, REM behavioral disorder, restless leg syndrome, periodic limb movement disorder, narcolepsy
8. TMSE score < 24
9. Inability to complete neuropsychological assessments or not fluent in Thai

10. Contraindications for MRI: presence of cardiac pacemaker or defibrillator, presence of metallic implants, claustrophobia, or uncomfortable or unable to lie down still for the MRI.

Sampling method

Consecutive cases

Sample size calculation

Previous studies from Sharma et al. and Ferini-Strambi et al. demonstrated weak to moderate correlation between measurements of hypoxia (T90) and scores from neuropsychological tests measuring executive function (59, 71).

The sample size that is required to demonstrate a moderate correlation (Pearson correlation coefficient = 0.5) between the degree of hypoxia (T90 or ODI) and scores from neuropsychological tests measuring executive function in the studied group is 29. The significance level is 0.05 and the statistical power is 0.8.

As demonstrated in the following equation (93)

$$n = 3 + \frac{2\left(Z_{\alpha/2} + Z_{\beta}\right)^2}{\left(\ln\left(\frac{1+\rho}{1-\rho}\right)\right)^2}$$

Where

n = sample size

α = 0.05 (two-tailed)

β = 0.2

ρ (correlation coefficient) = 0.5

$Z_{\alpha/2} = Z_{0.05} = 1.96$

$Z_{\beta} = Z_{0.2} = 0.84$

3.3 Observation and Measurement

Respiratory parameters

- Respiratory parameters from the split-night polysomnography were scored according to the AASM 2012 update for Rules for Scoring Respiratory Events in Sleep (36). All respiratory recordings were reviewed and reported by experts in sleep medicine.

1. Sleep-disordered breathing was rated by the apnea-hypopnea index (AHI).
    a. AHI is the sum of number of apneas and hypopneas per hour of sleep, a discreet variable which ranges from zero to infinity.
2. Degree of hypoxia was rated using indices of hypoxia including oxygen desaturation index (ODI), defined as the average number of oxygen desaturation ≥3% per hour of sleep, as well as the percentage of total sleep time spent below 90% oxygen saturation(T90), and nadir oxygen saturation.
    a. ODI is the average number of ≥3% arterial oxygen desaturations per hour of sleep, a discreet variable which ranges from zero to infinity.

b. T90 is the percentage of total sleep time spent below 90% arterial oxygen saturation, a continuous variable which ranges from zero to 100%.

c. Nadir oxygen saturation is the lowest oxygen saturation measured during the entire total sleep time, a continuous variable which ranges from zero to 100%.

3. Sleep fragmentation were rated by the arousal index (AI) defined as the number of arousals per hour of sleep.

a. Arousal index is the average number of arousals per an hour of sleep, a discreet variable which ranges from zero to infinity.

Parameters from the neuropsychological assessments

- Neuropsychological assessments were administered by neuropsychologist where tests were selected to cover the main cognitive domains as listed in Table 5.

Tests were selected on the basis that they are least affected by the subject's cultural difference, educational level, and literacy. Standardized scores were obtained to adjust for differences in age and educational level when available. Scores were then

expressed in a distribution-based scale to allow for comparison between tests. The main limitation to neuropsychological assessment was the test duration, a more comprehensive and through assessment should be able to provide more information but exhaustion would ensue as time of assessment lengthens resulting in inaccurately lower test scores. All tests were administered in a semi-structured interview session according to the standardized manual for each tests. Summary of neuropsychological tests and the domains assessed are illustrated in Table 5.

Details of each test and its scoring are described as following:

1. D-KEFS Tower Test (94)

    - The test was designed to measure planning, rule learning, inhibition, and ability to maintain the instructional set.

    - The test features three wooden pegs of equal length and five disks of varying sizes. There are a total of 9 items to be completed consecutively, each item increases in difficulty from the former item. For each item, the examiner places the disks on the pegs in a predetermined starting position, then display the ending position of the disks. The examinee was asked to

move the disks to match the ending position with the fewest moves while adhering to the rule of moving only one disk at a time and never place a larger disk over a smaller disk.

- The number of moves to completion, the item-completion time and the final achievement were recorded.
- The total achievement score is the sum of achievement scores for each item. The scores for each item were determined by the total moves and whether the final ending position was achieved for that item.
- The total achievement score was converted to a 19-point scaled score that was adjusted for age, the minimum score is 1 and the maximum score is 19.

2. D-KEFS Design Fluency Test (94)
   - This test was designed to measure initiation, inhibition, and cognitive flexibility.
   - Row of boxes, with each containing an array of dots are presented to the examinee, who was asked to draw a different design in each box using only filled dots and only four lines to connect the dots.

- Three conditions are tested, a time limit of 60-second per condition is given:

  a. Boxes contained only filled dots.

  b. Boxes contained both filled and unfilled dots, examinee was required to connect only the unfilled dots.

  c. Boxes contained both filled and unfilled dots, examinee was asked to draw the designs by alternatively connecting filled and empty dots.

- The Design Fluency total correct measure is a 19-point composite measurement that is derived from a sum of 19-point scaled scores from all three conditions, the minimum score is 1 and the maximum score is 19. Scaled score from each condition is determined by the number of correct designs achieved in that condition adjusted for each age group.

3. D-KEFS Color-Word Interference Test (94)

- This test is based on the Stroop procedure, designed to measure inhibition and cognitive flexibility.

- The examinee was instructed to name the color or read the word printed on a page according to each condition. There were a total of four conditions.

The first condition, the examinee was asked to name the color patches. The second condition, the examinee was asked to read the color-words printed in blank ink. The third condition, the examinee was asked to name the dissonant ink color in which those words are printed. The fourth condition, the examinee was asked to switch between naming the dissonant ink colors and reading the words. The first and second condition have a 90-second time limit, while the third and fourth condition have a 180-second time limit.

- The completion time in seconds for each condition was recorded.
- The 19-point contrast scaled score was derived by comparing the scaled score from the fourth condition (inhibition/switching) and combination of scaled scores from the first and second condition (naming and reading). The scaled score was also adjusted for age, the minimum score is 1 and the maximum score is 19.

4. WAIS-IV Digit Span (95)

- This test is designed to assess the attention and working memory domain.

- Comprises of three subtests

  a. Digit Span Forward: examinee was read a sequence of numbers and asked to recall the numbers in the same order.

  b. Digit Span Backward: examinee was read a sequence of numbers and asked to recall the numbers in reverse order.

  c. Digit Span Sequencing: examinee was read a sequence of number and asked to recall the numbers in ascending order.

- Each item consists of two trials. The test would be discontinued when the examinee failed both trials of an item.

- Correct response for each trial of each item was recorded.

- The Digit Span Total Raw Score was obtained by summing the raw scores from Digit Span Forward, Digit Span Backward and Digit Span Sequencing.

- The 19-point Digit Span scaled score derived from the Digit Span Total Raw Score corrected by age group, the minimum score is 1 and the maximum score is 19.

5. WAIS-IV Symbol Search (95)

- This test was designed to assess the processing speed.
- Examinee was given a task to match one item among the two target symbols with one of the five items in the search group.
- The examinee was asked to complete the items as fast as possible within the time limit of 120 seconds, there are a total of 80 items.
- Correct and incorrect responses were recorded for each item. The total raw score was the number of correct responses minus the number of incorrect responses, items that have not been completed would not be scored.
- The total raw score was then converted to a 19-point scaled score adjusted for each age group, the minimum score is 1 and the maximum score is 19.

6. WAIS-IV Coding (95)

- This test was designed to assess the processing speed.
- Examinee was given a task to copy symbols that are paired with numbers by using a key, the time limit is 120 seconds.

- Correct responses were given a score of 1 point, incorrect responses or items that the examinee did not complete would not be given any point. The total raw score was the sum of items with correct responses.
- The total raw score was converted to a 19-point scaled score adjusted for each age group, the minimum score is 1 and the maximum score is 19.

7. WMS-IV Verbal Pair Association Test (96)

- This test was designed to assess the immediate and delayed auditory memory.
- In the first subtest, the Verbal Paired Associates I, the examinee was read 10 or 14 word pairs and asked to recall the word-pair when read the first word of each pair. There were a total of four trials with varying word sequence. The score was obtained by summing the correct responses from the four trials then transformed to an age-adjusted 19-point scaled score
- In the second subtest, the Verbal Paired Associates II, which was administered 20-30 minutes after the Verbal Pair Associates I, the examinee was asked to recall the paired word when presented with the first word of

each pair for the delayed recall. The total correct responses was transformed to an age-adjusted 19-point scaled score, the minimum score is 1 and the maximum score is 19.

8. WMS-IV Visual Reproduction Test (96)

- This test was designed to assess the immediate and delayed visual memory.
- In the first subtest, the Visual Reproduction I, the examinee was shown a design for 10 seconds per item and asked to draw the design from memory. There were a total of five items. Each design was scored according to a prespecified criteria, the total scores of the five items was summed and transformed to an age-adjusted 19-point scaled score.

- In the second subtest, the Visual Reproduction II, which was administered 20-30 minutes after the Visual Reproduction II, the examinee was asked to draw the designs which were shown to them in the Visual Reproduction I test. Each design was scored according to a prespecified criteria, the total scores of the five items was summed and transformed to an age-adjusted

19-point scaled score, the minimum score is 1 and the maximum score is 19.

The composite measurement of each domain – attention, executive function, memory, processing speed, derived from the average of the age-adjusted 19-point scaled score of tests in each domain. Additionally, a composite measurement of 2 subdomains of memory, the immediate memory domain and the delayed memory domain, derived from the immediate auditory and visual memory and the delayed auditory and visual memory, respectively.

