Université de Montréal

# Dysfonctions cérébrales et changements neuroanatomiques dans l'apnée obstructive du sommeil chez les personnes âgées

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# Résumé

L'apnée obstructive du sommeil (AOS) est un trouble du sommeil particulièrement prévalent dans la population âgée, qui peut se présenter par différents niveaux de sévérité. Des études épidémiologiques récentes ont montré une association entre l'AOS et l'incidence de la démence. De plus, l'AOS a été identifiée de façon répétée comme un facteur de risque d'accident vasculaire cérébral. Ces conséquences potentielles de l'AOS sur le cerveau pourraient être dues à l'hypoxémie intermittente et à la fragmentation du sommeil causées par les obstructions respiratoires répétées. Bien que l'AOS soit impliquée dans l'incidence de conséquences graves sur le cerveau, son impact sur la fonction et la structure du cerveau vieillissant reste sous-évalué.

Ainsi, l'objectif de cette thèse est d'évaluer l'association entre l'AOS et sa sévérité sur le fonctionnement cérébral et la structure neuroanatomique chez des personnes âgées de plus de 55 ans. Nous avons émis l'hypothèse que les changements cérébraux chez les personnes avec AOS pourraient s'apparenter aux profils observés dans les stades précurseurs de déclin cognitif. Pour ce faire, diverses méthodes de neuroimagerie ont été utilisées pour caractériser l'ensemble du cerveau des personnes avec AOS. Le fonctionnement cérébral au repos éveillé a été évalué par le biais de la tomographie par émission monophotonique en mesurant le flot sanguin cérébral régional. La structure anatomique de la matière grise et de la matière blanche a été évaluée en imagerie par résonance magnétique. La structure de la matière grise a été évaluée grâce à diverses techniques structurelles, mesurant le volume de la matière grise et l'épaisseur corticale. La structure de la matière blanche a été évaluée avec des méthodes d'imagerie de diffusion, mesurant la diffusivité des molécules d'eau dans la matière blanche.

Dans notre premier article, nous observons que l'AOS sévère, ainsi que plusieurs marqueurs de sévérité de l'AOS sont associés avec des régions d'hypoperfusion au repos éveillé. Ces réductions régionales de la perfusion cérébrales pourraient être dues à un moins bon fonctionnement des neurones et cellules gliales. Dans notre deuxième article, nous montrons que le profil régional d'hypoperfusion cérébrale diurne diffère selon que l'AOS soit observée en sommeil paradoxal ou en sommeil lent. Chez des personnes avec une sévérité plus faible d'AOS, la présence d'évènements respiratoires en sommeil paradoxal était tout de

même associée avec une réduction de la perfusion cérébrale. Ceci suggère que les évènements respiratoires en sommeil paradoxal pourraient être plus dommageables pour le cerveau que ceux en sommeil lent. Nos résultats suggèrent que l'AOS entraine une réduction du fonctionnement cérébral mesuré par une réduction régionale de la perfusion cérébrale. De plus, ces articles suggèrent également que plusieurs facteurs dans l'AOS contribuent différemment aux dysfonctions cérébrales.

Dans notre troisième article, nous observons que les perturbations respiratoires, la fragmentation du sommeil, mais surtout l'hypoxémie contribuent à l'hypertrophie de la matière grise. Nous suggérons qu'un processus d'œdème, ou d'autres processus réactifs et aigus pourraient être en cause dans l'augmentation de la taille de la matière grise. Ce processus pourrait également expliquer nos résultats du dernier article. Dans notre quatrième et dernier article, nous montrons que l'AOS est associée avec une réduction de la diffusivité des molécules d'eau dans la matière blanche, surtout dans les cas légers d'AOS. Un processus d'œdème intracellulaire pourrait restreindre la diffusivité des molécules d'eau dans les cellules de la matière blanche.

Les résultats de cette thèse clarifient les changements cérébraux observés dans la population vieillissante avec l'AOS. Ainsi, malgré des réductions de la perfusion cérébrale suggérant un dysfonctionnement cérébral, l'AOS est également associée avec des changements de structure de la matière grise et de la matière blanche suggérant des processus réactifs et aigus. Puisque ce profil a été rapporté dans les stades précurseurs de déclin cognitif et de démence, nos résultats soulèvent l'importance d'identifier les facteurs dans l'AOS qui sont associés avec les changements cérébraux, afin d'identifier les individus à risque de conséquences cérébrales négatives. De plus, nos résultats soulèvent également l'importance d'évaluer les effets du traitement de l'AOS pour éviter ou ralentir les conséquences de celle-ci sur la santé cérébrale et cognitive.

**Mots-clés** : Apnée obstructive du sommeil, Vieillissement, Biomarqueurs, Démence, Neuroimagerie, Matière blanche, Matière grise, Imagerie par résonance magnétique, Flot sanguin cérébral régional, Tomographie par émission monophotonique.

# Abstract

Obstructive sleep apnea (OSA) is a sleep disorder especially common in the older population, which can present itself at different levels of severity. Recent epidemiological studies showed an association between OSA and incident dementia. In addition, AOS was repeatedly identified as a risk factor for stroke. These potential consequences of OSA on the brain could be caused by intermittent hypoxemia and sleep fragmentation, which is observed following repeated respiratory obstructions. Although OSA has been implicated in the incidence of serious consequences on brain health, its impact on the function and structure of the aging brain remains unclear.

Thus, the objective of this thesis was to evaluate the association between OSA as well as its severity with cerebral functioning and structure in adults aged 55 years old and over. We hypothesized that cerebral changes in individuals with OSA would be similar to profiles observed in preclinical stages of cognitive decline. In order to achieve this goal, various neuroimaging methods were used to characterize the brain of individuals with OSA as a whole. Cerebral functioning during wakeful rest was evaluated with single-photon emission computed tomography by measuring regional cerebral blood flow. Grey matter and white matter structure were evaluated with magnetic resonance imaging. Grey matter structure was assessed with structural techniques that measure grey matter volume and cortical thickness. White matter was assessed with diffusion tensor imaging that measures water molecules diffusion.

In our first study, we observed that severe OSA as well as many markers associated with OSA severity were correlated with hypoperfused regions during wakeful rest. These regions of reduced cerebral perfusion could present altered neuronal and glial functioning. In our second study, we showed that the daytime regional pattern of cerebral hypoperfusion was different whether apneas and hypopneas were observed during rapid eye movement sleep or non-rapid eye movement sleep. In individuals with a milder OSA severity, respiratory events during rapid eye movement sleep were still associated with regions of hypoperfusion. This suggests that respiratory events during rapid eye movement sleep may be more detrimental to brain health than those in non-rapid eye movement sleep. Overall, these results suggest that OSA

leads to an altered cerebral functioning as evidenced by decreased regional cerebral perfusion. In addition, these studies also suggest that many factors contribute differently to cerebral dysfunction in OSA.

In our third study, we observed that respiratory disturbances, sleep fragmentation, and mostly hypoxemia all contributed to grey matter hypertrophy. We suggest that oedema or other reactive or acute processes could cause these increased in grey matter structure. These processes may also explain our results observed in our last study. In that fourth study, we showed that OSA is associated with reduced white matter diffusivities, especially in milder OSA cases. An intracellular oedema process may restrict the diffusion of water molecules inside cells.

The results of this thesis clarify the cerebral changes observed in the aging population with OSA. Although reduced regional brain perfusion suggests cerebral dysfunctions, OSA was also associated with grey and white matter structural changes that suggest reactive and acute processes. Because this pattern was reported previously in preclinical stages of cognitive decline and dementia, our results highlight the importance of identifying individuals at higher risk of negative outcomes to brain health. In addition, our results also emphasize the importance of understanding the efficiency of treating OSA in order to prevent or slow its impact on cerebral functioning and structure.

**Keywords**: Obstructive sleep apnea, Aging, Biomarkers, Dementia, Neuroimaging, White matter, Grey matter, Magnetic resonance imaging, Regional cerebral blood flow, Single-photon emission computed tomography.

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# Liste des sigles

| Version anglaise | | Version française | |
|---|---|---|---|
| 8-OHdg | 8-hydroxy-2-desoxyguanosine | | |
| Aβ | Amyloid-beta | - | Bêta-amyloïde |
| ABCA7 | ATP-binding cassette transporter | | |
| ACT | α1-antichymotrypsin | | |
| AD* | Alzheimer's disease | - | Maladie d'Alzheimer |
| AD* | Axial diffusivity | - | Diffusivité axiale |
| AH | Apneas+hypopneas | - | Apnées + hypopnées |
| AHI | Apnea-hypopnea index | IAH | Index d'apnée-hypopnée |
| APOE4 | Apolipoprotein E4 | APOE4 | Apolipoproétine E4 |
| APOJ | Apolipoprotein J, clusterin | APOJ | Apolipoproétine J, clusterine |
| ASL | Arterial Spin Labelling | | |
| BA | Brodmann area | | |
| BACE1 | Beta-secretase 1 | | |
| BBB | Blood-Brain Barrier | - | Barrière hématoencéphalique |
| BDNF | Brain-derived neurotrophic factor | - | |
| BIN1 | Bridging integrator 1 | | |
| BMI | Body mass index | - | Indice de masse corporelle |
| CLU | Clusterin | - | Clusterine |
| CPAP | Continuous positive airway pressure | PPC | Pression positive continue |
| CR1 | Complement component receptor | | |
| CRP | C-reactive protein | | |
| CSF | Cerebrospinal fluid | - | |
| DARTEL | Diffeomorphic Anatomical Registration using Exponentiated Lie | | |
| DTI | Diffusion tensor imaging | - | Imagerie par tenseur de diffusion |
| EEG | Electroencephalogram | EEG | Électroencéphalographie |
| F | Females | - | Femmes |

| | | | |
|---|---|---|---|
| FA | Fractional anisotropy | - | Anisotropie fractionnelle |
| FDR | False discovery rate | | |
| FERMT2 | Fermitin family member 2 | | |
| FLAIR | Fluid-attenuated inversion recovery | | |
| FW | Free-water imaging | - | Imagerie d'eau libre |
| FWE | Family-wise error | | |
| FWHM | Full width at half maximum | | |
| HDL-C | High-density lipoprotein cholesterol | | |
| HIF-α | Hypoxia-inducible factor-α | | |
| HLA | Major histocompatibility complex | | |
| ICAM-1 | Intercellular adhesion molecule 1 | | |
| ICV | Intracranial volume | - | Volume intracrânien |
| IFN | Interferon | | |
| IL | Interleukins | | |
| L | Left | - | gauche |
| M | Males | - | Hommes |
| MCI | Mild cognitive impairment | - | Trouble cognitif léger |
| MD | Mean diffusivity | - | Diffusivité moyenne |
| MDA | Malondialdehyde | | |
| MNI | Montreal Neurological Institute | | |
| MRI | Magnetic resonance imaging | IRM | Imagerie par résonance magnétique |
| MTHFR | 5,10-methylenetetrahydrofolate reductase | | |
| NREM | Non-rapid eye movement sleep | - | Sommeil lent |
| OSA | Obstructive sleep apnea | AOS | Apnée obstructive du sommeil |
| PD | Parkinson's disease | - | Maladie de Parkinson |
| PET | Positron emission tomography | - | Tomographie par émission de positrons |
| PICALM | Phosphatidylinositol-binding clathrin assembly molecule | | |

| | | | |
|---|---|---|---|
| PS | Polygenic scores | - | Scores polygéniques |
| R | Right | - | Droit |
| rCBF | Regional cerebral blood flow | - | Flot sanguin cérébral régional |
| RD | Radial diffusivity | - | Diffusivité radiale |
| REM | Rapid eye movement sleep | - | Sommeil paradoxal |
| SOD | Superoxide dismutase | | |
| SORL1 | Sortilin-related receptor 1 | | |
| SPECT | Single-photon emission computed tomography | TEMP | Tomographie par émission monophotonique |
| SPM | Statistical Parametric Mapping | | |
| $SpO_2$ | Oxygen saturation | - | Saturation en oxygène |
| - | Stroke | AVC | Accident vasculaire cérébral |
| SWS | Slow wave sleep | - | Sommeil N3, sommeil lent profond |
| TGF-β1 | Transforming growth factor β1 | | |
| TNF- α | Tumor necrosis factor α | | |
| TST | Total sleep time | - | Durée de sommeil totale |
| HMPAO | Hexa-methyl-propylene-amine-oxime | | |
| VaD | Vascular dementia | - | Démence vasculaire |
| VBM | Voxel-based morphometry | - | Morphométrie basée sur le voxel |
| VCAM-1 | Vascular cellular adhesion molecule 1 | | |
| VILIP-1 | Visinin-like protein 1 | | |
| WMH | White matter hyperintensités | - | Hyperintensités de la matière blanche |
| YKL-40 | Chitinase-3-like protein 1 | | |

*Note : Les sigles AD ont été utilisés soit pour « Alzheimer's disease » et « Axial diffusivity » dans des articles différents.

# Liste des abréviations

| | |
|---|---|
| c.-à-d. | C'est-à-dire |
| cc | Centimètre cubique / cubic centimetre |
| cm | Centimètre /centimetre |
| e.g. | Exempli gratia |
| etc. | Et cætera |
| Fig. | Figure |
| h | Heure / hour |
| Hz | Hertz |
| i.e. | Id est |
| kg | Kilogramme / kilogram |
| m | Mètre / meter |
| MBq | Millibecquerel |
| min | Minute |
| mm | Millimètre / millimeter |
| ms | Milliseconde / millisecond |
| n/a | Non applicable |
| ns | Non significant |
| p. ex. | Par exemple |
| Px | Pixel |
| s | Seconde / second |

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# Chapitre 1. Introduction

## 1.1. Aperçu de la problématique

Le sommeil joue un rôle important dans la santé physique, cognitive et psychologique. Des perturbations du sommeil ont été associées à certaines maladies métaboliques et cardiovasculaires, une réponse au stress altérée, une moins bonne qualité de vie, de la détresse émotionnelle et une performance cognitive diminuée (Medic *et al.*, 2017). Un des troubles du sommeil le plus fréquent est l'apnée obstructive du sommeil (AOS), qui se caractérise par des arrêts respiratoires causant une perturbation du sommeil. Malgré sa forte prévalence (Senaratna *et al.*, 2017), une minorité de la population connait l'existence de l'AOS (Sia *et al.*, 2017), qui demeure à ce jour sous-diagnostiqué (Iqbal *et al.*, 2016; Hsu *et al.*, 2018). Au-delà de ses conséquences sur la santé des individus, l'AOS représente un important problème de santé publique. En effet, le coût lié au diagnostic et au traitement de l'AOS est largement inférieur au fardeau économique lié à l'AOS non diagnostiquée et non traitée (Watson, 2016). Le sommeil de mauvaise qualité et la somnolence associés à l'AOS entrainent une perte de productivité au travail, de l'absentéisme, des accidents du travail et des accidents de la route (Watson, 2016). De plus, l'AOS joue un rôle dans le développement de plusieurs conditions médicales accompagnées de coûts élevés pour la société, incluant des maladies cardiovasculaires, la dépression et des troubles cognitifs (Watson, 2016).