- Mood symptoms were assessed using the Symptom Checklist-90-Revised (SCL-90-R).
- Sleepiness was measured using the Epworth Sleepiness Scale (ESS). Measured using an 8-item self-administered questionnaire assessing the degree of sleepiness in everyday situation. The minimum score is 0 and the maximum score is 24. A score over 10 signifies excessive sleepiness (97, 98).

Table 5 Details of the neuropsychological tests

(95, 96, 99, 100)

Cognitive Domain	Test	Primary Domains	Other Domains
Global cognition	Thai Mental State Examination (TMSE)	Global cognition	-
Attention	WAIS-IV Digit span - digit span forward - digit span backward - digit span sequencing	Attention, working memory	Encoding process, manipulation
Executive function	D-KEFS Tower test	Planning	Rule learning, inhibition, establishing and maintaining cognitive set
	D-KEFS Design fluency test	Initiation, flexibility	Inhibitory control
	D-KEFS Color-word interference test	Inhibitory control	Cognitive flexibility, naming, reading
Memory	WMS-IV auditory memory (verbal pair association test)	Auditory immediate and delayed memory	
	WMS-IV visual memory (visual reproduction test)	Visual immediate and delayed memory	
Processing speed	WAIS-IV processing speed index - Symbol search - Coding	Processing speed	Attention, short-term visual memory, psychomotor speed, visual-motor coordination

Parameters from magnetic resonance imaging of the brain

Image acquisition

- Brain magnetic resonance imaging (MRI) of the whole brain was performed using a 3.0 Tesla system. The following sequences were conducted for all subjects:

    1. 3D-T1-weighted image
    2. T2-weighted image
    3. Fluid attenuated inversion recovery image (FLAIR)
    4. Diffusion weighted image (DWI)
    5. Resting state functional magnetic resonance imaging (rs-FMRI)

Image pre-processing

Digital Imaging and Communications in Medicine (DICOM) files of all MRI sequences are converted into Neuroimaging informatics Technology Initiative (NifTI) files.

Structural MRI image pre-processing

- Cortical reconstruction process was carried out by the recon-all command from the Freesurfer software, version 4.1.0 (http://surfer.nmr.mgh.harvard.edu/) on each

subject's 3D-T1-weighted image which performs all of the reconstruction process automatically (101-118). The preprocessed white and pial surfaces, the reconstructed cortical surface and its labelling are illustrated in Figure 2.

- The steps include:

    1. Motion correction
    2. Non-parametric non-uniform intensity normalization
    3. Computes the affine transform from the subject's image to the Montreal Neurological Institute (MNI) 305 atlas
    4. Intensity normalization
    5. Skull stripping
    6. Subcortical segmentation
    7. Second intensity normalization
    8. White matter segmentation
    9. The midbrain is cut from the cerebrum and the hemispheres are cut from each other
    10. Creation of the cortical surface (Tessellation)

11. Smoothing of the cortical surface
12. Inflation of the cortical surface
13. Automatic topology fixing (QSphere)
14. Creation of the final white and pial surfaces (outputs the cortical thickness data and curvature data)
15. Creates the cortical ribbon mask
16. Inflates the cortical surface into a sphere
17. Register the cortical surface to the ipsilateral spherical atlas
18. Register the cortical surface to the contralateral atlas
19. Outputs the average curvature
20. Cortical parcellation and labelling of each cortical surface
21. Outputs the statistics from the cortical parcellation of each structure

- All images were visually inspected before further measurement.
- Measurement of cortical thickness of each gyrus was measured in centimeter. The value of cortical thickness of each area is the average of the measurement from the outer surface of the white matter, “white surface”, to the cortical surface of that area or “pial

surface". Measurement of the cortical thickness was undertaken by measuring the distance radially from the "white surface" to the "pial surface" at each vertex on the surface. The value of the cortical thickness measurement of each gyri derived from averaging the measurement of cortical thickness of the vertexes on the surface in that gyri (104).

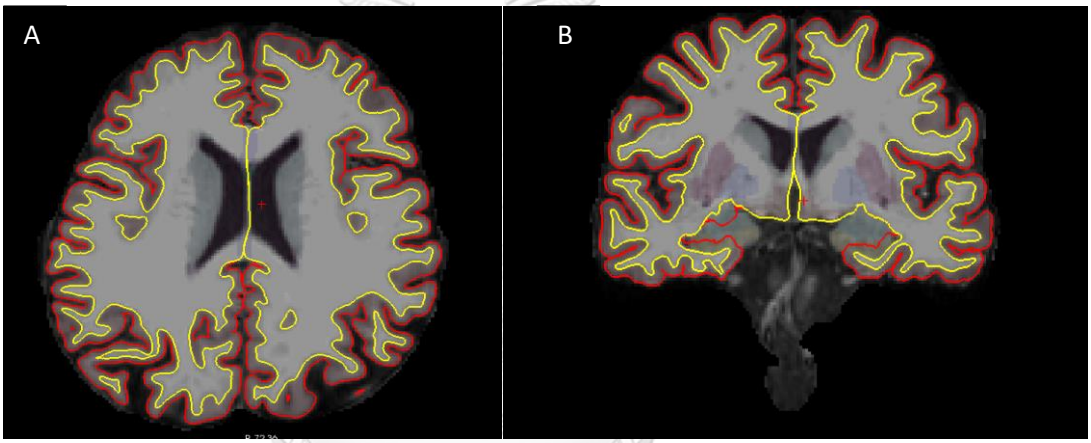


Figure 2 Cortical ribbon mask.
Demonstrate the axial (A) and coronal (B) view of the T1-weighted image of the brain. The red line delineates the "pial surface" or cortical surface and the yellow line delineates the "white surface". The measurement of cortical thicknesss is the distance measured radially from the "white surface" (yellow line) to the "pial surface" (red line).

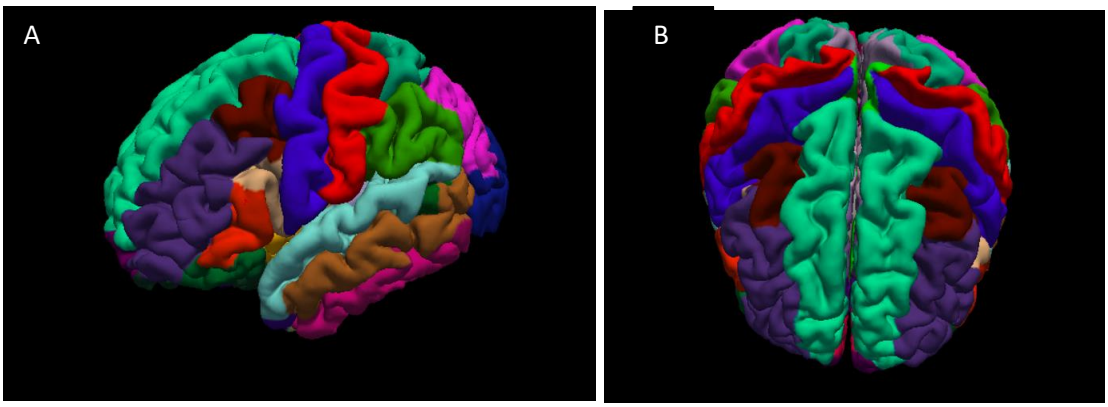


Figure 3 Gray matter parcellation.

Demonstrate the left cortical surface (A) and bilateral frontal and parietal surface (B) of the brain. Each gyrus is labeled in different color according to the brain atlas of the program where one color is designated for one specific gyrus. The same gyrus on both cerebral hemispheres are labeled with the same color.

Diffusion tensor image pre-processing

- The preprocessing of the diffusion weighted images were carried out using the FMRIB's Diffusion Toolbox (FDT) under the FMRIB's Software Library (FSL) (119).

- The following process were applied to each subject's diffusion weighted images:

    1. Brain extraction of the diffusion weighted images by the Brain Extraction Tool (BET) (120), the fractional intensity threshold was set at 0.4.

    2. Correction for Eddy current distortions and subject motion was done by using the Eddy Current Correction (121).

3. DTIFIT was used to fit the tensor models onto the diffusion weighted image at each voxel. Three eigenvalues and its' corresponding eigenvectors were obtained from the diffusion tensor matrix. The fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity and radial diffusivity images were created from the eigenvalues.

    i. The FA represents the degree of anisotropic diffusion which represents the alignment and integrity of structures in each area of the white matter with values ranging from 0 – 1. A value of zero means there is no anisotropic diffusion (isotropic diffusion), for example the CSF has an FA value of zero. While value of one means the diffusion occurs only in one axis. Therefore, a lower FA value in the white matter could infer decreased integrity and alignment of the white matter in that area. The MD represents the average of all diffusivity in that area and is measured in square of millimeter per second, a lower MD could represent decreased integrity of structures in that area (122).

ii. The axial diffusivity measures the diffusivity of water parallel to the axons and radial diffusivity measures the diffusivity of water perpendicular to the axons. The increase in axial diffusivity is rather specific to axonal degeneration while the increase in radial diffusivity is more specific to pathology of the myelin (123, 124)

4. Tract-Based Spatial Statistic (TBSS) tool, part of the FSL, was used to process the images for statistical analysis (120, 125-129).

i. Each subject's FA image was normalized to the standard FMRIB58 template and transformed into a common space.

ii. The mean of all FA images was created from the normalized FA and narrowed down to create the mean FA skeleton, a single line at the center of each tract. A FA threshold of 0.2 was used to exclude the voxels that were either gray matter or cerebrospinal fluid.

iii. Each subject's FA data was then projected onto the mean FA skeleton illustrated in Figure 4.

iv. Similar procedures were carried out for MD, axial diffusivity, and radial diffusivity images.

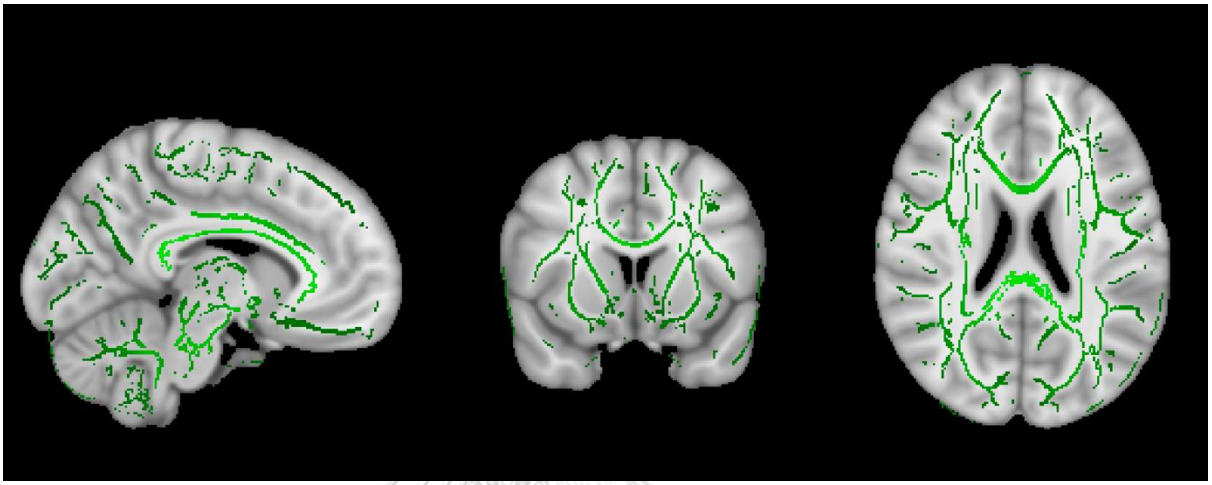


Figure 4 White matter tract FA skeleton.
Demonstrate the sagittal, coronal, and axial view of the mean FA skeleton (green) of all of the subjects projected onto the T1-weighted image of the brain.

fMRI preprocessing

The preprocessing was done with tools that are part of the FMRIB's Software Library (FSL) (119).

- Single subject ICA

1. Each subject's resting 4D fMRI image was input into the FMRI Expert Analysis Tool (FEAT) (130).

2. High-pass filtering was set at 0.01 Hz (100 seconds).

3. Motion correction was done using MCFLIRT (131). Slice timing correction and brain extraction was done.

4. Linear registration of 4D fMRI image to subject's brain-extracted 3D-T1-weighted image was done using boundary-based registration in FMRIB's Linear Image Registration Tool (FLIRT) (132).

5. 3D linear registration to standard space (Montreal Neurological Institute 305 atlas) was done using FLIRT) (132) with 12 degrees of freedom.

6. Non-linear transformation was done using FMRIB's Nonlinear Registration Tool (FNIRT) (128) with a warp resolution of 10 mm.

7. Independent component analysis for each individual subject was done using Multivariate Exploratory Linear Optimized Decomposition into Independent Components tool (MELODIC) (133).

- Classifying and removing noise components from single-subject ICA

1. Classification and labelling of each ICA component into signal or noise was done manually for all subjects.

2. Removal of noise components in each subject was done using the fsl_regfilt tool.

3. Cleaned single-subject ICA was then registered to the standard space (Montreal Neurological Institute 305 atlas) using apply warp from FNIRT (128).

- Group ICA

1. Group ICA was done using MELODIC (133).

2. Subjects were divided into the mild and severe group of each hypoxic parameters based on the value of that parameter relative to the median value of the group.

3. ICA components of the group were set at 30 components.

Demographic data

- Basic characteristics (e.g., age, sex, years of education, occupation, medical history, medication use, BMI) will be obtained by an interview and recorded in the case record form

3.4 Research Process

1. Recruitment of subjects with newly-diagnosed moderate to severe obstructive sleep apnea by split-night polysomnography from the Excellence Center for Sleep Disorders, King Chulalongkorn Memorial Hospital.

2. Subjects were informed of details of the research and its methodology, written information documents were given to each participant, all inquiries from participants were addressed by the principle investigator, after that, participants were given time to decide to sign the informed consent.

3. Basic characteristics, medical history, and current medication were obtained by an interview with the subject and recorded in the case record form.

4. Schedule for cognitive assessment and brain MR imaging were within one month from the date of polysomnography. The participants would only be required to be present at the venue of study only for these two visits, the two visits were preferably scheduled within the same day.

5. Assessment of cognitive function by a battery of selected neuropsychological tests administered by neuropsychologists, a regular session should take approximately one hour and a half.

6. Brain MR imaging would be acquired according to the prespecified protocol. In cases where abnormal findings are found on the brain MR imaging, the patient was informed of the result within a week of the brain MR imaging and advised to pursue further diagnostic tests or treatment.

7. Respiratory parameters from the split-night polysomnography was assessed by trained sleep technicians and interpreted by sleep medicine specialists in which the parameter was recorded in the polysomnography report.

3.5 Data Collection

Data of the basic characteristics, medical history, and medications were collected in an interview session between the investigator and the subject and recorded in the case record form. All neuropsychological tests and mood assessments will be administered and data collected by neuropsychologists in the clinic. Respiratory parameters from the split-night polysomnography was recorded in the

polysomnography report. Digital Imaging and Communications in Medicine (DICOM) files of brain MR imaging will be converted to the Neuroimaging Informatics Technology Initiative (NifTI) format for further analysis.

3.6 Data Analysis

Analysis of demographic data, clinical data, and neuropsychological test scores

- The characteristics of the subjects were summarized as median and range for continuous variables and as frequencies and percentages for categorical variables.
- The correlation between respiratory parameters and z-scores of each cognitive domain were analyzed using the Spearman rank correlation analysis. The effect sizes of the correlations were defined as small (0.30), medium (0.50), or large (0.80).
- Multiple linear regression was used to determine factors that contribute to cognitive impairment in each domain. Z-scores of each cognitive domain were used as dependent variables. Respiratory parameters were used as independent

variables. Confounders, namely, years of education and the presence of cardiovascular risks were added to the model as covariates.

- Participants were divided in to two groups based on the severity of the respiratory parameters. The degree of severity of hypoxia was determined by the frequency of the desaturation (ODI), the duration of the desaturation (T90), and the severity of the desaturation (nadir oxygen saturation). The degree of arousal was determined by the arousal index. Participants were classified as mild when their value of the given feature were below the median for ODI, T90 and arousal index; higher than the median for nadir oxygen saturation. Participants were classified as severe when their value of the given feature were equal to or above the median for ODI, T90 and arousal index; lower or equal to the median for nadir oxygen saturation.

- Demographics, respiratory parameters, and neuropsychological test results were compared between the mild and severe groups using the Mann-Whitney U test and the Fisher Exact test.

- All tests are two-tailed and $p < 0.05$ is considered statistically significant.

- All statistical analyses were performed using Python version 3.7.6.

Analysis of cortical thickness

- General linear model (GLM) was used to determine the difference of the cortical thickness between each groups of mild and severe hypoxia in OSA, as well as the correlation of the respiratory parameters to cortical thickness of each area.
- The vertex-wise gray matter cortical thickness was the dependent variable.
- The frequency of the desaturation (ODI), the duration of the desaturation (T90), the severity of the desaturation (nadir oxygen saturation), and the degree of arousal (AI) were used to classify patients into mild and severe groups for the analysis by GLM.

- ODI, T90, nadir oxygen saturation, and AI were also assessed for their correlation to the cortical thickness of each area.
- Cluster-wise correction for multiple comparison through Monte Carlo simulation was done, cluster-forming threshold $p<0.05$ (one-tailed).
- The analysis was performed with the Freesurfer Qdec (134).

Analysis of diffusion tensor imaging

- The nonparametric permutation inference for the general linear model, randomise tool, in FSL was used to test for voxel-wise statistical difference of FA between groups (125, 135).
- The Threshold-Free Cluster Enhancement (TFCE) approach was used and the p level of < 0.05 was considered statistically significant.
- Similar process was carried out for MD, axial diffusivity, and radial diffusivity images.

Analysis of resting-state fMRI

Comparison of resting-state functional connectivity in each resting-state network between groups.

- Dual Regression (136, 137) was done to generate the subject-specific spatial maps and associated timeseries from the group-average analysis.
- The nonparametric permutation inference for the general linear model, randomise tool, was used to test for voxelwise statistical difference (135).

- The Threshold-Free Cluster Enhancement (TFCE) approach was used and the p level of < 0.05 was considered statistically significant.

Chapter 4 Result

There were 62 OSA patients from the Excellence Center for Sleep Disorders, King Chulalongkorn Memorial Hospital who met the inclusion criteria from January 2019 to January 2020. Four participants were excluded according to the exclusion criteria, 40 participants declined to participate in the study, and 1 participant was not able to undergo the MRI study due to a problem with the MRI machine. The study was terminated earlier than the prespecified date due to an unprecedented technical problem with the MRI machines. Ultimately, 17 participants were enrolled in this study. The details of the process are depicted in figure 5.