L'AOS a une forte prévalence dans la population vieillissante (Tufik *et al.*, 2010). Récemment, les perturbations du sommeil, spécifiquement l'AOS, ont été identifiées comme facteurs de risque de démence (Leng *et al.*, 2017; Shi *et al.*, 2017a). Ces récentes découvertes nous amènent à nous demander comment l'AOS affecte le cerveau vieillissant pour éventuellement pouvoir identifier et traiter les individus à risque de développer des conséquences néfastes comme la démence. En effet, les obstructions respiratoires répétées dans l'AOS entrainent de l'hypoxémie intermittente et une fragmentation du sommeil importante, ayant le potentiel d'affecter la santé cérébrale.

## 1.2. Introduction à l'AOS

### *1.2.1. Définition et diagnostic de l'AOS*

L'AOS est un trouble du sommeil caractérisé par des pauses respiratoires répétitives dues à l'obstruction répétée des voies respiratoires, notamment au niveau du pharynx (Malhotra and White, 2002). Les obstructions respiratoires dans l'AOS ont plusieurs causes. Elles peuvent être dues à des dysfonctions des muscles dilatateurs ou à des particularités anatomiques qui entravent les voies respiratoires (p. ex. la morphologie crâniofaciale, l'expansion des tissus adipeux au cou et au thorax, et la morphologie de la langue, du palais et des amygdales). Elle peut aussi être causée par une instabilité du contrôle respiratoire en réaction aux chémorécepteurs (Eckert and Malhotra, 2008).

Les évènements respiratoires sont identifiés idéalement à l'aide d'un enregistrement polysomnographique en laboratoire, mais peuvent également l'être grâce à des systèmes ambulatoires mesurant les efforts respiratoires et la saturation en oxygène. Deux grands types d'évènements obstructifs peuvent être identifiés : les apnées et les hypopnées. Les apnées obstructives sont des cessations du flot respiratoire qui durent au moins 10 s et qui sont accompagnées d'efforts respiratoires (Berry *et al.*, 2012). Les hypopnées sont quant à elles des obstructions partielles associées à une réduction du flot respiratoire d'au moins 30 % d'une durée d'au moins 10 s. Les hypopnées sont également accompagnées d'une désaturation en oxygène d'au moins 3 % ou encore d'un microéveil cortical observable à l'électroencéphalographie (EEG) (Berry *et al.*, 2012). Il est à noter que différents critères définissant les hypopnées ont été proposés en 1990, 1999, 2007 et 2012 (Duce *et al.*, 2015). , alors que la réduction du flot respiratoire est passée de 50 % à 30 % et la désaturation en oxygène accompagnant l'hypopnée a varié entre 3 et 4 %.

La sévérité de l'AOS est normalement décrite par l'index d'apnées et d'hypopnées (IAH), c'est-à-dire le nombre d'évènements respiratoires par heure de sommeil. Un IAH sous cinq est considéré comme une absence d'AOS, un IAH entre cinq et 15 est associé à une AOS légère, un IAH entre 15 et 30 est associé à une AOS modérée et finalement, les personnes ayant un IAH plus grand que 30 sont apnéiques sévères (American Academy of Sleep Medicine Task Force, 1999). L'IAH étant un continuum, il existe toutefois une grande

variabilité par rapport au seuil utilisé pour diagnostiquer l'AOS, et il demeure un indicateur de sévérité imparfait avec des seuils été établis de façon plutôt arbitraire.

Bien que le diagnostic de l'AOS soit basé majoritairement sur l'IAH, son dépistage est basé sur les symptômes rapportés par le patient, incluant la somnolence diurne, le ronflement, le sentiment de fatigue, et le rapport d'un partenaire de lit ayant observé des pauses respiratoires. La somnolence diurne est considérée comme une conséquence directe de la mauvaise qualité du sommeil causée par l'AOS, mais pourrait également être causée par des dommages hypoxiques aux neurones, dont ceux impliqués dans le maintien de l'éveil (Zhu *et al.*, 2007). La somnolence diurne dans le contexte de l'AOS est associée à plusieurs conséquences sur la vie des individus, incluant un risque élevé d'accidents de la route, un niveau de qualité de vie plus faible et de la fatigue (Lieberman, 2009). Il n'est donc pas étonnant que l'inclusion de la somnolence dans les critères diagnostiques de l'AOS puisse être recommandée (American Academy of Sleep Medicine Task Force, 1999). Cependant, puisque la somnolence est rapportée par seulement 49 % des individus apnéiques de tout âge (Budhiraja *et al.*, 2017) et entre 11 % à 23 % des individus apnéiques plus âgés (Sforza *et al.*, 2015), celle-ci ne devrait pas faire partie intégrante du diagnostic de l'AOS.

### *1.2.2. Traitement de l'AOS*

Le traitement le plus utilisé dans l'AOS est la thérapie par pression positive continue (PPC). Cet appareil exerce une pression d'air positive dans les voies respiratoires pour les maintenir ouvertes et diminue de façon importante ou complète les évènements respiratoires. En effet, la majorité des individus traités par PPC présentent un IAH < 5 évènements par heure (Jonas *et al.*, 2017). Une méta-analyse rapporte que la PPC est efficace pour réduire la somnolence diurne et la pression artérielle (Jonas *et al.*, 2017). Les traitements alternatifs à la PPC incluent l'appareil d'avancement mandibulaire, une intervention chirurgicale au niveau des voies respiratoires ou des interventions visant la perte de poids (Jonas *et al.*, 2017). Malgré l'efficacité de la PPC, jusqu'à 42 % des personnes diagnostiquées avec de l'AOS refuse le traitement et jusqu'à 47 % de ceux ayant débuté la PPC l'abandonne dans la première année (Lee *et al.*, 2017). De plus, l'adhérence chez les individus sous traitement par PPC reste très faible, alors qu'une utilisation sur peu d'heures par nuit ou ne couvrant pas toutes les nuits

peut être observée. En effet, une étude a montré que 63 % des utilisateurs de la PPC ont une bonne adhérence, qualifiée par une utilisation de plus de 4 heures par nuit sur plus de 70 % des nuits (Krakow *et al.*, 2016). Ce critère a cependant été jugé comme étant potentiellement trop faible pour réduire les risques de l'AOS sur la santé (Masa and Corral-Penafiel, 2014). Chez les utilisateurs de la PPC, l'adhérence est influencée par plusieurs sentiments et opinions négatifs par rapport au traitement. Malgré le sentiment de se sentir reposé, les utilisateurs de la PPC rapportent de l'inconfort, une moins bonne perception de soi due au manque d'esthétisme de l'appareil, des restrictions supplémentaires pour voyager, et une déception face à l'utilisation de l'appareil comme traitement pour contrôler et non guérir l'AOS (Zarhin and Oksenberg, 2017). Les utilisateurs de la PPC rapportent qu'ils pensent aux bénéfices de l'appareil sur leur sommeil et sur leur qualité de vie comme motivation pour poursuivre l'utilisation (Zarhin and Oksenberg, 2017). L'éducation des patients apnéiques sur les impacts néfastes de l'AOS sur la santé pourrait affecter positivement l'adhérence au traitement, d'où l'importance de bien comprendre comment l'AOS  et ses conséquences.

### *1.2.3. Facteurs de risque et prévalence de l'AOS*

Il est difficile d'établir la prévalence de l'AOS. En effet, celle-ci varie de façon considérable dans la population selon divers facteurs de risque, incluant les critères de sévérité de l'AOS basé sur l'IAH, l'âge, le sexe, l'obésité, l'ethnicité et la structure crâniofaciale (Malhotra and White, 2002). Comme mentionné précédemment, il existe différents critères de sévérité de l'AOS (léger, modéré et sévère). Le critère sélectionné par une étude influence bien sûr la prévalence qui sera observée. Lorsque toutes les sévérités sont incluses, la prévalence de l'AOS varie entre 9 et 38 %, alors qu'elle varie entre 6 et 17 % dans la population adulte lorsque l'AOS modérée à sévère est considérée (Senaratna *et al.*, 2017).

L'âge est l'un des facteurs de risque les plus importants pour l'AOS. Avec l'âge, l'expansion des tissus adipeux au niveau du cou et du thorax ainsi qu'une détérioration des réflexes respiratoires contribuent à l'affaissement des voies respiratoires (Eckert and Malhotra, 2008). La prévalence de l'AOS augmente graduellement avec l'âge, atteignant plus de 50 % chez les personnes âgées de plus de 60 ans dans certaines cohortes (Senaratna *et al.*, 2017). Le sexe masculin augmente le risque de présenter de l'AOS par le biais de l'expansion des tissus

adipeux du cou et du thorax, un niveau d'activité réduit des muscles dilatateurs des voies respiratoires supérieures, ainsi qu'un effet négatif de la testostérone sur la stabilité respiratoire (Eckert and Malhotra, 2008). Dans une revue de littérature incluant 25 études, toutes les études ayant évalué la prévalence chez les hommes et les femmes ont rapporté une prévalence plus élevée chez les hommes (Senaratna *et al.*, 2017), montrant que ce facteur de risque est important et robuste. Dans une étude de plus de 1000 participants, la prévalence de l'AOS modérée à sévère atteint 85 % chez les hommes de 70 à 80 ans (Tufik *et al.*, 2010). Chez les femmes de cette même tranche d'âge, la prévalence était aussi très haute, mais l'AOS se présentait majoritairement avec une sévérité légère (Tufik *et al.*, 2010).

L'obésité est directement liée au développement de l'AOS. L'accumulation des tissus adipeux au niveau du cou et du thorax facilite l'affaissement des voies respiratoires, et l'obésité entraine des changements au niveau de la stabilité du contrôle respiratoire et de l'activité des muscles des voies respiratoires (Eckert and Malhotra, 2008). L'obésité est associée à une prévalence d'AOS plus élevée chez les hommes et les femmes (Tufik *et al.*, 2010). Finalement, l'ethnicité et les facteurs crâniofaciaux qui y sont associés affectent également la prévalence de l'AOS dans la population. Une occlusion crânienne plus petite, par exemple, semble jouer un rôle important dans la prévalence de l'AOS dans la population asiatique, tandis que l'obésité joue un plus grand rôle dans la population caucasienne (Lee *et al.*, 2010). De plus, la population noire présente plus d'AOS indépendamment de l'obésité (Ancoli-Israel *et al.*, 1995; Villaneuva *et al.*, 2005), ce qui pourrait être lié à la dimension des tissus mous tels que la langue (Redline *et al.*, 1997).

### *1.2.4. Sous-types d'AOS posant des dilemmes cliniques*

Dans la population générale, la prévalence de l'AOS non diagnostiquée est d'environ 5 à 15 % (Simpson *et al.*, 2013), tandis que cette prévalence augmente drastiquement dans certaines populations. En effet, la prévalence de l'AOS non diagnostiquée est de 87 % chez les vétérans âgés et 82 % chez les personnes avec hypertension (Iqbal *et al.*, 2016; Hsu *et al.*, 2018). On peut penser que les personnes présentant de l'AOS asymptomatique (c.-à-d., sans somnolence ou autres plaintes liées à l'AOS) sont à risque de ne pas être diagnostiquées. La formation reçue par les médecins en ce qui trait aux troubles du sommeil est très limitée.

Plusieurs médecins rapportent ne pas être certains de savoir comment identifier les symptômes de l'AOS (Jonas *et al.*, 2017). De plus, les questions servant à dépister l'AOS ne sont pas toujours posées aux patients en pratique clinique, et les patients ne rapportent pas nécessairement ces symptômes à leur médecin si des questions spécifiques ne leur sont pas posées (Redline, 2017). Une étude a montré que le délai moyen entre la reconnaissance des symptômes par le patient et la référence en clinique du sommeil est de plus de sept ans (Rahaghi and Basner, 1999). De plus, l'accessibilité au diagnostic est souvent limitée : il est estimé qu'il n'y a qu'un spécialiste du sommeil pour 30 000 personnes dans la population (Carter, 2017). Ceci amène une question importante : quels sont les impacts de l'AOS asymptomatique sur la santé ? Le *US Preventive Service Task Force* s'est penché sur la question et rapporte que l'état actuel de la littérature est insuffisant pour recommander le dépistage et le traitement systématique des adultes avec AOS asymptomatique (U. S. Preventive Services Task Force *et al.*, 2017).

L'AOS légère reçoit de plus en plus d'attention dans le milieu de la recherche et en contexte clinique. En effet, certains suggèrent que l'AOS légère devrait être traitée tandis que d'autres ne recommandent pas de traitement (Brown, 2007; Littner, 2007). À ce jour, les études évaluant l'impact de l'AOS légère sur la santé restent limitées, mais ce thème de recherche se développe (Chowdhuri *et al.*, 2016). Fait intéressant, l'AOS légère tend à devenir plus sévère avec le temps lorsqu'elle est non traitée : environ la moitié des individus avec AOS légère qui présenteront une AOS modérée à sévère environ quatre ans plus tard (Sahlman *et al.*, 2007). En plus des différents niveaux de sévérité de l'AOS, quelques autres phénotypes sont retrouvés dans la population. Certains individus présentent de l'AOS majoritairement en sommeil paradoxal ou principalement lorsque la personne dort sur le dos (Zinchuk *et al.*, 2017), qui sont deux circonstances facilitant l'affaissement des voies respiratoires supérieures pendant le sommeil. Comme pour l'AOS légère, les personnes avec ces phénotypes d'AOS sont le sujet d'un dilemme clinique. En effet ces phénotypes présentent des évènements respiratoires obstructifs dans des conditions très spécifiques, et donc, la sévérité globale peut être légère. Par contre, il n'est pas connu si la consolidation de leurs évènements respiratoires dans une période spécifique (sommeil paradoxal ou sommeil sur le dos) est dommageable sur la santé.

## 1.3. Conséquences de l'AOS

### *1.3.1. Hypoxie, fluctuations hémodynamiques et autres mécanismes pathologiques*

Les obstructions respiratoires dans l'AOS provoquent divers changements hémodynamiques et métaboliques. Premièrement, la réduction ou la cessation du flot respiratoire provoque une hypoxémie (diminution du taux d'oxygène dans le sang) ainsi qu'une hypoxie (diminution du niveau d'oxygène dans les tissus), notamment dans le cerveau en raison de sa grande consommation en oxygène. Cette hypoxémie est accompagnée d'une augmentation de la pression partielle de dioxyde de carbone dans le sang. L'hypoxie entraine une augmentation du tonus du système nerveux sympathique et une augmentation rapide de la pression artérielle (Dempsey *et al.*, 2010). Au niveau du cerveau, les évènements respiratoires causent d'abord une augmentation du flot sanguin cérébral suivi d'une diminution sous les valeurs de base (Franklin, 2002), causant de l'hypoperfusion. Ces variations importantes de flot sanguin cérébral suggèrent que les mécanismes vasculaires cérébraux ne sont pas suffisants pour maintenir une pression artérielle stable pendant les apnées et hypopnées. Les variations de pression artérielle pendant les évènements respiratoires peuvent avoir des effets néfastes sur les organes, ce qui est aussi le cas pour les variations du flot sanguin cérébral qui provoque une hypoperfusion et augmente ainsi l'effet de l'hypoxie sur les tissus.

Suite à l'hypoxie, une cascade de mécanismes pathologiques secondaires est enclenchée. L'AOS est associée à une dysfonction des mitochondries et à une grande production de stress oxydatif (Kim *et al.*, 2014; Gaspar *et al.*, 2017), qui ont provoqué la mort neuronale dans un modèle animal d'AOS (Douglas *et al.*, 2010). Les personnes avec AOS présentent des niveaux élevés des marqueurs d'inflammation dans le sang et les modèles animaux suggèrent un rôle causal de l'hypoxie et du stress oxydatif dans les processus inflammatoires (Unnikrishnan *et al.*, 2015). Au niveau central, l'AOS peut activer la microglie pro-inflammatoire du cerveau (Yang *et al.*, 2013), ce qui a le potentiel d'être un effectif pathologique de dysfonctions et dommages cérébraux. La fonction endothéliale est affectée dans la majorité des études sur l'AOS et ces dysfonctions sont réversibles avec le traitement par PPC, suggérant un rôle causal de l'AOS (Hoyos *et al.*, 2015). Puisque la fonction endothéliale est affectée, il n'est pas

surprenant d'observer dans l'AOS de l'athérosclérose (Dempsey *et al.*, 2010), c'est-à-dire l'épaississement en plaque de la paroi des vaisseaux sanguins, réduisant son élasticité et sa lumière. Chez l'humain et l'animal, l'AOS est associée à des lésions et plaques d'athérosclérose, qui peuvent être trouvées au niveau cérébral intracrânien chez des patients avec OAS modérée à sévère (Song *et al.*, 2017) et qui peuvent être réduites par un traitement PPC (Dempsey *et al.*, 2010).

### *1.3.2. Qualité du sommeil*

Le sommeil des personnes avec AOS est grandement affecté. La fin des apnées et hypopnées est fréquemment associée à un éveil cortical, c'est-à-dire une augmentation des fréquences de l'EEG ou un microéveil, ce qui facilite la restauration de l'ouverture des voies respiratoires (Eckert and Malhotra, 2008). Toutefois, ces éveils corticaux entrainent une fragmentation importante du sommeil. Les éveils corticaux sont également associés à des changements hémodynamiques, activant le système nerveux sympathique et augmentant la pression artérielle (Yoon and Jeong, 2001).

Le sommeil est caractérisé par des cycles répétés de sommeil paradoxal et de sommeil lent. Ce dernier se subdivise en stades de plus en plus profonds : N1, N2 et N3 (Iber *et al.*, 2007). Le sommeil N3, ou sommeil lent profond, est présent en plus grande quantité en début de nuit, tandis que le sommeil paradoxal apparait en plus grande proportion en fin de nuit. Les enfants avec AOS ont moins de sommeil N3 et plus de sommeil N1 (Durdik *et al.*, 2018). Chez les adultes, l'AOS est associée à moins de sommeil N3 (Wang *et al.*, 1998). Comparativement à des personnes d'âge moyen avec AOS, les personnes âgées avec AOS ont une augmentation du sommeil N1 et une réduction du sommeil paradoxal (Wang and Li, 2008). L'AOS affecte également la microstructure du sommeil. Le sommeil lent profond se caractérise par de l'activité à ondes lentes (0.5-4 Hz) (Abel *et al.*, 2013). Bien que la majorité des études aient montré une réduction de l'activité à ondes lentes et de l'activité delta dans l'AOS, ces résultats n'ont pas été répliqués dans certains groupes de recherche alors que alors que d'autres études ont plutôt des augmentations de l'activité à ondes lentes (voir (D'Rozario *et al.*, 2017) pour une revue de la littérature). Les autres bandes de fréquences fréquemment mesurées lors d'une analyse spectrale de l'EEG sont les bandes bêta (13-31 Hz), alpha (8-12

Hz), et thêta (4-7 Hz) (D'Rozario *et al.*, 2017). Les résultats liés à ces bandes de fréquence dans le sommeil des personnes avec de l'AOS sont inconsistants. Certaines études ne montrent aucun changement dans les bandes bêta, alpha et thêta dans l'AOS en sommeil paradoxal ou en sommeil lent, alors que d'autres rapportent une réduction du thêta et une augmentation du bêta en sommeil lent (D'Rozario *et al.*, 2017). De plus, des augmentations ou réductions de la puissance spectrale dans la bande alpha furent aussi observées en sommeil lent (D'Rozario *et al.*, 2017). Il est à noté par contre que les limites des bandes de fréquences varient entre les études, ce qui peut expliquer une portion des inconsistances. Les changements observés au niveau des fuseaux de sommeil, qui sont des oscillations observées principalement en sommeil N2 (11-15 Hz) (Abel *et al.*, 2013), semblent plus consistants que les changements observés dans l'activité à ondes lentes et les autres bandes de fréquence dans l'AOS. En effet, plusieurs études rapportent une réduction de la puissance spectrale de la bande sigma et une réduction de la densité des fuseaux de sommeil, et ce même chez les sujets avec AOS léger (Ondze *et al.*, 2003; D'Rozario *et al.*, 2017).

Il est clair que l'AOS entraine des perturbations du sommeil, et ce, en dépit des résultats parfois divergents rapportés dans la littérature. Celles-ci se caractérisent par de la fragmentation du sommeil et une réduction de la densité des fuseaux de sommeil. Il a été proposé que le rôle principal du sommeil se situe au niveau de la régulation de la plasticité synaptique (Abel *et al.*, 2013).Les perturbations du sommeil dans l'AOS ont donc le potentiel d'affecter le fonctionnement cérébral. Les fuseaux de sommeil jouant un rôle dans l'intégration de nouveaux apprentissages dans des réseaux corticaux existants (Tamminen *et al.*, 2010), ils pourraient présenter un mécanisme idéal pour les changements de plasticité synaptique du néocortex (Fogel and Smith, 2011) et les habiletés cognitives générales (Lustenberger *et al.*, 2012).

## 1.4. Impacts de l'AOS sur la santé cognitive et cérébrale

En plus de la somnolence diurne, les personnes avec AOS rapportent plusieurs autres plaintes et symptômes neurocognitifs. Une revue de la littérature a présenté plusieurs études montrant que l'AOS est associée à des symptômes dépressifs et anxieux d'intensité variable (Saunamaki and Jehkonen, 2007). De plus, bien que ce résultat ne soit pas observé dans toutes

les études, les personnes avec AOS rapportent plus de plaintes au niveau de la concentration, la mémoire, la motivation et le contrôle émotif (Vaessen *et al.*, 2015). Des déficits cognitifs dans plusieurs domaines sont souvent observés dans l'AOS lorsque mesurés objectivement, entre autres au niveau de l'attention et la vigilance, la mémoire épisodique, la mémoire de travail et les fonctions exécutives (Gagnon *et al.*, 2014). Une nouvelle méta-analyse incluant 19 études démontre que les changements cognitifs liés à l'AOS touchent également d'autres fonctions : la mémoire non-verbale, la formation de concepts, la vitesse psychomotrice et de traitement de l'information, la construction, la performance et le contrôle moteur, le raisonnement verbal et le langage (Stranks and Crowe, 2016). Certains domaines cognitifs pourraient être préférentiellement affectés chez les personnes avec de l'AOS et présentant de la somnolence diurne (Zhou *et al.*, 2016a). Des marqueurs inflammatoires et de stress oxydatif corrèlent également avec la fonction cognitive des personnes avec de l'AOS (Haensel *et al.*, 2009; Zhou *et al.*, 2016b), alors que le niveau d'hypoxémie a été associé au déclin cognitif des personnes âgées avec de l'AOS (Blackwell *et al.*, 2015).

Plusieurs études transversales et longitudinales ont évalué le risque d'accident vasculaire cérébral (AVC) en lien avec la présence d'AOS. La plupart des études rapportent que l'AOS sévère est un facteur de risque indépendant d'AVC (Dempsey *et al.*, 2010; King and Cuellar, 2016). Il a aussi été démontré que l'AOS est liée à des évènements cérébrovasculaires cliniquement silencieux, c'est-à-dire un AVC asymptomatique. L'AOS modérée à sévère a été associée à la leucoaraïose (dommages vasculaires à la matière blanche cérébrale) et à des infarctus lacunaires (pathologie des petits vaisseaux des structures profondes du cerveau) (Cho *et al.*, 2013; Kepplinger *et al.*, 2014). Chez les patients ayant subi un AVC, la présence d'AOS aggrave les troubles cognitifs au niveau de la mémoire (Zhang *et al.*, 2017).

Récemment, l'AOS a émergé comme étant un facteur de risque indépendant de déclin cognitif et de démence (Leng *et al.*, 2017). Les récents développements sur les risques de démence en lien avec l'AOS sont décrits dans la revue de la littérature au Chapitre 2 (Revue de littérature 1; Gosselin, Baril et al.). Les biomarqueurs de démence et leur potentiel dans la recherche sur l'AOS chez les personnes âgées sont présentés dans une deuxième revue de la littérature présentée dans le Chapitre 2 (Revue de littérature 2; Baril et al.).

## 1.5. Neuroimagerie de l'AOS

### *1.5.1. Perfusion cérébrale régionale*

Le cerveau est l'un des plus grands consommateurs d'énergie et possède très peu de réserve. L'énergie qui lui permet de fonctionner correctement provient d'une bonne irrigation sanguine bien contrôlée. Le phénomène du couplage neurovasculaire correspond à la réponse régionale et rapide du flot sanguin cérébral suite à une activation neuronale (Phillips *et al.*, 2016). Suite à une activation neuronale, la consommation en oxygène et en glucose augmente et certains métabolites ayant un rôle vasoactif sont relâchés. Plusieurs méthodes de neuroimagerie se basent sur ce principe, c'est-à-dire en mesurant le flot sanguin cérébral régional comme marqueur de l'activité neuronale et du métabolisme cérébral d'une région. Certains ligands lipophiles comme l'hexa-methyl-amino-propylenamine-oxime (HMPAO) traversent la barrière hématoencéphalique et se lient aux cellules sous une forme hydrophile qui ne traverse pas cette barrière (Andersen, 1989). Après l'injection d'un ligand comme le HMPAO, celui-ci est absorbé en quelques minutes et devient lipophile dans les cellules du cerveau. Ainsi, le ligand reste emprisonné dans les cellules avec une demi-vie biologique de quatre heures, permettant l'acquisition d'une image. Cette absorption rapide est proportionnelle au flot sanguin cérébral régional et permet donc de le mesurer *in vivo*. Pour capter la distribution du ligand, on lie tout d'abord celui-ci à une substance radioactive comme le Technétium 99m ($^{99m}$Tc) pour en faire un radioligand ($^{99m}$Tc-HMPAO). La tomographie par émission monophotonique (TEMP) est une méthode de neuroimagerie dans laquelle une caméra gamma qui enregistre la radioactivité émise par le radioligand distribué aux tissus. L'intensité de la radioactivité mesurée correspond donc au flot sanguin cérébral régional, une mesure indirecte du métabolisme cérébral et de l'activité neuronale.

Très peu d'études ont utilisé la TEMP dans le contexte de l'AOS à l'éveil. Ces études ont évalué des adultes âgés environ entre 30 et 60 ans. Chez des apnéiques sévères, des hypoperfusions temporales et pariétales médiales ont été observées comparativement à des sujets témoins (Joo *et al.*, 2007). Dans une deuxième étude, des personnes avec de l'AOS sévère ont été évaluées en TEMP à l'éveil avant et après trois mois de traitement par PPC (Shiota *et al.*, 2014). Avant le traitement, les personnes avec de l'AOS montraient une

hypoperfusion du cortex préfrontal dorsolatéral, qui s'est normalisée après le traitement par PPC. De façon similaire, chez des hommes avec de l'AOS sévère les hypoperfusions observées à l'éveil au niveau du cortex frontal médian, pariétal latéral, cingulaire, temporal médian et au niveau du cervelet se sont partiellement normalisées avec un traitement de six mois (Kim *et al.*, 2017). L'hypoperfusion à l'éveil de certaines régions était complètement renversée après le traitement, tandis qu'elle n'était que partiellement renversée dans d'autres.

En imagerie par résonance magnétique (IRM), une méthode nommée *Arterial Spin Labelling* (ASL) magnétise le sang artériel et permet aussi de mesurer le flot sanguin cérébral régional. Chez des personnes avec AOS de toutes sévérités comparativement à des sujets témoins, une étude a montré plusieurs régions hypoperfusées de la matière grise et blanche (Yadav *et al.*, 2013). Chez des personnes avec AOS modérée à sévère, des hypoperfusions à l'éveil ont été observées dans le cortex orbitofrontal, temporal médian, et cingulaire ainsi que dans des régions sous-corticales (hippocampes, thalamus, putamen) (Innes *et al.*, 2015). Aucune hypoperfusion n'a été observée chez les personnes avec de l'AOS légère. Une autre étude chez des hommes avec AOS modérée à sévère a montré une hypoperfusion à l'éveil dans le cortex préfrontal médian et latéral, insulaire, cingulaire et temporal ainsi que dans des régions sous-corticales (putamen, thalamus, noyau caudé, cervelet) (Chen *et al.*, 2017). Ces hypoperfusions à l'éveil corrélaient avec une augmentation des marqueurs inflammatoires, c.-à-d. l'apoptose des leucocytes. Chez des hommes avec AOS sévère, des hypoperfusions médiales frontales et temporales ainsi qu'au niveau du cervelet ont été observées à l'éveil comparativement à un groupe témoin (Nie *et al.*, 2017). Par contre, une hyperperfusion du cortex préfrontal a également été rapportée et celle-ci corrélait avec la durée des apnées (Nie *et al.*, 2017). Ces études utilisant la méthode ASL ont évalué des adultes âgés environ entre 30 et 60 ans environ.