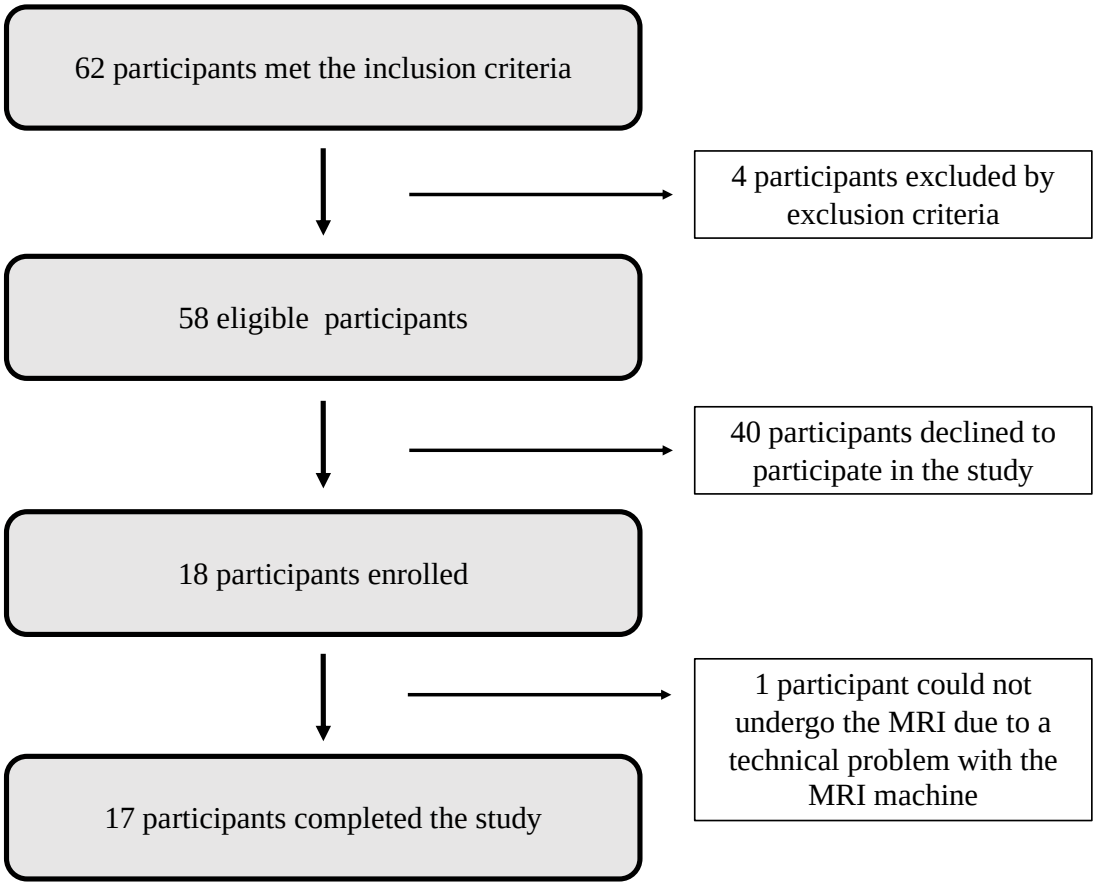


Figure 5 Outline of the research process

4.1 Demographic data, clinical data, and neuropsychological test results

Of the 17 participants, 8 (47%) were men and 9 (53%) were women. The median age was 57 years and the median years of education was 16 years. Fourteen of the participants were identified with either a history of cardiovascular disease or had cardiovascular risk such as diabetes mellitus, hypertension, or dyslipidemia prior to enrollment. The median BMI was 25.2 kg/m^2 (range 21.1 kg/m^2 -52.3 kg/m^2). All of the

participants had been recently diagnosed with moderate or severe OSA by a split-night polysomnography. None has received treatment for OSA.

The median AHI was 60.6 with a range between 15 and 110. The median nadir oxygen saturation was 77% (range, 51% – 95%), the median ODI was 26.9 (range, 0 – 105.5), and the median T90 was 3.15% (range, 0% – 16.8%). The median sleepiness measured by ESS was 12 signifying excessive sleepiness.

All participants scored over 23 on the TMSE test, the median TMSE score was 30 (range, 27 – 30). A summary of the demographic, clinical data, respiratory parameters, and neuropsychological tests results are illustrated in table 6 and 7.

Comparison of the demographic and clinical features of those included and excluded in the research are demonstrated in table 8.

Table 6 Demographics, clinical characteristics, and respiratory parameters

Characteristics	All subjects	Severe desaturation	Mild desaturation	Frequent desaturation	Infrequent desaturation	Long desaturation	Short desaturation
No. of subject	17	9	8	9	8	9	8
Age	57 (51 - 76)	57 (52 – 76)	56 (51 – 66)	57 (51 – 76)	56.5 (52 – 65)	60 (54 – 76)	55 (51 – 66)
Male (%)	8 (47%)	5 (55%)	3 (37.5%)	4 (44%)	4 (50%)	5 (55%)	3 (37.5%)
Education (years)	16 (6 - 23)	16 (12 – 23)	16 (6 – 19)	16 (12 - 23)	16 (6 – 18)	16 (12 – 23)	16 (6 – 19)
BMI	25.2 (21.1 – 52.3)	25.2 (23.3 – 52.3)	25.2 (21.1 – 31.1)	28.9 (23.4 – 52.3)	24.89 (21.1 – 30.9)	25.2 (23.3 -52.3)	24.99 (21.1 - 31)
AHI	60.6 (15 – 110.3)	47.8 (22.7-110.3)	60.9 (15 – 81.1)	63.7 (35.1 – 110.3)*	27.6 (15 – 81.1)*	61.7 (22.7 – 110.3)	49.95 (15 - 81.1)
Mean oxygen saturation (%)	94 (90 – 98)	93 (90 - 95)*	95.5 (92 – 98)*	92 (90 – 94)*	95.5 (93 – 98)*	92 (90 – 95)*	95.5 (93 – 98)*
Nadir oxygen saturation (%)	77 (51 – 95)	72 (51 – 77)*	82.5 (78 – 95)*	77 (51 – 88)	80 (67 – 95)	73 (51 – 78)*	82.5 (67 – 95)*
ODI	26.9 (0 - 105.5)	41.17 (16.35 – 105.5)	18.32 (0 – 49.6)	41.96 (26.91 – 105.5)*	13.72 (0 – 25.54)*	41.68 (16.35 – 105.5)*	17.58 (0 - 49.6)*
T90 (%)	3.15 (0 – 16.8)	6.01 (3.01 – 16.78)*	1.09 (0 – 9.05)*	6.11 (0.2 – 16.78)*	1.53 (0 – 4.02)*	6.11 (3.15 – 16.78)*	1.09 (0 - 3.01)*
AI	32 (14.9 – 67.6)	34.2 (14.9 – 67.6)	30.7 (15.3 – 66.8)	35.6 (14.9 – 67.6)	24.65 (15.3 - 66.8)	32 (14.9 - 67.6)	32.5 (15.3 - 66.8)
ESS	12 (3 – 21)	12 (5– 18)	12 (3 – 21)	12 (3 – 16)	12 (5 – 21)	12 (3 – 18)	12 (6 – 21)

Data are presented as median or count (range or proportion).

*Significant at p <0.05 based on Mann-Whitney U test or Fisher Exact test.

AHI, apnea-hypopnea index. AI, arousal index. BMI, body mass index. ESS, Epworth Sleepiness Scale. ODI, oxygen desaturation index. T90, percentage of total sleep time spent below 90% oxygen saturation.

Table 7 Neuropsychological test results

Cognitive test/domain	All subjects	Severe desaturation	Mild desaturation	Frequent desaturation	Infrequent desaturation	Long desaturation	Short desaturation
No. of subject	17	9	8	9	8	9	8
TMSE	30 (27 – 30)	30 (28 - 30)	29.5 (27 – 30)	30 (28 – 30)	29 (27 – 30)	30 (28 – 30)	29.5 (27 – 30)
Executive function	0.22 (-1 – 1)	0.44* (-0.44 – 1)	-0.17* (-1 – 0.33)	0.33 (-0.89 – 1)	-0.06 (-1 – 0.89)	0.33 (-0.44 – 1)	-0.17 (-1 – 0.44)
Memory	0.17 (-0.75 – 1.83)	0.17 (-0.75 – 1.83)	0.34 (-0.16 – 1.25)	0 (-0.75 – 1.83)	0.55 (-0.16 – 1.25)	0 (-0.75 – 1.83)	0.8 (-0.16 – 1.25)
Attention	0 (-0.67 – 1.17)	0 (-0.67 – 1.17)	0 (-0.67 – 0.67)	0 (-0.67 – 0.67)	0.17 (-0.5 – 1.17)	0 (-0.67 – 1.17)	0.09 (-0.5 – 0.67)
Processing speed	0.34 (-2.17 – 2)	0.67 (-0.34 – 2)	0.25 (-2.17 – 0.83)	0.67 (-0.33 – 2)	0.08 (-2.17 – 1.87)	0.34 (-0.34 – 2)	0.34 (-2.17 – 1.84)

Data are presented as median (range). The neuropsychological test result of each cognitive domain are presented as z-score.

*Significant at $p < 0.05$ based on Mann-Whitney U test or Fisher Exact test.

Table 8 Comparison of included and excluded participants

	Included	Excluded
No.	17	41
Age	57	56
Male (%)	47%	63%
BMI	25.2	27.4
CV risk (%)	82.4	65%
AHI	60.6	54.5
ODI	26.9	20.6
T90	3.15	2.8
Nadir O_2	77	77.5
AI	32	49.3
ESS	12	11

4.2 Association between respiratory parameters and neuropsychological test results

The Spearman's rank correlation analysis was used to assess the correlation between the respiratory parameters and the neuropsychological test results. The results are illustrated in Table 9. There was no correlation between ODI, as well as other respiratory parameters, with the z-score of the tower test. In addition, there was no correlation between ODI and any cognitive domain tested in this study.

However, we found a significantly negative correlation between nadir oxygen saturation level and the z-score of the executive function domain. Also, there was a significantly positive correlation between T90 and the z-score of the executive domain.

Lastly, a positive correlation was found between ESS and the z-score of the attention domain.

Next, a multivariate linear regression analysis was used to assess the association between the respiratory parameters and the neuropsychological test results. The number of years of education and the presence of cardiovascular disease or cardiovascular risks were added to the model as covariates. There was no association between the respiratory parameters including nadir oxygen saturation, ODI, T90, ESS, or AI and any z-score neuropsychological test results. The results of the analysis are shown in Table 10.