En résumé, malgré le peu d'études ayant évalué le flot sanguin cérébral régional dans l'AOS à l'éveil, de l'hypoperfusion régionale est retrouvée de façon consistante à travers les études, ce qui semble être au moins partiellement réversible lorsque le traitement par PPC est utilisé. Ceci suggère que les personnes avec de l'AOS présentent une réduction du fonctionnement cérébral dans certaines régions du cerveau au repos éveillé. Ces régions varient beaucoup d'une étude à l'autre, incluant le cortex frontal, pariétal et temporal ainsi que

l'insula, le cortex cingulaire, et les régions sous-corticales. Il est à noter que ces études ont majoritairement été réalisées chez des personnes d'âge moyen; il n'est donc pas clair si ces résultats peuvent être généralisés à une population plus âgée. De plus, très peu d'études ont évalué la perfusion cérébrale régionale dans le contexte de l'AOS légère.

### *1.5.2. Matière grise cérébrale – morphométrie basée sur le voxel*

L'IRM anatomique permet l'évaluation de plusieurs variables structurelles par ses diverses séquences. La technique de morphométrie basée sur le voxel est la plus utilisée pour mesurer la matière grise cérébrale. Celle-ci permet d'évaluer la densité ou le volume de matière grise sur des images anatomiques T1 normalisées dans l'espace (Ashburner, 2007). Cette méthode comprend plusieurs étapes, dont la normalisation qui utilise un algorithme ajustant la forme globale de l'image du cerveau à un modèle. Après cette étape, les images des participants d'une même étude sont dans le même espace anatomique, permettant une comparaison statistique directe. Les analyses statistiques sont faites sur les valeurs de densité ou de volume de chacun des voxels de matière grise. Une réduction du volume correspondant à de l'atrophie de la matière grise est généralement considérée pathologique, bien qu'une augmentation du volume puisse aussi sous-tendre des mécanismes pathologiques, comme de l'œdème (Morocz *et al.*, 2001; Lawley *et al.*, 2014).

La méthode de morphométrie basée sur le voxel a été utilisée à plusieurs reprises pour décrire la structure de la matière grise dans l'AOS depuis 2002 (Macey *et al.*, 2002), dans lequel une atrophie de la matière grise a été retrouvée dans plusieurs régions cérébrales chez des adultes âgés de 28 à 67 ans. Plusieurs études ont été publiées depuis, et des méta-analyses se sont penchées récemment sur la question. La méta-analyse publiée par Shi et coll. inclut les résultats de 15 études récentes (Shi *et al.*, 2017b). La moyenne d'âge des personnes avec de l'AOS incluses dans cette méta-analyse variait entre 40 et 55 ans, sauf pour deux études dont les moyennes d'âge étaient de 57 et 66 ans. La sévérité moyenne des personnes avec AOS était très élevée pour la plupart des études, avec un IAH >30. La majorité des études ont rapporté de l'atrophie de la matière grise dans différentes régions localisées dans le cortex et dans des régions sous-corticales. Les résultats de cette méta-analyse rapportent que plusieurs régions aux niveaux cortical et sous-cortical présentent de l'atrophie de la matière grise dans

un contexte d'AOS (Shi *et al.*, 2017b). Spécifiquement, les régions affectées étaient le cortex cingulaire, le gyrus frontal supérieur, le cervelet dans l'hémisphère gauche, le gyrus moyen du cortex temporal dans l'hémisphère droit et le cortex prémoteur droit. Il est à noter que six études incluses dans cette méta-analyse ont cependant montré des résultats différents. Quatre d'entre elles ne montraient aucune différence entre les personnes avec de l'AOS et un groupe témoin. Deux études montraient une hypertrophie de la matière grise au niveau de l'insula, de certaines régions sous-corticales (c.-à-d. le cervelet, l'hippocampe et le tronc cérébral) et des aires sensorimotrices. De plus, dans deux autres études qui n'étaient pas incluses dans cette méta-analyse, une hypertrophie de la matière grise localisée dans le tronc cérébral (Lundblad *et al.*, 2014) et dans le thalamus (Taylor *et al.*, 2017) a également été observée chez des patients avec une AOS de toute sévérité et de l'AOS modérée à sévère respectivement.

Quelques études utilisant la méthode de morphométrie basée sur le voxel ont évalué l'effet d'un traitement par PPC sur le volume de matière grise. Ces études ont évalué des participants âgés entre 30 et 60 ans environ. Après un traitement de trois mois chez des personnes avec AOS sévère, l'amélioration des symptômes de somnolence diurne, de l'humeur, ainsi que la performance cognitive était combinée à des augmentations du volume de matière grise (Canessa *et al.*, 2011). Plusieurs régions atrophiées (c.-à-d. frontales, pariétales et hippocampiques) étaient observées avant le traitement en comparaison aux sujets témoins, qui se sont toutes normalisées après le traitement. Une autre étude chez des personnes avec de l'AOS modérée à sévère a évalué l'impact de l'utilisation du traitement par PPC sur une longue durée, c'est-à-dire durant plus de 8 mois (Kim *et al.*, 2016). Avant le traitement, des régions d'atrophie étendues étaient observées dans le cortex préfrontal et orbitofrontal, cingulaire, insulaire, temporal latéral, occipital latéral et médian et dans les régions sous-corticales (hippocampes, thalamus, cervelet). Plusieurs de ces régions ont montré une hypertrophie de la matière grise après le traitement. Une autre étude chez des personnes avec de l'AOS de toute sévérité a évalué l'effet d'un traitement par chirurgie des voies respiratoires supérieures (Lin *et al.*, 2016). Avant la chirurgie, des marqueurs inflammatoires étaient anormalement élevés dans le sang et étaient combinés à une hypertrophie de l'insula et une atrophie du cortex cingulaire. Après la chirurgie, l'atrophie du cortex cingulaire était toujours présente tandis que l'hypertrophie de l'insula s'était normalisée. Ces études montrent que les

changements de matière grise dans l'AOS, qu'il s'agisse d'atrophie ou d'hypertrophie, sont au moins partiellement réversibles.

### *1.5.3. Matière grise cérébrale – volumétrie*

Une autre méthode permettant l'évaluation du volume de la matière grise sur des images anatomiques T1 en IRM est la volumétrie. Cette méthode vise à tracer manuellement ou automatiquement des structures cérébrales prédéterminées pour en calculer leur volume. Ainsi, comparativement à la méthode de morphométrie basée sur le voxel qui évalue le volume de matière grise dans chaque voxel, la volumétrie calcule le volume global d'une structure donnée. Des études de volumétrie ont évalué les volumes de structures sous-corticales chez des personnes avec de l'AOS. Celles-ci ont inclus des adultes avec de l'AOS de toute sévérité ou modérée à sévère âgés entre 30 et 60 ans environ (sauf pour une étude évaluant des personnes âgées de 75 ans) (Sforza *et al.*, 2016). Une atrophie des hippocampes, du thalamus, du noyau caudé et des corps mamillaires a été rapportée dans l'AOS, mais une hypertrophie de l'hippocampe et du putamen a également été observée (Kumar *et al.*, 2008; Torelli *et al.*, 2011; Rosenzweig *et al.*, 2013; Kumar *et al.*, 2014a). Une atrophie de l'hippocampe a d'ailleurs corrélé avec une plus grande somnolence chez des personnes avec de l'AOS de toute sévérité (Dusak *et al.*, 2013; Sforza *et al.*, 2016).

### *1.5.4. Matière grise cérébrale – épaisseur corticale*

Finalement, une autre méthode permet d'évaluer la matière grise en calculant son épaisseur plutôt que son volume. Ces études ont évalué des participants âgés entre 30 et 60 ans environ, sauf pour l'étude de Dalmases et coll. incluant exclusivement des personnes âgées (Dalmases *et al.*, 2015b). Les études ayant utilisé cette méthode dans un contexte d'AOS sont nouvelles. La première étude, publiée en 2013, montrait un amincissement du cortex dans l'AOS sévère (Joo *et al.*, 2013), s'étendant à tous les lobes, y compris le cortex frontal latéral et médian, orbitofrontal, pariétal latéral et médian, cingulaire, temporal latéral et médian et occipital. Certaines de ces régions, de même que les aires sensorimotrices et le cortex temporal latéral, étaient aussi amincies, chez des adultes avec de l'AOS de toutes sévérités (Macey *et al.*, 2018). Toujours dans cette même étude, en séparant les analyses selon le sexe, seulement

les femmes avec de l'AOS avaient un amincissement du cortex frontal. Ces résultats d'amincissement cortical n'ont par contre pas été répliqués dans deux études, dont la première auprès d'apnéiques modérés à sévères (Yun *et al.*, 2017), et la deuxième auprès d'individus avec de l'AOS âgés de plus de 65 ans (Dalmases *et al.*, 2015b). Dans cette dernière étude, bien qu'aucun amincissement n'a été observé comparativement au groupe témoin (analyse transversale), les auteurs ont observé un amincissement sur une période de trois mois chez les personnes âgées avec de l'AOS (analyse longitudinale). Cet amincissement était observé au niveau du cortex préfrontal latéral, pariétal latéral et médian, et occipital médian, ce qui n'était pas observé chez les personnes traitées (Dalmases *et al.*, 2015b). Finalement, une étude récente a montré un amincissement de la région cingulaire, mais aussi un épaississement de l'insula dans l'AOS modérée à sévère (Taylor *et al.*, 2017).

En résumé, bien que la majorité des études ait montré une réduction du volume de la matière grise ou de l'épaisseur corticale, quelques études n'ont pas observé de changement dans l'AOS, tandis que d'autres ont rapporté des augmentations de volume ou d'épaisseur corticale. Les régions atteintes, surtout pour l'atrophie, sont très variées. Inversement, l'hypertrophie de la matière grise dans l'AOS a été principalement retrouvée dans des régions sous-corticales ainsi que dans quelques régions corticales plus médianes, comme l'insula. Les traitements de l'AOS semblent efficaces pour renverser au moins partiellement les changements de structure de matière grise, que ce soit de l'atrophie ou de l'hypertrophie. Certains facteurs semblent également jouer un rôle dans la relation entre l'AOS et la structure de la matière grise, y compris le sexe et la présence de somnolence. D'autres études sont nécessaires pour comprendre ce qui prédit l'atrophie et l'hypertrophie de la matière grise dans l'AOS. De plus, puisque très peu d'études ont inclus spécifiquement des personnes âgées, il n'est pas clair comment l'AOS pourrait affecter la matière grise dans cette population.

### *1.5.5. Matière blanche cérébrale - hyperintensités*

Les régions de signal hyperintense, ou hyperintensités, observées sur la séquence T2 et sur la séquence *fluid-attenuated inversion recovery* (FLAIR) de l'IRM sont appelées leucoaraïoses et représenteraient des dommages ischémiques à la matière blanche (Brickman *et al.*, 2009). Comparativement aux autres études de neuroimagerie, la population évaluée dans

les études évaluant les hyperintensités dans l'AOS est beaucoup plus âgée. Tandis que certaines études incluaient des adultes d'âge moyen et des personnes âgées, d'autres ont inclus uniquement des personnes âgées. La présence et la quantité d'hyperintensités de la matière blanche ont été associées à de multiples reprises à l'AOS modérée à sévère (Kim *et al.*, 2013; Peng *et al.*, 2014b; Baik *et al.*, 2015; Del Brutto *et al.*, 2017; Song *et al.*, 2017), de même qu'à l'AOS auto-rapportée (Rostanski *et al.*, 2016). L'hypoxémie pendant le sommeil montre une corrélation positive avec les hyperintensités de la matière blanche (Yilmaz Avci *et al.*, 2017), suggérant que celles-ci pourraient bel et bien être représentatives de dommages ischémiques. De plus, l'AOS semble interagir avec d'autres facteurs de risque vasculaires sur la présentation des hyperintensités de la matière blanche. Chez des personnes normotensives (40-69 ans), un profil de *dipping* inverse (c.-à-d., pression artérielle plus élevée la nuit que le jour), combiné à de l'AOS modérée à sévère, a été associé à plus d'hyperintensités de la matière blanche (Lee *et al.*, 2014). En présence d'une AOS modérée à sévère combinée à la présence de télomères courts, qui sont un marqueur de sénescence, les individus âgés montrent plus d'hyperintensités de la matière blanche (Choi *et al.*, 2016). Par contre, quelques études n'ont pas observé d'association entre l'AOS et les hyperintensités (Schulz *et al.*, 2013; Castillo *et al.*, 2015; Lutsey *et al.*, 2016) et ce, même chez des patients avec hypertension (Kiernan *et al.*, 2011).