Table 9 Correlation between demographics, respiratory parameters and neuropsychological test results

Characteristics	Tower test	Design fluency	Color-word interference	Executive function	Memory	Attention	Processing speed
Age	-0.13	-0.35	0.11	-0.24	-0.16	-0.5	-0.23
Education (years)	0.22	0.32	0.38	0.43	0.38	0.47	0.27
AHI	0.37	0.36	-0.1	0.33	0.25	-0.11	0.34
Nadir oxygen saturation (%)	-0.39	-0.52*	-0.1	-0.52*	-0.13	0.04	-0.26
ODI	0.21	0.15	-0.03	0.22	-0.17	-0.32	0.41
T90 (%)	0.35	0.41	0.19	0.49*	-0.11	-0.17	0.25
AI	0.42	0.16	-0.34	0.07	0.25	-0.07	0.30
ESS	0.34	0.18	-0.01	0.08	0.12	0.6*	-0.18

Data are presented as Spearman's rank correlation coefficient.

*Significant at $p < 0.05$.

AHI, apnea-hypopnea index. AI, arousal index. ESS, Epworth Sleepiness Scale. ODI, oxygen desaturation index. T90, percentage of total sleep time spent below 90% oxygen saturation.

Table 10 Association between respiratory parameters and cognitive function

Cognitive domain	Respiratory parameters	Beta	p-value
Tower test	AHI	0.006	0.39
	Nadir O2	-0.012	0.47
	ODI	0.003	0.69
	T90	0.015	0.64
	AI	0.064	0.08
	ESS	0.012	0.22
Executive function	AHI	0.006	0.31
	Nadir O2	-0.013	0.34
	ODI	0.007	0.20
	T90	0.033	0.22
	AI	-0.004	0.63
	ESS	0.038	0.25
Memory	AHI	0.002	0.79
	Nadir O2	-0.003	0.85
	ODI	-0.008	0.27
	T90	-0.017	0.63
	AI	0.01	0.33
	ESS	0.039	0.35
Attention	AHI	-0.001	0.86
	Nadir O2	0.002	0.84
	ODI	-0.0004	0.93
	T90	0.001	0.96
	AI	-0.005	0.49
	ESS	0.046	0.06
Processing speed	AHI	0.012	0.21
	Nadir O2	-0.023	0.36
	ODI	0.017	0.08
	T90	0.049	0.32
	AI	0.017	0.29
	ESS	0.037	0.53

All multivariate linear regression analyses were adjusted for years of education and presence of cardiovascular risk factors or cardiovascular disease. AHI, apnea-hypopnea index. ESS, Epworth Sleepiness Scale. O2, oxygen. ODI, oxygen desaturation index. T90, percentage of total sleep time spent below 90% oxygen saturation.

4.3 Defining the characteristics and severity of hypoxia in OSA

As previously mentioned, one of the main mechanisms causing injury to the brain is through hypoxia. In this study, we aimed to study the effect of hypoxia on the brain using parameters of hypoxia severity rather than the AHI commonly used to measure the severity of OSA. We have identified the characteristic of hypoxia in OSA by three features that were measured by the polysomnography, namely, the degree of desaturation (nadir oxygen saturation), the duration of the desaturation (T90), and the frequency of the desaturation (ODI), as mentioned above. Of note, the correlation of AHI to each of the hypoxia features and the arousal index (AI) are demonstrated in figure 6. Interestingly, only ODI and AI demonstrated a moderately positive correlation to AHI. We did not observe any correlation between T90 or nadir oxygen saturation level to AHI in this study.

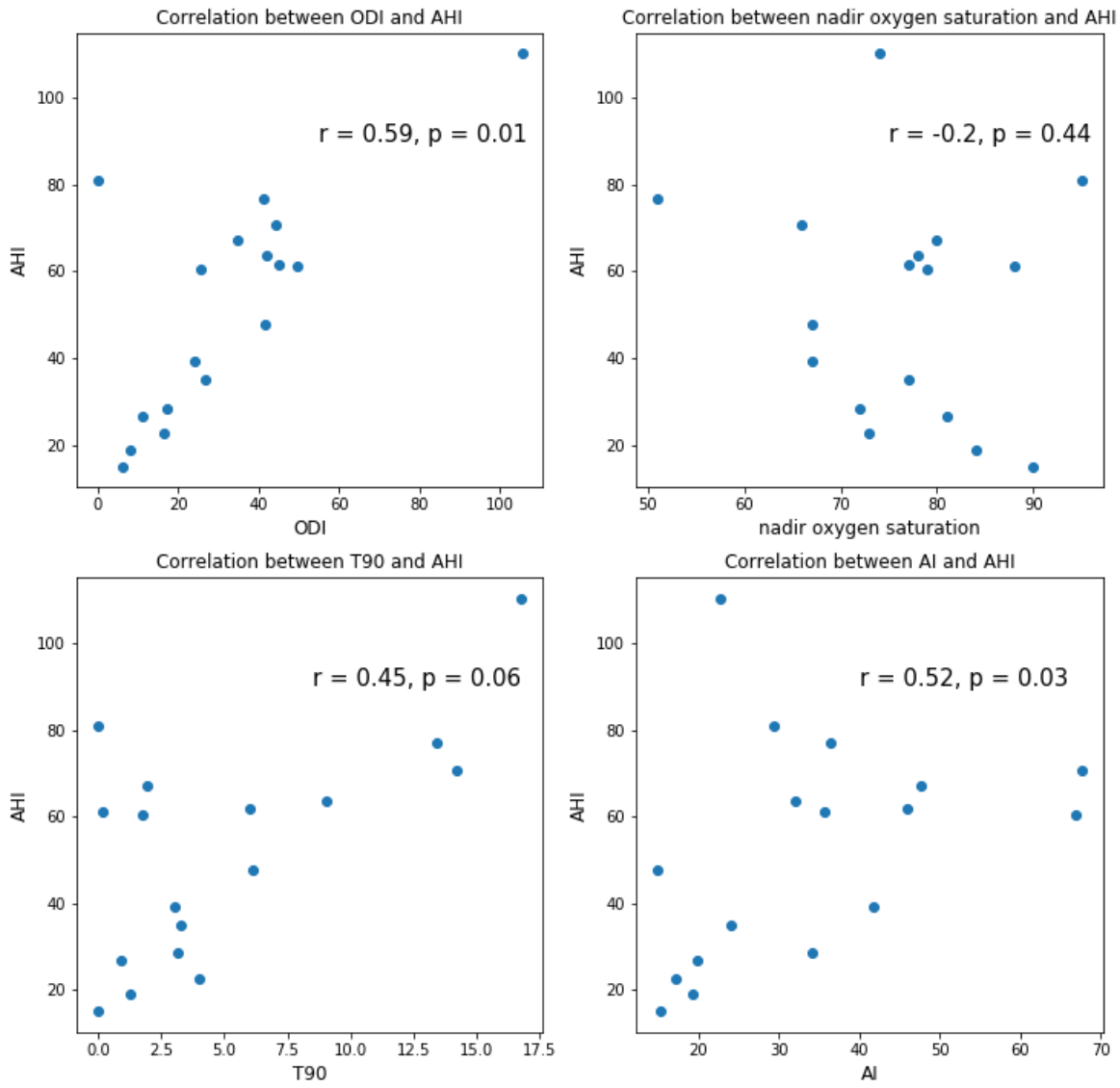


Figure 6 Correlation of hypoxic parameters and arousal index to AHI.
Spearman's rank correlation coefficient and p-value are demonstrated.

Participants were classified into two groups, the severe group and the mild group, per each feature of hypoxia with regards to their value of each hypoxic feature relative to the median value of the group. Consequently, the number of participants

classified as severe and mild for each hypoxic feature are 9 and 8, respectively. The characteristics, respiratory parameters, and neuropsychological test results of the groups are illustrated in Table 6 and 7. Between the severe and the mild groups of each hypoxic feature, there was no difference in age, years of education or BMI. There was also no difference noted in sleep fragmentation or sleepiness measured by the arousal index and ESS, respectively. The AHI was comparable between the severe and the mild groups except between the more frequent and less frequent desaturation groups measured by ODI.

Neuropsychological test results demonstrated higher z-score in only the executive function domain in the severe desaturation group compared to the mild desaturation group. Comparing between the severe and mild groups of hypoxia when the frequency and the duration of hypoxia were considered, there was no significant difference in any of the cognitive domains z-score between the groups.

4.4 Neuroimaging results

Cortical thickness analysis: correlation of respiratory parameters to the cortical thickness

A whole-brain voxel-wise analysis of correlation between respiratory parameters and cortical thickness of each region was undertaken for the following respiratory parameters: ODI, T90, nadir oxygen saturation, and AI.

There was no correlation between the aforementioned respiratory parameters and the cortical thickness in any region of the brain.

Cortical thickness analysis: difference between mild and severe hypoxia groups

Whole-brain cortical thickness analysis was done to compare cortical gray matter thickness between the severe group and the mild group for each hypoxic feature. Total brain volume, age, and gender were added as covariates. Monte Carlo cluster correction was performed with a significant level of $p < 0.05$, one-tailed.

Compared to mild degree of desaturation, the group with severe desaturation, lower nadir oxygen saturation, demonstrated two clusters of decreased cortical thickness at the right pars triangularis (Tailarach coordinates x, y, z mm, size mm^2: 39.7,

33.1, 9.8, 1365.57) and the right inferior parietal (Tailarach coordinates x, y, z mm, size mm^2: 40.9, -66.7, 37.9, 1443.02) demonstrated in Figure 7.

Those with higher frequency of desaturation, higher ODI, showed one cluster of cortical thinning compared to patients with lower frequency of desaturation. The cluster was identified at the right superior parietal (Tailarach coordinates x, y, z mm, size mm^2: 19.2, -81.2, 36.4, 1381.35) as demonstrated in Figure 8.