### *1.5.6. Matière blanche cérébrale - imagerie de diffusion*

Une autre séquence d'IRM permet de mesurer la magnitude et l'orientation de la diffusion des molécules d'eau dans le cerveau, ce qui donne de l'information sur les structures cellulaires qui restreint leur mouvement. Dans la matière blanche cérébrale, l'orientation des axones restreint le mouvement des molécules d'eau dans un sens préférentiel, ce qui donne lieu à une diffusion de type anisotrope. Une perte cellulaire permet à l'eau de diffuser davantage (augmentation de la diffusivité), dans tous les directions (réduction de l'anisotropie). Avec la méthode d'imagerie par tenseur de diffusion, on peut mesurer l'anisotropie et la magnitude de la diffusion des molécules d'eau de façon régionale. Dans l'AOS, les études ont montré une réduction étendue de l'anisotropie étendue dans la matière blanche chez des personnes avec de l'AOS modérée à sévère âgées entre 30 et 60 environ (Macey *et al.*, 2008; Macey *et al.*, 2012; Castronovo *et al.*, 2014; Chen *et al.*, 2015). Cette

diminution d'anisotropie était présente chez les femmes avec AOS seulement (Macey *et al.*, 2012), alors qu'une association positive entre les changements à la matière blanche et des processus inflammatoires systémiques a été rapportée (Chen *et al.*, 2015). Au niveau de la diffusivité moyenne, axiale et radiale, les résultats varient. Bien qu'une étude ait montré une augmentation de la diffusivité radiale (Chen *et al.*, 2015), les autres ont rapporté des réductions de la diffusivité moyenne, axiale et radiale dans la matière blanche cérébrale des personnes avec de l'AOS (Kumar *et al.*, 2012; Castronovo *et al.*, 2014; Kumar *et al.*, 2014b). En ce qui concerne l'effet du traitement, cette réduction de diffusivité observée au départ était réversible après un an de traitement par PPC (Castronovo *et al.*, 2014). Par contre, malgré le traitement au PPC, des augmentations de diffusivité ont été observées en relation avec une somnolence résiduelle (Xiong *et al.*, 2017), suggérant la présence d'un processus demeurant irréversible malgré le traitement. Alors que les augmentations de diffusivité pourraient représenter une perte d'intégrité de la matière blanche, les réductions pourraient représenter des changements plus transitoires dans le contexte de l'AOS, comme des processus d'œdème intracellulaire ou des processus inflammatoires diminuant la diffusion des molécules d'eau. Une nouvelle technique d'IRM de diffusion permet d'évaluer *in vivo* la proportion d'eau libre dans l'espace extracellulaire par rapport à l'eau intracellulaire (Pasternak *et al.*, 2009). Des changements d'eau libre suggérant des processus neuro-inflammatoires ont été montrés dans plusieurs conditions, incluant la maladie de Parkinson, la schizophrénie, la raideur aortique, la maladie des petits vaisseaux, l'AVC et la maladie d'Alzheimer (Pasternak *et al.*, 2012; Pasternak *et al.*, 2015; Planetta *et al.*, 2016; Archer *et al.*, 2017; Ji *et al.*, 2017; Maillard *et al.*, 2017; Duering *et al.*, 2018; Montal *et al.*, 2018). Cette méthode pourrait donc permettre d'évaluer si l'AOS est en effet associée à un processus d'œdème, mais elle n'a pas été utilisée jusqu'à présent dans la population apnéique.

En résumé, la majorité des études chez les personnes âgées avec de l'AOS modérée à sévère suggèrent la présence de dommages ischémiques mesurés par les hyperintensités de la matière blanche, bien que ce résultat ne soit pas observé dans toutes les études. Chez les personnes d'âge moyen avec de l'AOS modérée à sévère, une diffusion restreinte des molécules d'eau est majoritairement retrouvée dans la matière blanche, bien qu'un profil différent ait aussi été observé dans certaines études. Les études de traitement par PPC

suggèrent que certaines atteintes cérébrales sont réversibles tandis que d'autres ne le sont pas. Comme pour la matière grise, certains facteurs semblent moduler la relation entre l'AOS et l'intégrité de la matière blanche comme la présence d'hypertension, des processus de sénescence ou d'inflammation et le sexe. Cependant, l'effet de l'AOS légère sur la matière blanche n'a pas été évalué.

## 1.6. Importance de la neuroimagerie dans le vieillissement pathologique

Bien que les impacts de l'AOS sur les fonctions cérébrales et les caractéristiques neuroanatomiques soient sous-étudiés dans le vieillissement, les méthodes de neuroimagerie sont particulièrement importantes et utiles dans le vieillissement pathologique. Dans la progression du vieillissement normal au développement de la démence comme la maladie d'Alzheimer, les marqueurs de neuroimagerie ont plusieurs utilités. Ils permettent d'appuyer le diagnostic d'un type de démence en particulier, de prédire la progression du vieillissement normal vers le trouble cognitif léger, et, subséquemment, la démence, et de mieux comprendre comment le cerveau est affecté dans les processus neurodégénératifs.

Les méthodes présentées précédemment ont toutes été utilisées dans les stades précurseurs de la neurodégénérescence. En TEMP, l'hypoperfusion du cortex temporal et pariétal permet de prédire la progression vers la maladie d'Alzheimer avec de bonnes sensibilité et spécificité (entre 82-96 % et 83-89 %, respectivement) (Henderson, 2012). L'atrophie mesurée en IRM peut être détectée 15 ans avant l'apparition des symptômes cliniques de démence (Bateman *et al.*, 2012). Au niveau clinique, l'atrophie du cortex temporal médian et de l'hippocampe est en processus de validation pour identifier les personnes avec un trouble cognitif léger à risque de progresser vers une maladie d'Alzheimer (Ten Kate *et al.*, 2017). Chez des individus génétiquement susceptibles de développer une démence ou avec un historique familial de démence, des hypertrophies localisées aux régions frontales et temporales ont été rapportées, tandis que d'autres régions comme l'hippocampe et l'amygdale montrent de l'atrophie (Mak *et al.*, 2017). En effet, une hypertrophie est présente dans les premiers stades de neurodégénérescence tandis que de l'atrophie est observée plus tard dans la progression (Montal *et al.*, 2018). Toujours chez les individus génétiquement

susceptibles ou avec un historique familial de démence, des changements de microstructure de la matière blanche ont aussi été observés, incluant des fluctuations de diffusivité et une réduction de l'anisotropie (Mak *et al.*, 2017). Les mesures d'eau libre montrent également des fluctuations selon les stades de neurodégénérescence, avec des réductions de l'eau libre dans les stades précurseurs qui deviennent des augmentations de l'eau libre dans les stades plus avancés (Montal *et al.*, 2018). Les hyperintensités de la matière blanche ont été associées à une moins bonne performance cognitive et au risque de développer une démence (Brickman *et al.*, 2009). En résumé, les changements cérébraux observés en neuroimagerie apparaissent dans les stades précliniques des processus neurodégénératifs et ont le potentiel de clarifier comment une condition comme l'AOS affecte le cerveau vieillissant.

# Chapitre 2. Articles de revues de la littérature

## 2.1. **Revue de littérature 1 :** Obstructive sleep apnea and the risk of cognitive decline

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**ABSTRACT**

Obstructive sleep apnea causes intermittent hypoxia and sleep fragmentation and affects at least 20 % of individuals after the age of 65. There is accumulating evidence that obstructive sleep apnea may impact brain structure and function. Recent cohort studies suggest that it is a risk factor for stroke, mild cognitive impairment and Alzheimer's disease. Because prevention through treatment of risk factors is currently the main intervention for reducing the incidence of dementia, how obstructive sleep apnea affects brain health and whether its treatment can slow neurodegeneration are relevant questions. This Perspective Article presents the most recent findings on the neurocognitive consequences of obstructive sleep apnea in the elderly. We focus on the aging brain and the link between obstructive sleep apnea, brain health, cognitive decline and dementia. We present how new discoveries from animal models, human sleep experiments, Alzheimer's disease biomarkers, and epidemiological studies will impact future OSA management in older individuals. We explore how sex, genetics, physical exercise or cognitive reserve has the potential to moderate the association between obstructive sleep apnea and dementia. We discuss the effect of obstructive sleep apnea treatment, which may slow, stop or reverse neurodegenerative processes accentuated by obstructive sleep apnea, even in individuals already affected by a neurodegenerative disease. We propose a research agenda that includes studies on mild/moderate untreated obstructive sleep apnea, the evaluation of continuous positive airway pressure treatment to slow neurodegeneration and follow-up studies of older patients that include predictors/markers of dementia.

***Introduction***

Adults should sleep seven or more hours per night on a regular basis to promote optimal health (Watson *et al.*, 2015). Insufficient or poor-quality sleep affects the immune system, weight management, glucose metabolism, cardiovascular and cerebrovascular health, cognition, work productivity, psychological well-being, and public safety. Recent findings indicate that sleep participates in the clearance of brain metabolic products (Xie *et al.*, 2013) including those involved in dementia pathogenesis (Musiek and Holtzman, 2016). How these new discoveries from animal models provide information on the impact of sleep disorders on brain health is a significant question.

The harmful effect of disturbed sleep on brain health is particularly important for older adults presenting obstructive sleep apnea (OSA). Not only does OSA cause severe sleep fragmentation, but also intermittent hypoxia, which may both affect brain structure and function. OSA is common, particularly after the age of 65 when it has an estimated prevalence of at least 20 % (Punjabi, 2008). Despite the increasing awareness of OSA and its consequences, 80 % of adults remain undiagnosed and untreated (Kapur *et al.*, 2002). When OSA is diagnosed in older adults, clinicians face a dilemma as to whether patients with the most common forms of mild to moderate OSA and/or those without daytime sleepiness or comorbid health problems should be treated or not. Even when treatment is recommended, 30 % of adults will refuse it (Wolkove *et al.*, 2008) and more than 33 % will not use it on the long-term (Doff *et al.*, 2013). These statistics suggest that many individuals that could benefit from treatment to possibly prevent neurodegeneration remain untreated. To improve treatment decision and increase adherence, we need to clearly depict the impact of OSA and its treatment on the aging brain. This *Perspective Article* presents the most recent findings on the neurocognitive consequences of OSA in older adults, a research field that has shown major growth in the past few years.

***Epidemiological Evidence Linking OSA to Cognitive Decline***

Recent meta-reviews have confirmed that OSA in middle-aged adults is associated with deficits in multiple cognitive domains. Attention, vigilance, episodic memory, working memory, and executive function are the cognitive domains most commonly impaired, whereas psychomotor abilities, language and visuospatial function remain less systematically affected

(Bucks *et al.*, 2013; Leng *et al.*, 2017). Studies show, however, an important heterogeneity in results due to differences in OSA definitions (e.g. self-reported versus objectively confirmed OSA, apnea-hypopnea index cut-offs, changes in hypopnea definition), neuropsychological tests (screening tests versus comprehensive assessments), and variables adjusted in statistical analyses (e.g. age, sex, apolipoprotein epsilon 4 allele [*APOE4*], body mass index, cardiovascular disease or depression).

In the older population, the link between OSA and risk of cognitive decline or dementia was only recently documented in prospective cohorts. A study published in 2011 showed that among 298 women aged 82.3 years-old in average, a higher risk of developing mild cognitive impairment (MCI) or dementia at the 4.7-year follow-up was associated with OSA, especially the severity of hypoxia (Yaffe *et al.*, 2011). More recently, a study performed with the Alzheimer's Disease Neuroimaging Initiative cohort showed that OSA was associated with an earlier age of progression to MCI or Alzheimer's Disease (AD) (Osorio *et al.*, 2015). A study using the Proof-SYNAPSE cohort has only shown small longitudinal changes in selected cognitive functions (Martin *et al.*, 2015). This weak link between OSA and cognitive decline was also the conclusion drawn in one recent systematic review and meta-analysis (Cross *et al.*, 2017). However, in another meta-analysis of six prospective studies that included 212,943 participants aged >40 years-old, the authors concluded that adults with OSA were 26 % more likely to develop significant cognitive decline or dementia at the 3 to 15-year follow-up (Leng *et al.*, 2017). With these new findings in mind, clinicians now face the challenge of correctly identifying patients at greater risk of cognitive decline, particularly in those without daytime symptoms in whom treatment is not systematically proposed.

***Candidate Mechanisms That Could Link OSA to Cognitive Decline***

Why and how OSA is linked to dementia are questions that are generating intensive research efforts. Untreated OSA can make the brain more vulnerable to neurodegenerative processes by gradually altering its structure and functioning (Rosenzweig *et al.*, 2014). One potential mechanism relates to the crucial role of sleep for optimal cognitive functioning. In fact, studies consistently show that sleep continuity, slow-wave sleep (SWS), Rapid-Eye-Movement (REM) sleep and sleep spindles have specific and essential roles in neurogenesis (Meerlo *et al.*, 2009), synaptic plasticity (Cirelli, 2013), next day vigilance (Van Dongen and

Dinges, 2005), as well as in memory formation and consolidation (Born and Wilhelm, 2012). OSA is associated with major and chronic changes in sleep characteristics, including severe sleep fragmentation, decrease of SWS and REM sleep (Heinzer *et al.*, 2001), and possible changes in sleep spindles (Carvalho *et al.*, 2014). Although hypothetical, these repetitive sleep architecture alterations may lead not only to next day neurocognitive deficits, but also to changes in brain structure (e.g. alteration of white and gray matter, changes in cerebral networks) due to chronic impairment in sleep-dependent neurogenesis and synaptic plasticity. Consequently, when a neurodegenerative process occurs, the apneic brain could be more vulnerable to the clinical expression of dementia (Stern, 2002).

There are also recent studies that link OSA to AD biomarkers, namely Aβ42 and tau proteins, that accumulate excessively in the forms of plaques or tangles in the AD brain (Polanco *et al.*, 2018). In humans, a study performed in a sleep clinic reported lower cerebrospinal fluid (CSF) Aβ42 and a higher total tau/Aβ42 ratio levels in untreated OSA individuals compared to treated OSA and controls (Liguori *et al.*, 2017b). These CSF findings suggest an accumulation of amyloid plaques and hyperphosphorylated tau protein in the brain. A similar study performed in community dwelling elderly adults confirmed these findings by showing that severity of OSA was associated with 2-year longitudinal decreases in CSF Aβ42 (Sharma *et al.*, 2017). Furthermore, in a recent study, neuronally derived proteins (CSF Aβ40, Aβ42, neurogranin and VILIP-1) were lower in a group of 10 OSA patients compared to 31 controls (Ju *et al.*, 2016).

In terms of mechanistic hypotheses, hypoxia, sleep disruption and impaired SWS in OSA could all be responsible for accentuation of AD biomarkers. Animal models and a few human studies support a link between Aβ generation, production and clearance in association with disturbed sleep and hypoxia. More specifically, recent studies suggest that sleep fragmentation and reduced SWS can increase Aβ deposition (Brown *et al.*, 2016). Interestingly, in a mouse model, chronic sleep deprivation doubles Aβ levels in the brain (Kang *et al.*, 2009). Moreover, sleep is implicated in the clearance of toxic proteins and metabolic waste accumulated during wakefulness through interstitial space expansion during sleep, which promotes fluid exchange with CSF (Xie *et al.*, 2013). Regarding this latter mechanistic hypothesis, three potential mechanisms could be involved: i) intrathoracic pressure swings from respiratory efforts against a closed airway that would impede the

glymphatic flow of metabolites from interstitial fluid to the CSF (Dreha-Kulaczewski *et al.*, 2017); ii) a reduction in the clearance of subarachnoid CSF directly into dural lymphatic channels due to increased venous pressure that is typically elevated in OSA; and, iii) cerebral edema secondary to intermittent hypoxia that reduces interstitial space expansion (Baronio *et al.*, 2013). Finally, several animal models showed that hypoxia plays an important role in the Aβ cascade via the hypoxia-inducible-factor-1α (HIF-1α) that increases the activity of various secretases (including BACE1), leading to an elevated production of Aβ peptides (Salminen *et al.*, 2017). In addition to increased Aβ generation, hypoxia affects peptidases that degrade Aβ peptides, and thus, hypoxia reduces Aβ clearance. Finally, hypoxia reduces the activity of the neuroprotective α-secretase, furthering the Aβ cascade.

Responses to upper airway obstructions can also affect brain health with age. In fact, apneas and hypopneas provoke adaptive (e.g. ischemic preconditioning) but also maladaptive and potentially harmful responses (e.g. oxidative stress, inflammation, hypertension, dysautonomia, impaired glucose tolerance, and blood-brain barrier dysfunction) that may damage cerebral cells and organelles, and make neurons more susceptible to cellular death (Rosenzweig *et al.*, 2014). Not surprisingly, studies have shown that severe OSA increases the risk of cerebral small vessel disease (Kim *et al.*, 2013) and stroke (Xie *et al.*, 2017). In a post-mortem study of 167 older adults, hypoxemia measured on prior polysomnographic recording was associated with more brain microinfarcts at autopsy (Gelber *et al.*, 2015). When only hypoxemia during REM sleep was considered, a significant association was also found for gliosis and neuronal loss in the locus coeruleus, a brainstem region responsible for norepinephrine supply that shows early neurofibrillary tangle formation due to aggregation of hyperphosphorylated tau protein in AD (Braak and Del Tredici, 2015). These studies suggest that OSA could increase the risk of both AD and vascular dementia.

***How Brain Structure and Function Change in Older Adults with OSA***

Most neuroimaging studies on OSA have been performed in young and middle-aged adults. Whether these findings can be generalized to an aged brain is unclear, as neuroimaging studies with older adults have only just emerged. Neuroimaging techniques allow indirect and large-scale measurements of neuroanatomical structures and their functioning. Given the complexity of changes that can occur in response to OSA (e.g. cellular death, edema, increase

in brain water content, neuroinflammation, changes in cerebral perfusion, increase in Aβ deposition), heterogeneous results can be obtained depending on participants' age, severity of intermittent hypoxia and sleep fragmentation, clinical stages of dementia, etc. OSA may also lead to non-linear changes in brain structure and function due to phasic adaptive and maladaptive responses. As an example, studies in young and middle-aged adults usually show gray matter atrophy in OSA patients as compared to controls and the parahippocampal and the fronto-temporal cortex are the brain regions most consistently affected (Weng *et al.*, 2014). However, in a study of adults aged 55 to 76 years old, OSA severity was associated with gray matter hypertrophy and higher cortical thickness in frontal, parietal and cingulate regions, as well as in the amygdala (Baril *et al.*, 2017b). The opposite pattern of gray matter hypertrophy and thickening in older OSA patients may be due to local increases in brain water content secondary to hypoxia and/or with Aβ deposition not yet present in younger adults with OSA. In accordance with this hypothesis, recent studies showed that more severe OSA is associated with increased rates of Aβ deposition using PiB-PET imaging in older adults (Sharma *et al.*, 2017; Yun *et al.*, 2017).

Cerebral white matter is vulnerable to hypoxia as well and results from the literature also underline the complex changes in brain structure associated with OSA. Rather than reporting the typical patterns of diffusion associated with white matter loss, most studies using diffusion tensor imaging in young and middle-aged adults have found reduced diffusivities along white matter tracks in OSA (Kumar *et al.*, 2012; Castronovo *et al.*, 2014; Kumar *et al.*, 2014b). Reduced diffusivity suggests that an ongoing brain response to OSA, such as swelling or increase brain water content, prevents water movement. This pattern of reduced diffusivities was previously observed in acute and/or preclinical stages of familial AD and stroke (Pitkonen *et al.*, 2012; Ryan *et al.*, 2013). Whether these changes evolve into neuronal death still needs to be verified with longitudinal studies.

Regarding cerebral functioning, a systematic review that included six studies of young and middle-aged adults reported reduced resting-state functional connectivity within and between several regions including the hippocampus, the posterior cingulate, the medial prefrontal cortex, the medial temporal lobe, the basal ganglia, the insula, and the cerebellum (Khazaie *et al.*, 2017). In parallel, a functional neuroimaging study in adults aged 55 and older measured regional cerebral blood flow using single photon emission computed tomography

and showed that participants with severe OSA had hypoperfusion in sensorimotor areas and the parietal lobes (Baril *et al.*, 2015). Moreover, hypoperfusions in the parietal, temporal and frontal lobes were associated with higher levels of respiratory disturbances, daytime sleepiness and obesity. Hence, functional neuroimaging is sensitive to changes associated with OSA. However, studies with elderly participants are needed to verify whether anomalies observed in younger subjects are applicable to the older population and are predictive of a cognitive decline. In that context, longitudinal neuroimaging studies would allow to clarify the evolution of brain functional changes in elderly OSA individuals.

***How Treating OSA Impacts the Aging Brain***

OSA treatment, such as continuous positive airway pressure (CPAP), is effective for reducing hypopneic and apneic events. However, patients generally suffer from OSA for several years before being diagnosed and treated. Whether CPAP treatment can slow down, stop or reverse neurodegenerative processes potentially accentuated by OSA is a crucial question, particularly for patients who start their treatment after the age of 65. Unfortunately, most published studies investigating the effect of CPAP on brain health were performed among young and middle-aged patients. However, in a randomized study of 33 OSA patients aged 71.3 ± 5.5 years old, three months of CPAP improved short-term memory, working memory, selective attention and executive functions as well as functional connectivity in the right middle frontal gyrus (Dalmases *et al.*, 2015b). More recently, preliminary evidence in a non-demented cohort of elderly participants, involved in a study from the Alzheimer's Disease Neuroimaging Initiative cohort, showed that CPAP treatment delays the age of MCI onset by approximately 10 years (72 versus 82 years old), while age at MCI onset in participants reporting treated OSA was similar to the non-OSA group (Osorio *et al.*, 2015). A recent case study of a patient with OSA and subjective cognitive impairment showed that 1-year CPAP treatment normalized the CSF Aβ42 and t-tau/Aβ42 ratio levels (Liguori *et al.*, 2017a), suggesting that OSA might be a reversible risk factor for dementia. More studies are urgently needed to confirm these preliminary findings and expand our knowledge regarding the effect of OSA treatment on neurodegeneration in the elderly.

Another important issue relates to the effect of OSA in patients already presenting a neurodegenerative disease. According to a recent meta-analysis, patients with AD have 50 %

chance of experiencing OSA after their dementia diagnosis (Emamian *et al.*, 2016). The authors hypothesized that this high rate of OSA in AD could be due to the possible role of OSA in dementia pathogenesis. In a series of pioneer studies by Ancoli-Israel and colleagues, reduced daytime sleepiness and cognitive deficits, as well as improvement in sleep quality were observed after treatment with CPAP in patients with AD (Chong *et al.*, 2006; Ancoli-Israel *et al.*, 2008; Cooke *et al.*, 2009). These results support the hypothesis that OSA aggravates cognitive dysfunction when neurodegenerative processes are already present and that CPAP can have a positive impact on cognitive functioning in the demented population.

This aggravation effect of OSA on cognition is not limited to patients with AD and is also common in patients with Parkinson's disease (PD). This neurodegenerative disorder is characterized by a progressive motor syndrome, but also cognitive dysfunction and dementia in up to 83 % of patients (Hely *et al.*, 2008). OSA in non-demented patients with PD increases sleepiness and reduces global cognition (Mery *et al.*, 2017). Treatment of OSA was associated with improvement in sleep quality and sleepiness (Neikrug *et al.*, 2014) and cognitive function (Kaminska *et al.*, 2018), though a shorter trial found no change in cognition (Harmell *et al.*, 2016). Longer randomized trials are needed to assess whether treating OSA in PD can improve cognitive function and delay onset of dementia. Another important question is whether OSA has an impact on the progression of the motor dysfunction and the overall neurodegenerative process of PD. A recent study suggests that antecedent OSA increases the risk of developing PD in women (Sheu *et al.*, 2015). Hence, OSA might be a risk factor for neurodegenerative disorders, with the predominant pathology and clinical manifestations depending on predisposing factors.

CPAP therapy is challenging in patients with a neurodegenerative disease or dementia due to anxiety, nocturia, insomnia, and cognitive and motor impairment affecting the ability to wear the mask, but studies have shown that it is feasible (Chong *et al.*, 2006; Ancoli-Israel *et al.*, 2008; Cooke *et al.*, 2009; Mery *et al.*, 2017).

### *Risk Factors and Prevention of Cognitive Decline in the Context of OSA*

Very few studies have investigated whether some factors moderate, i.e. reinforce or weaken, the association between OSA severity and cognitive impairment. It is possible that individual characteristics or comorbidities can make some older OSA adults more or less at

risk of developing dementia. For example, a 5-year longitudinal cohort study of 7547 men showed that self-reported OSA was only associated with risk of dementia in *APOE4* non-carriers (Ding *et al.*, 2016). However, the reverse result was found in three cross-sectional studies where the association between OSA and impaired cognition was stronger in *APOE4* carriers than in non-carriers (Spira *et al.*, 2008; Nikodemova *et al.*, 2013a; Johnson *et al.*, 2017).

***Research Agenda***

Research on the long-term neurocognitive consequences of OSA is just emerging, but recent studies have transformed this field by moving the focus from middle-aged to older adults. Still, very few longitudinal studies with objective monitoring for OSA have been published. This type of study design is necessary to reveal how cognitive functioning in the elderly evolves in the context of OSA.

- One of the first lines of research should be to identify vulnerable OSA patients that could benefit the most from treatment. In addition, whether mild to moderate OSA patients who are asymptomatic or present mild daytime symptoms could lead to dementia in the long term is not clear. We urgently need to characterize genetic, sleep and/or respiratory characteristics that put patients at greater risk of dementia. For clinical purposes, we have to validate screening tests and biomarkers (e.g. genetics, blood biomarkers, neuroimaging) that could identify vulnerable patients.
- There is a need to study how factors that are already known to affect the clinical expression of dementia, e.g. age, sex, hypertension, hypercholesterolemia, diabetes, smoking, depression, metabolic syndrome, and obesity (Baumgart *et al.*, 2015), influence the evolution of cognitive decline in adults with OSA. Considering that OSA is frequently caused by obesity and is a risk factor for hypertension, diabetes, and depression (Jennum and Riha, 2009), studying their additive or interacting role could help identify those adults more vulnerable to the neurocognitive effects of OSA.
- We also need to understand how lifestyle (e.g. high education or cognitive reserve, healthy diet, physical exercise, social activities) could prevent the deleterious effects of OSA on brain health. For example, exercise training has been described as having

positive effects on OSA severity in sedentary overweight/obese young and middle-aged adults (Kline *et al.*, 2011). Moreover, we need to verify whether physical activity can reduce Aβ deposition, as previously described in non-apneic participants (Merrill *et al.*, 2016).

— Another line of research is to clarify the mechanistic processes that link OSA to dementia in order to identify novel targets for intervention. Preliminary evidence suggests that cognitive decline in OSA may share similar mechanisms to those already described in AD (i.e. aggregation of Aβ and tau in the brain) or vascular dementia. These results should be confirmed in longitudinal studies. In the same manner, whether brain structure and function anomalies in non-demented older adults with OSA evolve into dementia is unknown. Testing mechanistic hypotheses explaining the impact of OSA on human cerebral physiology and function warrants the use of the most advanced neuroimaging methodologies.

— Another priority is to determine the long-term effects of OSA treatment on neurocognitive health. Several variables will need to be considered, including the age at OSA diagnosis and age when treatment was started. We need to determine thresholds for minimum CPAP use and duration to be effective on cognitive function. Whether OSA treatment can stop or reverse the cognitive decline of older adults presenting MCI needs to be investigated.

— It will be necessary to evaluate the therapeutic and economic costs and benefits of CPAP in older people, particularly in those with mild or moderate OSA, and include a particular consideration of cognitive decline in the cost-effectiveness analysis.

— The long-term neurocognitive consequences of untreated OSA are generally not considered in treatment decision-making. It is noteworthy that we now have sufficient evidence supporting the role of sleep quality and duration on neurocognitive health to make sustained efforts to translate this knowledge. Although this latter point is not a research objective, it should be considered as a priority in order to transform clinical practice and public health policies.

## 2.2. **Revue de littérature 2 :** Biomarkers of dementia in obstructive sleep apnea

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**Revue invitée et en révision à :** Sleep Medicine Reviews

**Contribution de la candidate:** écriture et révision de la revue suite aux commentaires des co-auteurs, processus de soumission et de révision par les pairs auprès du journal scientifique.

**SUMMARY**

Epidemiologic and mechanistic evidence is increasingly supporting the notion that obstructive sleep apnea is a risk factor for dementia. Hence, the identification of patients at risk of cognitive decline due to obstructive sleep apnea may significantly improve preventive strategies and treatment decision-making. Cerebrospinal fluid and blood biomarkers obtained through genomic, proteomic and metabolomic approaches are improving the ability to predict incident dementia. Therefore, fluid biomarkers have the potential to predict vulnerability to neurodegeneration in individuals with obstructive sleep apnea, as well as deepen our understanding of pathophysiological processes linking obstructive sleep apnea and dementia. Many fluid biomarkers linked to Alzheimer's disease and vascular dementia show abnormal levels in individuals with obstructive sleep apnea, suggesting that these conditions share common underlying mechanisms, including amyloid and tau protein neuropathology, inflammation, oxidative stress, and metabolic disturbances. Markers of these processes include amyloid-β, tau proteins, inflammatory cytokines, acute-phase proteins, antioxydants and oxidized products, homocysteine and clusterin (apolipoprotein J). Thus, these biomarkers may have the ability to identify adults with obstructive sleep apnea at high risk of dementia and provide an opportunity for therapeutic intervention. Large cohort studies are necessary to establish a specific fluid biomarker panel linking obstructive sleep apnea to dementia risk.