There was no demonstrable difference in cortical thickness between the long and short duration groups (higher T90 vs. lower T90).

There was no demonstrable difference in cortical thickness between the groups with high AI compared to low AI.

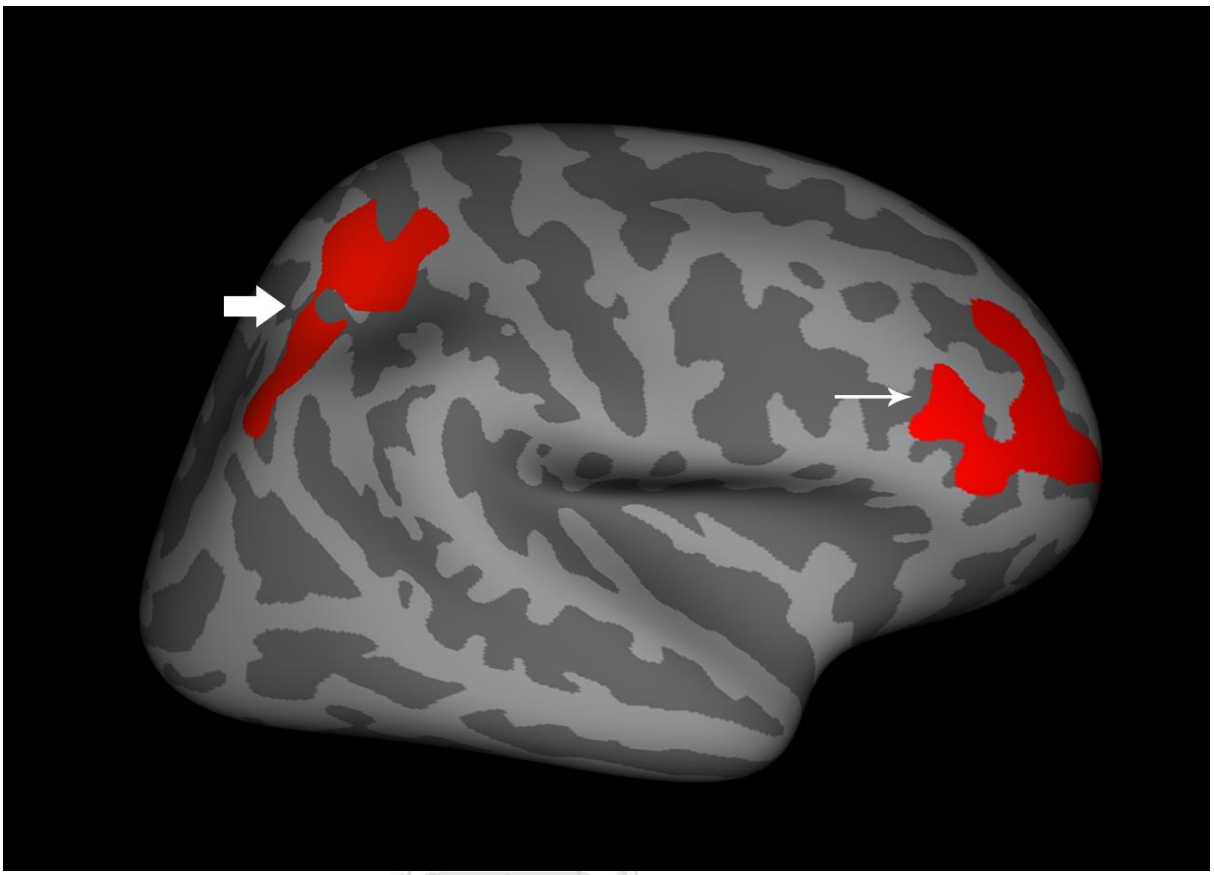


Figure 7 Cortical thickness analysis: desaturation groups.

An inflated pial surface of the right cerebral hemisphere demonstrating two clusters of cortical thinning at the right pars triangularis (Tailarach coordinates x, y, z mm, size mm^2 : 39.7, 33.1, 9.8, 1365.57; cluster-wise p-value = 0.0083) (small arrow) and the right inferior parietal (Tailarach coordinates x, y, z mm, size mm^2: 40.9, -66.7, 37.9, 1443.02; cluster-wise p-value = 0.0057) (large arrow) when compared between the group with severe desaturation to the group with mild desaturation. The mean cortical thickness of the severe and mild desaturation groups were 2.21 mm and 2.27 mm at the right pars triangularis and 2.27 mm and 2.37 mm at the right inferior parietal (thickness of the structure from cortical parcellation).

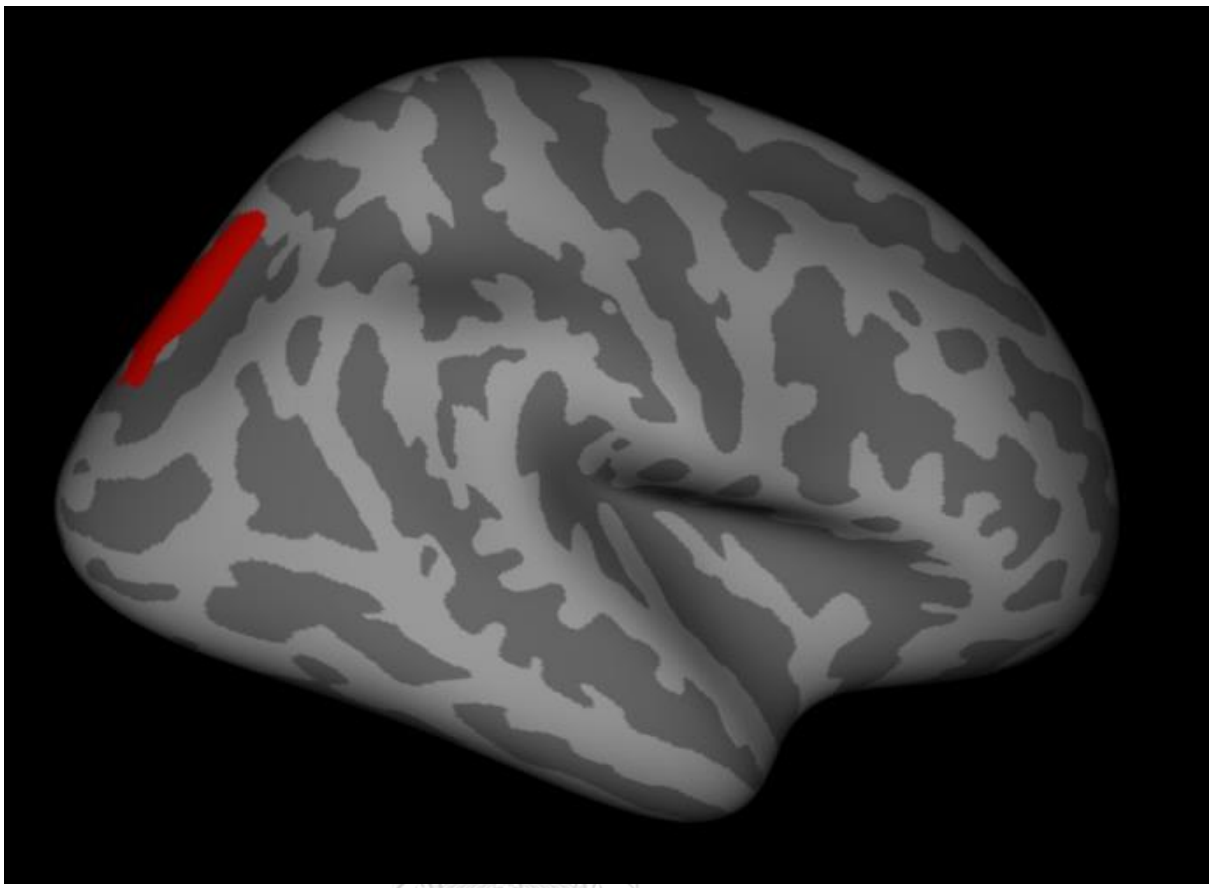


Figure 8 Cortical thickness analysis: ODI groups.

An inflated pial surface of the right cerebral hemisphere demonstrating one cluster of decreased cortical thickness at the right superior parietal (Tailarach coordinates x, y, z mm, size mm^2: 19.2, -81.2, 36.4, 1381.35; cluster-wise p-value = 0.0077) (red) when compared between the group with high ODI to the group with low ODI. The mean cortical thickness of the high and low frequency groups were 2.00 mm and 2.08 mm (thickness of the structure from cortical parcellation).

Diffusion tensor imaging analysis

The Tract-Based Spatial Statistic (TBSS) tool was used to analyzed the voxel-wise statistical difference in FA, MD, radial diffusivity, and axial diffusivity between the mild and the severe groups in each hypoxia feature.

Fractional anisotropy (FA)

Comparison between the mild and the severe desaturation groups (nadir oxygen saturation) revealed no statistically difference in FA between both groups.

Comparison between the short and long desaturation groups (T90) revealed no statistically difference in FA between both groups.

Comparison between the less frequent and more frequent desaturation groups (ODI) revealed no statistically difference in FA between both groups.

Comparison between the high AI and low AI revealed no statistically difference in FA between both groups.

Median diffusivity (MD)

Comparison between the mild and the severe desaturation groups (nadir oxygen saturation) revealed no statistically difference in MD between both groups.

Comparison between the short and long desaturation groups (T90) revealed no statistically difference in MD between both groups.

Comparison between the less frequent and more frequent desaturation groups (ODI) revealed no statistically difference in MD between both groups.

Comparison between the high AI and low AI revealed no statistically difference in MD between both groups.

Axial diffusivity

Comparison between the mild and the severe desaturation groups (nadir oxygen saturation) revealed no statistically difference in axial diffusivity between both groups.