## INTRODUCTION

Approximately 36 million people worldwide have dementia and this number is expected to reach 115 million in 2050 (Prince *et al.*, 2013). Alzheimer's disease (AD) is the most common type of dementia and is characterized by aggregation of extracellular amyloid-β (Aβ) and intracellular hyperphosphorylation of tau proteins, leading to amyloid plaques and neurofibrillary tangles respectively (Scheltens *et al.*, 2016). Vascular dementia (VaD) is the second most common type of dementia and is caused by cerebrovascular events (O'Brien and Thomas, 2015). About 20 % of dementia cases are mixed, with the presence of both AD and VaD pathophysiological processes (Custodio *et al.*, 2017). Targeting modifiable risk factors are of outmost importance to reduce the occurrence and progression of dementia. An emerging modifiable risk factor for dementia is obstructive sleep apnea (OSA), which corresponds to repeated respiratory obstructions during sleep (Malhotra and White, 2002). Recently, several cohort studies and a meta-analysis have identified OSA as a risk factor for mild cognitive impairment (MCI), an earlier age at cognitive decline, all-cause dementia, and AD (Yaffe *et al.*, 2011; Chang *et al.*, 2013; Osorio *et al.*, 2015; Ding *et al.*, 2016; Leng *et al.*, 2017; Lutsey *et al.*, 2017). OSA can be effectively treated by continuous positive airway pressure (CPAP) (Calik, 2016). With a prevalence in the elderly that reaches over 50 % in some studies (Senaratna *et al.*, 2017), OSA could therefore become an important target to prevent dementia. CPAP may delay the onset of cognitive decline (Osorio *et al.*, 2015), although results on the cognitive effects of CPAP in middle-aged individuals are inconsistent (Pan *et al.*, 2015). CPAP in patients with both AD and OSA has shown to improve neuropsychological function over a few weeks (Ancoli-Israel *et al.*, 2008) and slowed the rate of cognitive decline over three years (Troussiere *et al.*, 2014).

Many pathophysiological mechanisms have been proposed to explain the relationship between OSA and dementia. First, it is likely that OSA plays an indirect role in the development of dementia by increasing the incidence of cardiovascular and metabolic diseases, including hypertension, obesity, metabolic syndrome, stroke and diabetes (Drager *et al.*, 2015), which are independent risk factors of dementia (Baumgart *et al.*, 2015; O'Brien and Thomas, 2015). Secondly, sleep fragmentation and intermittent hypoxia in OSA induce inflammation, oxidative stress, mitochondrial dysfunction, endothelial dysfunction, and metabolic deregulations (Polsek *et al.*, 2018), have been proposed to foster the development of

dementia (Candore *et al.*, 2010; Calabrese *et al.*, 2016). Finally, recent evidence suggests that sleep fragmentation and intermittent hypoxia may induce AD neuropathology. In fact, in animal models, disturbed sleep and hypoxia facilitate tau proteins hyperphosphorylation and enhance Aβ generation while diminishing its clearance (Rothman *et al.*, 2013; Zhang *et al.*, 2014; Brown *et al.*, 2016; Salminen *et al.*, 2017). A human study using Pittsburgh compound B positron emission tomography (PiB-PET) also revealed that OSA individuals had increased Aβ burden (Yun *et al.*, 2017). AD and VaD were selected for this review because they are the two most common causes of dementia and epidemiological and mechanistic evidence suggests a relationship with OSA.

The neuropathological process starts years before the clinical manifestation of AD (Bateman *et al.*, 2012). Early biomarkers are receiving increasing attention because of their potential for dementia prevention and treatment. Fluid biomarker have the potential to be easily implemented in large cohort studies or clinical settings and may be used to identify prodromal stages (i.e., MCI patients who will later convert to dementia) and pre-symptomatic dementia (i.e., cognitively normal subjects who will later develop dementia) (Breitner *et al.*, 2016).

This theoretical review aims at identifying the most promising fluid biomarkers of dementia that should be included in future large research cohorts of individuals with OSA. Ultimately, a panel of fluid biomarker could improve direct patient care significantly by identifying adults with OSA at higher risk of developing dementia, and could be useful to unravel pathophysiological mechanisms linking OSA to dementia. To achieve this goal, we first present the most promising candidate biomarkers of dementia that emerged from the recent literature. We present evidence on cerebrospinal fluid (CSF) and blood biomarkers of AD and VaD, including those from genomics, proteomics, and metabolomics. We present corresponding findings within the OSA population. Finally, we propose a research agenda for testing fluid biomarkers of dementia in OSA.

## GENOMICS

### *Genetics of dementia*

Usually using blood samples, genetic and genome-wide association studies investigate specific polymorphisms, which are the occurrence of different alleles in the population. The

most important and well-established genetic risk factor for spontaneous AD is the *apolipoprotein E4* (*APOE4*) allele (see (Van Cauwenberghe *et al.*, 2016) for a review), which was first described in the early 90's (Poirier *et al.*, 1993). AD risk is increased by 300 % for one *APOE4* allele and 1500 % for two *APOE4* alleles, while the *APOE2* allele is protective against AD (Van Cauwenberghe *et al.*, 2016). APOE is involved in lipid transport and membrane integrity in the brain as well as in Aβ degradation (Leduc *et al.*, 2010).

Although none are associated with AD as strongly as *APOE*, several other polymorphisms modify the incidence of AD, including *clusterin (CLU), sortilin-related receptor-1 (SORL1), complement component receptor 1 (CR1), ATP-binding cassette transporter A (ABCA7), fermitin family member 2 (FERMT2), major histocompatibility complex class II (HLA-DRB5, HLA-DRB1), bridging integrator 1 (BIN1),* and *phosphatidylinositol-binding clathrin assembly molecule (PICALM)* (Van Cauwenberghe *et al.*, 2016). These genes affect the risk for AD by about 10-20 % each, and they code for proteins involved in Aβ production and clearance, tau toxicity, endosomal vesicle cycling, lipid transport, and the immune response. Because many polymorphisms are now linked to incident AD, genetic susceptibility to dementia for a given individual can be computed with a polygenic score (PS). The risk of developing AD and the age of onset can be predicted with a PS combining 31 polymorphisms, which correlates with several other biomarkers of AD, including CSF Aβ and tau proteins levels (Desikan *et al.*, 2017). A PS computed with thousands of polymorphisms have a high predictive accuracy for AD even when the most common polymorphisms such as *APOE* are not included (Escott-Price *et al.*, 2015), suggesting that the genetic susceptibility to AD include a large amount of genes with small effect.

VaD risk is increased by the *APOE4* allele as well as other specific genetic polymorphisms, including *5,10-methylenetetrahydrofolate reductase (MTHFR)*, which is involved in homocysteine conversion, as well as *TNF-α* and *transforming growth factor β1 (TGF-β1),* which are cytokines involved in the immune response (see (Ikram *et al.*, 2017) for a review). Genes increasing the risk of stroke have also the potential to modify the risk of VaD (Ikram *et al.*, 2017). Ischemic stroke can be predicted with a PS computed with thousands of polymorphisms (Hachiya *et al.*, 2017). Moreover, a PS computed with polymorphisms that are associated with stroke correlated with cognitive abilities in subjects without stroke (Harris *et al.*, 2016).

### *Genetics of OSA*

Genetic factors seem to have an influence over the development of OSA. Looking at genes related to dementia risk, meta-analyses concluded that there is no association of *APOE* polymorphism with the presence of OSA (Varvarigou *et al.*, 2011; Xu *et al.*, 2015). However, the *APOE4* allele may interacts with OSA to worsen cognitive performance: OSA severity is associated with worse memory, attention, executive functioning as well as worse global cognition only in *APOE4* carriers (O'Hara *et al.*, 2005; Spira *et al.*, 2008; Nikodemova *et al.*, 2013b; Johnson *et al.*, 2017). Polymorphisms of *TNF-α* and *interleukin-6 (IL-6)*, which code for inflammatory cytokines, as well as *HLA-DRB1* have been significantly associated with the presence of OSA (Varvarigou *et al.*, 2011; Wu *et al.*, 2014; Silva *et al.*, 2015; Zhong *et al.*, 2016), although how inflammation may lead to OSA remains to be clarified.

## CSF BIOMARKERS

### *CSF biomarkers of dementia*

CSF biomarkers that are directly related to AD neuropathology can be used to diagnose probable AD (see (Humpel and Hochstrasser, 2011; Blennow *et al.*, 2012) for reviews). Lower CSF $A\beta_{42}$ and $A\beta_{42/40}$ ratio are the signature of AD and probably represent the brain deposition of Aβ in the form of plaques (Humpel and Hochstrasser, 2011; Blennow *et al.*, 2012). Reduced CSF $A\beta_{42}$ levels are also observed in pre-symptomatic AD (Blennow *et al.*, 2012), suggesting that Aβ deposition is a very early process. Reduced CSF $A\beta_{42}$ levels are observed in VaD but is less marked than that observed in AD (Llorens *et al.*, 2017). On the other hand, most reports show no $A\beta_{40}$ changes in AD patients (Humpel and Hochstrasser, 2011).

Higher tau levels in CSF have a high sensitivity and specificity for AD and prodromal AD, but were reported as unchanged in pre-symptomatic AD (Humpel and Hochstrasser, 2011). In fact, increased CSF tau level may occur later than the Aβ changes in the neurodegenerative process (Blennow *et al.*, 2012), which is confirmed with recent work using PET markers (McDade and Bateman, 2018). While CSF total tau levels that are elevated in both AD and VaD, phosphorylated tau levels are more specific to AD and can be useful to discriminate between these two types of dementia (Humpel and Hochstrasser, 2011; Blennow *et al.*, 2012). Chitinase-3-like protein 1 (YKL-40) and visinin-like protein 1 (VILIP-1), which

are markers of inflammation and neuronal injury respectively, are other promising CSF biomarkers of AD. Although only YKL-40 is higher in MCI and AD patients, higher levels of both YKL-40 and VILIP-1 predicted the conversion from MCI to AD (Kester *et al.*, 2015).

***CSF biomarkers in OSA***

Adults with OSA had lower CSF $A\beta_{40,}$ $A\beta_{42}$ and VILIP-1 levels, but unchanged CSF tau levels were found (Ju *et al.*, 2016). In a recent study in which all subjects reported subjective cognitive impairment, those with OSA exhibited lower CSF $A\beta_{42}$ levels, a higher tau/$A\beta_{42}$ ratio, but no tau level changes when compared to controls and OSA patients treated with CPAP (Liguori *et al.*, 2017b). A case-report of a 57-year-old man with severe OSA and subjective cognitive impairment showed abnormal low CSF levels of $A\beta_{42}$ and $A\beta_{42/40}$ and high total tau/$A\beta_{42}$ ratio levels that were normalized with a one-year treatment with CPAP (Liguori *et al.*, 2017a). In the largest cross-sectional and only longitudinal study to date performed in cognitively normal elderly, OSA severity indices were not associated with CSF $A\beta_{42}$ levels at cross-section but correlated with annual rates of CSF $A\beta_{42}$ decrease over the two year follow-up (Sharma *et al.*, 2017), which would be consistent with increases in amyloid burden over time. Overall, most of these recent reports performed in subjects aged 50-70 years old suggest that OSA is associated with reduced CSF $A\beta_{42}$ and as would be expected in the early stages of dementia.

**BLOOD-BASED PROTEOMIC BIOMARKERS OF AD NEUROPATHOLOGY**

***Blood-based biomarkers of AD neuropathology***

Most studies found lower blood $A\beta_{42}$ in AD and MCI patients compared to controls as well as in pre-symptomatic and prodromal AD (see (Baird *et al.*, 2015) for a review). However, studies failed to replicate these results and even reported high blood $A\beta_{42}$ levels in pre-symptomatic AD (Baird *et al.*, 2015). In fact, a meta-analysis of 7 studies showed that higher blood $A\beta_{42}$ levels were present in subjects with pre-symptomatic AD (Song *et al.*, 2011). Blood $A\beta_{42}$ levels may depend on the stage of the disease: enhanced levels are present in earlier stages of the disease, but these levels decrease as the cognitive decline progresses (Song *et al.*, 2011; Baird *et al.*, 2015). This pattern could represent increased Aβ production and reduced clearance at first, with aggregation into plaques later on. Results seem less

promising for blood $A\beta_{40}$ levels, as both increased and decreased levels were reported in AD patients (Baird *et al.*, 2015). A meta-analysis indicated higher blood $A\beta_{40}$ levels in pre-symptomatic AD (Song *et al.*, 2011) whereas unchanged levels in earlier stages were also reported (Baird *et al.*, 2015). Overall, mixed results were obtained on blood $A\beta_{40}$ levels at every stage of the disease. On the other hand, the blood $A\beta_{42/40}$ ratio yields promising results. A meta-analysis including over 10 000 subjects concluded that lower blood $A\beta_{42/40}$ ratio was associated with higher risk of developing all-cause dementia (Koyama *et al.*, 2012). A low blood $A\beta_{42/40}$ ratio was indeed reported in subjects with AD, MCI and with pre-symptomatic AD (Baird *et al.*, 2015).

Higher blood tau levels are a new tool and have been associated with the presence of AD and MCI (Baird *et al.*, 2015). A recent study with a three year follow-up found that higher tau protein levels were associated with the progression from cognitively normal to MCI, but not from MCI to all-cause dementia (Mielke *et al.*, 2017). This could be due to the short follow-up period and few dementia cases, and thus, other studies are needed to confirm blood tau protein levels as biomarkers for dementia and whether they are associated with neurofibrillary tangles in the brain.

***Blood-based biomarkers of AD neuropathology in OSA***

Interestingly, children with OSA have a higher blood $A\beta_{42}$ concentration (Kheirandish-Gozal *et al.*, 2016), which could be representative of increased Aβ production in the brain, but may also represent increased production by other cells in the periphery (e.g., platelets, muscle cells) or reduced clearance by the liver (Roher *et al.*, 2009; Kheirandish-Gozal *et al.*, 2016). $A\beta_{42}$ levels were decreased after adenotonsillectomy, a surgical procedure that either reduces OSA severity or cures it. In young adults, whereas OSA was not associated with blood $A\beta_{42}$ and $A\beta_{40}$ levels, moderate-severe OSA was associated with increased blood total tau levels compared to both mild OSA and controls (Motamedi *et al.*, 2018). In another study, middle-aged OSA subjects had significantly higher blood levels of both $A\beta_{40}$ and $A\beta_{42}$ as well as phosphorylated tau levels compared to controls, although unchanged total tau levels were observed (Bu *et al.*, 2015). Overall, these first reports suggest that OSA lead to increased blood tau and Aβ levels, regardless of age.