Comparison between the short and long desaturation groups (T90) revealed no statistically difference in axial diffusivity between both groups.

Comparison between the less frequent and more frequent desaturation groups (ODI) revealed no statistically difference in axial diffusivity between both groups.

Comparison between the high AI and low AI revealed no statistically difference in axial diffusivity between both groups.

Radial diffusivity

Comparison between the mild and the severe desaturation groups (nadir oxygen saturation) revealed no statistically difference in radial diffusivity between both groups.

Comparison between the short and long desaturation groups (T90) revealed no statistically difference in radial diffusivity between both groups.

Comparison between the less frequent and more frequent desaturation groups (ODI) revealed no statistically difference in radial diffusivity between both groups.

Comparison between the high AI and low AI revealed no statistically difference in radial diffusivity between both groups.

FMRI analysis

The default mode network (DMN), central executive network (CEN), sensorimotor network (SMN), language network, visual network, and the auditory network were identified from the resting-state fMRI group ICA analysis as demonstrated in figure 9-14.

Comparison between the mild and the severe desaturation groups (nadir oxygen saturation) revealed no statistically difference in the resting-state functional connectivity in any of the networks between both groups.

Comparison between the short and long desaturation groups (T90) revealed no statistically difference in the resting-state functional connectivity in any of the networks between both groups.

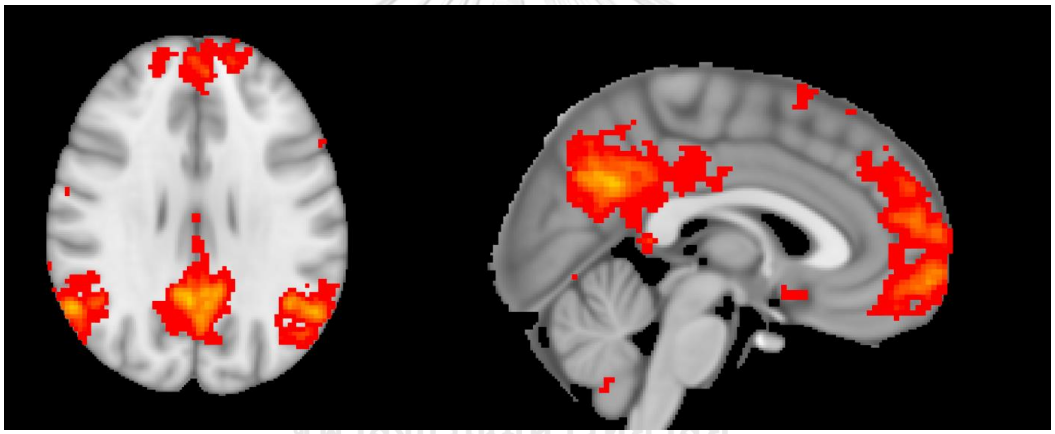


Figure 9 Default mode network (DMN) (axial view and sagittal view).

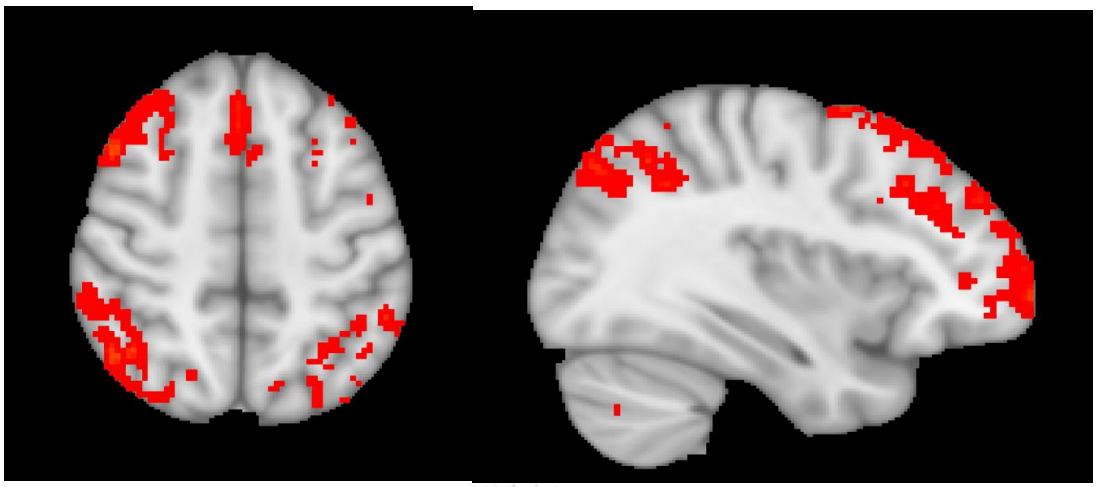


Figure 10 Central executive network (CEN) (axial view and sagittal view).

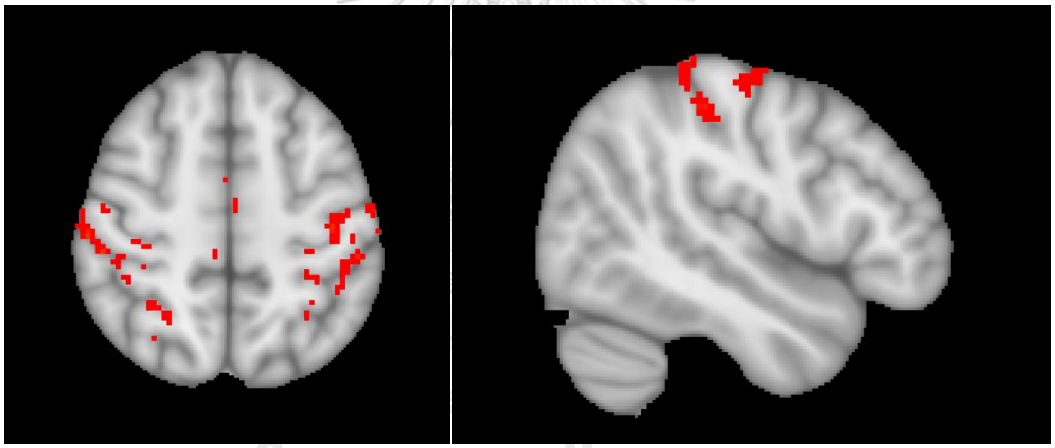


Figure 11 Sensory motor network (SMN) (axial view and sagittal view).

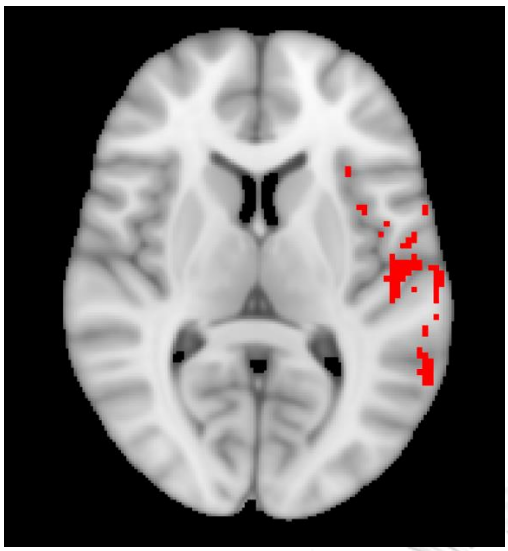


Figure 12 Language network (axial view).

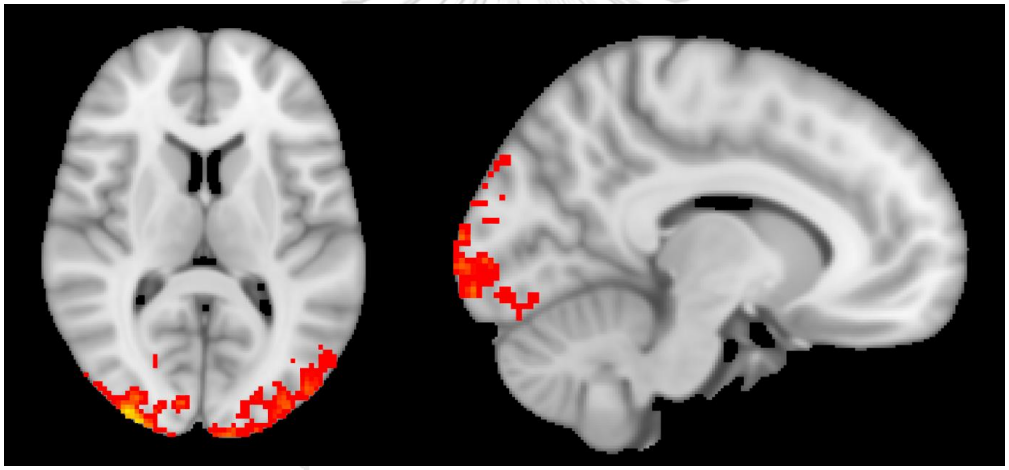


Figure 13 Visual network (axial and sagittal view).

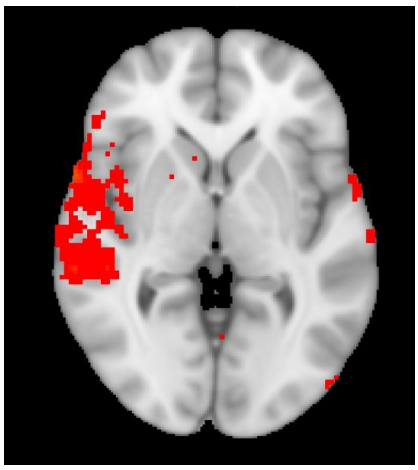


Figure 14 Auditory network (axial view).

Comparison between the less frequent and more frequent desaturation groups (ODI) revealed no statistically difference in the resting-state functional connectivity in any of the networks between both groups.

Comparison between the high AI and low AI revealed no statistically difference in the resting-state functional connectivity in any of the networks between both groups.

Chapter 5 Discussion

5.1 Association between hypoxia and cognitive function

This is the first study to assess the parameters measuring the degree of intermittent hypoxia in OSA and its effect on the brain. The degree of desaturation (nadir oxygen saturation), the duration of the desaturation (T90), and the frequency of the desaturation (ODI) were chose to represent the different parameters of intermittent hypoxia. Our study did not find any association between the features of hypoxia and cognitive function tests in any of the domain tested. There was no association between other respiratory parameters - AHI, AI, or ESS - with cognitive function tests as well. Other studies that explored this relationship have reported mixed findings. Ju et al. (56) had found that hypoxia measured by ODI was associated with lower scores on the auditory memory test. Two other studies found T90 to be associated with lower performance in executive function tests (59, 71), while another two studies reported no association between the two (69, 70). Moreover, two large community studies reported no significant relationship between ODI (68) or T90 (42, 68) and executive function (68). Several factors could explain this discrepant finding between the studies.

First, different tests were used for the measurement of executive function or memory in these studies. Second, the severity of OSA in participants also varies, ranging from the mildest severity in the community studies to more severe OSA in the sleep clinic studies. Finally, limitation of the sample size in our study as well as some other studies (69, 70) might prevent the outcome from reaching a statistically significant threshold.

5.2 Association of hypoxia in OSA to cortical gray matter thickness

Structural changes of the cortical gray matter between groups were assessed using the cortical thickness analysis. The result of the analysis revealed two clusters of cortical thinning at the right inferior frontal gyrus and right inferior parietal gyrus in the group with severe desaturation compared to the group with mild desaturation. Another cluster of cortical thinning was found at the superior parietal gyrus when comparing between the high ODI group and the low ODI group. Studies of the association between hypoxia and cortical thickness have reported mixed findings. A study by Cross et al. reported an association between the severity of the hypoxia component in OSA and a decreased in cortical thickness at the left temporal pole and right fusiform gyrus (76).

While, another study by Baril et al. reported an increase in cortical thickness at the left middle frontal gyrus, right frontal pole, right superior and inferior parietal lobule and left posterior cingulate gyrus in relation to the severity of hypoxia measured by nadir oxygen and T90 (74).

5.3 Association of hypoxia in OSA to white matter integrity

DTI analysis was used to identify changes in the white matter tracts of the brain. There was no significant difference in any of the DTI parameters when the severe and the mild groups of each hypoxic parameter were compared. No other study had investigated the relationship between hypoxia and parameters from DTI. Changes in the white matter integrity had been reported in OSA patients compared to controls in many of the known fiber tracts in the frontal, parietal, temporal, cingulate cortices and the brainstem and the cerebellum (57, 77, 79). Compared to our study where all of the participants were diagnosed with moderate or severe OSA, the difference of in the change of the white matter integrity between the two groups—

mild and severe hypoxia—might be too subtle to be detected.

5.4 Association of hypoxia in OSA to functional connectivity of the brain

Independent component analysis (ICA) of functional MRI data between the mild and severe group of each hypoxic parameter did not reveal any difference in resting-state functional connectivity in any of the networks. A study by Zhang et al. (91) using ICA to determine alteration in resting-state functional connectivity between OSA and controls reported decreased in resting-state functional connectivity in the anterior DMN, bilateral CEN and SMN and increased in resting-state functional connectivity in the posterior DMN. Other studies that used techniques such as ReHo, seed-based analysis, and ALFF found decreased, aberrant, or increased resting-state functional connectivity in areas that are part of the DMN, CEN, SN, and SMN networks (80, 83-85, 87-90, 92). Moreover, graph theoretical analysis in studies (81, 82, 86) comparing OSA and controls also reported reduced both global and regional efficiency, as well as reduced specialization and integration. This demonstrates that OSA affects many large scale networks in the brain as well as reduced the efficiency in these networks. Findings from fMRI studies resonate with the multi-domain impairment in cognitive functions reported in past studies. Apart from the small sample size, the lack

of detectable change in the resting-state functional connectivity across large scale networks in our study could be attributed to the multiple smoothing of the data in the preprocessing stage of the fMRI analysis to mitigate the effect of artifacts acquired during the fMRI scan.

5.5 Mechanisms causing pathological changes as a result of hypoxia in OSA

The main mechanisms causing cerebral insult in OSA are intermittent hypoxia and sleep fragmentation. The intermittent nature of the hypoxia in OSA is known to cause brain injury similar to the ischemic-reperfusion injury. The pathological cascade that follows includes excessive oxidative stress, production of reactive oxygen species, neuroinflammation, sympathetic activation, endothelial dysfunction, and subsequent neuronal loss (138). In the acute stage, hypoxia causes energy deprivation and produces cytotoxic edema as a result of the reactive and inflammatory process which later progress to cortical atrophy in the chronic stage. This pathological process could explain the mixed findings of the cortical thickness changes in OSA, with studies reporting an increased in cortical thickness and some studies reporting a decreased in cortical thickness. Another interesting aspect of our finding is the asymmetric structural

change of the cortical thickness which has also been reported in other studies. There is still no clear explanation but some postulated that the result is attributable to the difference in the vascular supply and perfusion to both sides of the brain and the lateralization of the brain (139, 140).

Our study further highlights the distinct effect of the intermittent hypoxia on the brain. Of interest, the areas affected by the higher degree of desaturation and the frequency of desaturation are localized to the frontal and parietal regions. This is in agreement with other studies that found changes in the gray matter cortical thickness in the frontal, parietal, temporal, and cingulate gyri region (74, 76). Contrary to common findings of hypoxic injury where the CA1 in the hippocampus and the cerebellum are most commonly affected (139). We hypothesize that the unique characteristic of the intermittent hypoxia, namely, the frequent and recurrent desaturation within a night reaching as high as 105 times per hour and the possibility of a significant desaturation with nocturnal oxygen saturation as low as 51% in this study, contributed to injuries in brain areas other than that affected by hypoxic injury in other conditions. However, due to the small size of the hippocampus, the cortical thickness analysis might merely

not be sensitive enough to detect changes in the structure. Future studies might employ a hippocampal subfield analysis to specifically explore the structural change in the hippocampus.

We did not find any difference in the cognitive profile of participants between the severe and mild groups of each hypoxic parameter. The fact that there is no detectable impairment in the cognitive functions measured by neuropsychological tests in light of an evident structural changes of the cortex lead us to three possible explanations. First, although the structural change is located within the central executive network associated with executive function and attention, the compensatory mechanism of the brain prevents impairment of those functions through mechanisms such as increased activation or loss of lateralization of the brain (141). The compensatory mechanisms of the brain have been described in many circumstances of brain pathology with the decrease or loss of lateralization of the brain and increased activation in the aging brain being one of prototype of the mechanism (141). This interpretation is further supported by findings from many functional MRI studies in OSA patients where increased resting-state connectivity was found in some regions, as well

as loss of specialization and integration in certain brain regions. Second, there are less confounder involved regarding cortical thickness change compared to neuropsychological tests or functional MRI. Cognitive reserve plays an important part in determining the outcome of the neuropsychological tests given the same pathological change of the brain. However, the number of years of education was the only surrogate marker of cognitive reserve in our study. Finally, the neuropsychological tests employed might lacked sensitivity to detect the subtle cognitive changes. Other studies that investigated the association between executive function and hypoxia in OSA have reported mixed results (59, 69-71). The results are difficult to conclude as the studies differ in both the parameters of hypoxia and the neuropsychological tests used to assess cognitive functions.

In this study, the structural change was detected only in the cortical gray matter but not the white matter. We have not found any study that reports both the cortical thickness analysis and the DTI analysis of the white matter in the same study. However, a study by Macey et al. have reported a reduction of gray-white matter ratio in OSA (50). Claiming that the neurons in the gray matter are more susceptible than axons to

the damage inflicted by recurrent intermittent apneic episodes in OSA. Taking into account the technical difference of analysing the gray and white matter in this study, we cannot conclude that the gray matter is more severely affected than the white matter. Finally, it remains to be clarified which part of the brain is more vulnerable.

5.6 Limitations

This study has several limitations. First, causality cannot be inferred of the association between hypoxia in OSA and the changes of the brain structures and functions due to the cross-sectional design of the study. Second, the power of the difference is generally limited by the small sample size which was due to an unforsseable obstacle in the research process and the lack of a control group. Third, there are no other quantifiable features for cognitive reserve to adjust for the results on neuropsychological tests other than years of education. Fourth, it is evident that duration of OSA, in addition to severity, contributes to the effects of OSA on end organs. However, we were not able to get an accurate estimate of OSA duration for each participant. Fifth, some neuroimaging studies such as fMRI are especially susceptible to artefacts that occurred during image acquisition and processing which

prevents accurate measurement and analysis of the data. Future studies should employ a longitudinal study design with larger sample size and measure the pre-post treatment effects on end organs in OSA patients. In addition, there are many novel imaging techniques to measure functional changes of the brain other than the neuropsychological tests and fMRI, such as Single-photon emission computed tomography (SPECT), fluorodeoxyglucose (FDG)-positron emission tomography (PET) or magnetoencephalography (MEG) scan that would allow further exploration of functional brain changes associated with hypoxia in OSA. Finally, due to the selection process of participants which were based on voluntary decision to participate in the research, participants who were more highly educated or concerned of their health were more likely to volunteer which might have resulted in a selection bias.

5.7 Conclusion

OSA is still largely underrecognized and underdiagnosed compared to other respiratory diseases. Our study demonstrates the association of the unique characteristic of intermittent hypoxia in OSA on structural changes of the brain, specifically cortical thinning at the frontal and parietal regions despite no detectable

cognitive symptom or changes on the neuropsychological evaluation. This finding calls for more attention to detect and treat OSA in its early or presymptomatic stage to prevent future cognitive impairment and mitigate cardiovascular risks.

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