## BLOOD-BASED PROTEOMIC BIMARKERS OF INFLAMMATION

### *Blood-based inflammatory biomarkers of dementia*

Inflammation is hypothesized to play a major role in VaD and AD (Candore *et al.*, 2010; Takeda *et al.*, 2014; Calabrese *et al.*, 2016). In fact, there may be a bidirectional relationship between inflammation and neurodegeneration: inflammation is caused by Aβ deposition, oxidative stress, and cellular damage; and inflammation is followed by Aβ generation, blood-brain barrier (BBB) pathology, and further oxidative stress. A recent meta-analysis investigating 51 biomarkers in 171 studies concluded that inflammatory biomarkers are increased in AD (Lai *et al.*, 2017), including IL-1β, IL-2, IL-6, IL-18, chemokine ligand-10, TNF-α converting enzyme and TNF receptors, and interferon gamma (IFN-γ). All of them are cytokines or chemokines involved in the immune response and glial activation (Lai *et al.*, 2017). Other elevated blood inflammatory biomarkers in AD patients included α1-antichymotrypsin (ACT) and high-sensitivity c-reactive protein (hsCRP), two acute-phase proteins involved in coagulation and lysis, and vascular cell adhesion molecule-1 (VCAM-1), an adhesion molecule which assists other markers to reach the inflammation site (Lai *et al.*, 2017). Most significant results were observed for IL-1β, IL-6, ACT, hsCRP and TNF receptors. However, a few studies showed either unchanged or reduced levels in AD patients (Lai *et al.*, 2017). As for VaD patients, they also show elevated cytokines compared to controls, including IL-1β, IL-4, IL-5, TNF-α, and IFN-γ (Schmitz *et al.*, 2015).

In MCI subjects, despite the fact that most blood inflammatory biomarkers are unchanged, some studies have reported that a few cytokines are upregulated, including IL-1β, TNF-α, intercellular adhesion molecule 1 (ICAM-1), and IFN-α (Brosseron *et al.*, 2014). In six large cohort studies, higher blood levels of hsCRP, ACT and IL-6 were all associated with either a higher risk of cognitive decline or all-cause dementia, AD and vascular dementia (see (Dziedzic, 2006) for a review), even though there are inconsistencies regarding which specific biomarkers are elevated.

### *Blood-based inflammatory biomarkers investigated in OSA*

It is well known that OSA leads to an inflammatory response (Lim and Pack, 2014; Polsek *et al.*, 2018). In a first meta-analysis of 15 studies, it was reported that blood hsCRP

levels are higher in OSA patients compared to controls, which are modulated by obesity and OSA severity (Li *et al.*, 2017a). The second meta-analysis of 47 articles found that blood TNF-α levels are also elevated in OSA subjects (Li and Zheng, 2017). Finally, the third meta-analysis of 51 studies showed that blood levels of CRP, TNF-α, IL-6, IL-8 and adhesion molecules (ICAM-1, Selectins and VCAM-1) are increased in OSA subjects (Nadeem *et al.*, 2013). In these meta-analyses, the large majority of studies showed elevated blood inflammatory biomarkers in OSA.

## BLOOD-BASED PROTEOMIC AND METABOLOMIC BIOMARKERS OF OXIDATIVE STRESS

### *Blood-based biomarkers of oxidative stress in dementia*

Oxidative stress is the production of highly reactive free radicals that damage nucleic acids, proteins and lipids (Garcia-Blanco *et al.*, 2017). In dementia, oxidative stress is hypothesized to be an important mechanism leading to tissue damage (see (Garcia-Blanco *et al.*, 2017) for a review). It occurs following inflammation and Aβ deposition (Candore *et al.*, 2010), suggesting that oxidative stress may be an effector between dementia pathology and neuronal death. Moreover, oxidative stress leads to atherosclerosis and is involved in VaD pathogenesis (Bennett *et al.*, 2009).

Homocysteine is an amino acid with proprieties that makes it one of the most promising blood biomarkers for all-cause dementia. Indirectly, hyperhomocysteinemia is a marker of B12 deficiency, which can cause cognitive decline (Smith and Refsum, 2016). Directly, high levels of homocysteine cause oxidative stress, and thus, it is involved in BBB dysfunction, cardiovascular and cerebrovascular diseases, neuronal death, enhanced Aβ toxicity, Aβ generation and deposition as well as tau protein phosphorylation (Smith and Refsum, 2016). In 2002, homocysteine was already shown to be associated with dementia (Seshadri *et al.*, 2002), and a meta-analysis of 10 studies concluded that homocysteine blood levels are elevated in AD patients (Lai *et al.*, 2017). This result was replicated in both AD and VaD patients in another meta-analysis of 13 studies (Ho *et al.*, 2011), with higher levels in VaD than AD (Ho *et al.*, 2011). Overall, many cohort studies showed that elevated blood levels of homocysteine are associated with the incidence of all-cause dementia up to 35 years later (Smith and Refsum, 2016).

Reduced blood levels of antioxidant were reported in AD and MCI, including superoxide dismutase (SOD), selenium, vitamin E, and total antioxidant capacity (Garcia-Blanco *et al.*, 2017). In VaD, blood levels of many antioxidants are also reduced, including vitamins E, C and A as well as SOD (Bennett *et al.*, 2009). Interestingly, supplements of vitamins C and E in the elderly may protect against the development of VaD, as well as mixed dementia (Masaki *et al.*, 2000), but more studies are needed to set the appropriate intake levels for these vitamins.

Biomarkers of free radicals, damaged proteins, lipid peroxidation and nucleic acid oxidation are increased in both AD and MCI patients compared to controls: hemo-oxygenase-1, proteins carbonyls, oxidized proteins products, malondialdehyde (MDA), hydroperoxides, 8,12-isoiPF(2alpha)-VI, 8-hydroxy-2-desoxyguanosine (8-OHdg) and 8-oxoguanine (Garcia-Blanco *et al.*, 2017). Overall, patients with dementia or at risk show reduced antioxidant capacity combined with increased oxidative stress production and damage.

***Blood-based biomarkers of oxidative stress in OSA***

OSA produces oxidative stress directly via intermittent hypoxia and mitochondrial dysfunction, as well as indirectly with associated comorbidities, such as obesity and hypertension (Zhou *et al.*, 2016b). Oxidative stress may be an important mechanism by which OSA is associated with neurodegeneration (Polsek *et al.*, 2018). Two meta-analyses of ten studies concluded that homocysteine levels are elevated in OSA, especially in subjects with severe OSA and in subjects under 50 years of age (Niu *et al.*, 2014; Li *et al.*, 2017b). In fact, all included studies indicated higher homocysteine levels in severe OSA subjects. In another meta-analysis of 6 studies, blood homocysteine levels were significantly reduced after three months of CPAP (Chen *et al.*, 2014).

A recent review has discussed oxidative stress in OSA in relation with altered neurocognitive functioning comprehensively (Zhou *et al.*, 2016b). Lower antioxidant blood levels were reported in OSA subjects, including SOD and vitamin E (Zhou *et al.*, 2016b). Moreover, OSA subjects exhibited increased blood levels of proteins and metabolites associated with oxidative stress and damage, including oxidized proteins products, MDA and 8-OHdg (Zhou *et al.*, 2016b). All of these were correlated with impaired cognition in various cognitive domains, such as attention, memory, language, and executive function (Zhou *et al.*,

2016b). Moreover, higher levels of MDA and oxidized proteins products were found in subjects with both MCI and OSA compared to OSA subjects without MCI (He *et al.*, 2016). These studies strongly suggest that oxidative stress in OSA is a mechanism underlying cognitive impairment.

## BLOOD-BASED PROTEOMIC AND METABOLOMIC BIOMARKERS OF LIPID METABOLISM

### *Blood lipoproteins and lipids as biomarkers of dementia*

Clusterin (also named APOJ) is one of the most promising biomarkers of dementia. Clusterin is involved in cholesterol homeostasis and transport in the brain in partnership with APOE (Leduc *et al.*, 2010), and interacts with Aβ: clusterin can play a neuroprotective role by increasing Aβ clearance and reducing its aggregation, while it can also play a neurotoxic role by mediating Aβ toxicity (Li *et al.*, 2014). Blood clusterin levels are increased in both AD and MCI subjects as compared to controls (Song *et al.*, 2012; Koch and Jensen, 2016), and are associated with the risk of developing AD (Jongbloed *et al.*, 2015) even though these results were not supported by all groups (see (Koch and Jensen, 2016) for a review). Moreover, higher clusterin levels predicted faster progression of cognitive decline in MCI and AD subjects (Song *et al.*, 2012; Jongbloed *et al.*, 2015). The relation between blood clusterin levels and cognitive decline seems, however, not linear: higher clusterin levels were associated with a higher risk of all-cause dementia in subjects over 80 years, but with a lower risk of all-cause dementia and stroke in subjects younger than 80 years (Weinstein *et al.*, 2016). This finding supports the neuroprotective/neurotoxic duality of clusterin that appears to be moderated by age.

Because both APOE and high-density lipoproteins cholesterol (HDL-C) have protective functions (i.e., Aβ clearance, metabolite exchanges between neurons and glia, transport of cholesterol to be eliminated and reduction of atherosclerosis), their reduced blood levels in association with dementia may represent reduced neuroprotection (Hauser *et al.*, 2011). Lower blood APOE levels are generally observed in prodromal AD and AD patients, particularly in *APOE4* carriers (Poirier, 2005), and are associated with increased risk of developing dementia (see (Koch and Jensen, 2016) for a review). However, other studies showed surprisingly unchanged blood APOE levels in AD patients (Koch and Jensen, 2016).

Although many studies were performed on HDL-C, only about half found lower HDL-C levels in AD patients or in pre-symptomatic/prodromal AD (Koch and Jensen, 2016).

### *Blood lipoproteins and lipids investigated in OSA*

To our knowledge, only one study investigated clusterin blood levels in OSA and found that clusterin levels were elevated and associated with a worse memory performance (Peng *et al.*, 2017). Blood APOE levels were also shown to be slightly elevated in middle-aged OSA subjects compared to controls (Xu *et al.*, 2016). This could represent compensatory mechanisms in order to protect against atherosclerosis processes. A large meta-analysis including 64 studies covering over 18 000 subjects showed that OSA is associated with abnormal lipid profiles, which include lower blood HDL-C levels (Nadeem *et al.*, 2014). The authors hypothesized that oxidative stress and inflammation in OSA might cause dyslipidemia, which could be followed by atherosclerosis.

## PROPOSED RESEARCH AGENDA TO INVESTIGATE PROMISING FLUID BIOMARKERS OF DEMENTIA IN OSA

### *Fluid biomarkers: strengths and limitations*

Neuroimaging biomarkers that measure brain atrophy, reduced brain glucose metabolism, or increased Aβ plaques can detect changes up to 15 years before dementia onset (Bateman *et al.*, 2012), but they have limited availability and are expensive. Cognitive assessment is easy and accessible, but cognitive impairment occurs later in the course of the disease (Bateman *et al.*, 2012). Fluid biomarkers of dementia are a great alternative to neuroimaging and cognitive biomarkers: they are inexpensive and have the potential to be easily implemented in cohort studies or used for screening dementia risk in OSA individuals. Moreover, they might help predict dementia several years before clinical manifestation. CSF Aβ and tau levels changes are observed about 25 and 15 years before AD onset respectively (Bateman *et al.*, 2012). Blood biomarkers such as hyperhomocysteinemia can predict all-cause dementia up to 35 years before clinical onset (Smith and Refsum, 2016).

However, fluid biomarkers have their own limitations, which should be considered when designing a cohort study or a clinical protocol. CSF collection is more invasive than blood collection and requires medical expertise, which may be more challenging in some

clinical settings, large cohort studies, and longitudinal studies with multiple testing. Thus, blood-based biomarkers are the easiest to perform, but they are limited by the BBB, which restricts the accessibility of neurodegeneration biomarkers to blood. Nevertheless, brain biomarkers can be cleared from the cerebral extracellular fluid into the blood by multiple normal and pathological mechanisms (Tarasoff-Conway *et al.*, 2015), giving partial access to neurodegenerative biomarkers through blood. Importantly, the BBB starts to break down relatively early in aging and with the progression of dementia (Takeda *et al.*, 2014). This phenomenon can also be observed in OSA (Lim and Pack, 2014). This suggests that the presence of OSA may allow detecting blood-based biomarkers of dementia even sooner because of the double insult on the BBB.

Another important limitation for blood biomarkers is their non-specificity: many organs other than the brain produce them. For example, Aβ peptides are not exclusive to the brain and can be produced by other peripheral cells such as platelets or muscle cells (Roher *et al.*, 2009). Another example is inflammation: many comorbid diseases occurring in the elderly are characterized by organ inflammation that may influence blood biomarkers (Henriksen *et al.*, 2014). The non-specificity of peripheral biomarkers is a limitation when we seek to measure cerebral rather than systemic processes. However, some argue that dementia is a systemic disease: processes in the neurodegenerative brain are also present in peripheral cells, such as Aβ production or systemic inflammation, and could also contribute to neurodegeneration (Bu *et al.*, 2017; Le Page *et al.*, 2017). Thus, understanding the potentially bidirectional relationship between peripheral and central pathophysiological mechanisms involved in dementia would clarify how and when blood biomarkers are the most useful in OSA research.

**Table 1.** Most promising fluid biomarkers of dementia investigated in OSA

| Biomarkers | Stages of neurodegeneration: Dementia (all-cause dementia, AD or VaD) | Stages of neurodegeneration: Early stages (MCI, pre-symptomatic or prodromal dementia) | OSA |
|---|---|---|---|
| **CSF** | | | |
| $A\beta_{42}$ | ↓ [1] | ↓ [2] | ↓ [3] |
| Tau proteins | ↑ [4] | ↑; unchanged [4] | unchanged [5] |
| **Blood** | | | |
| ***Proteomics – AD neuropathology*** | | | |
| $A\beta_{42}$ | mostly ↓ [6] | ↑; unchanged; ↓ [7] | ↑; unchanged [8] |
| $A\beta_{42/40}$ ratio | ↓ [6] | mostly ↓ [9] | - |
| Tau proteins | ↑ [6] | ↑ [10] | ↑ [11] |
| ***Proteomics – Inflammation*** | | | |
| Cytokines (IL-6, IL-1β, TNF-α) | mostly ↑ [12] | ↑; unchanged [13] | ↑ [14] |
| Acute-phase proteins (hsCRP, ACT) | mostly ↑ [15] | mostly ↑ [16] | ↑ [14] |
| ***Proteomics and metabolomics – Oxidative stress*** | | | |
| Homocysteine | ↑ [17] | ↑ [18] | ↑ [19] |
| Superoxide dismutase | mostly ↓ [20] | mostly ↓ [21] | ↓ [22] |
| Vitamin E | ↓ [23] | ↓ [21] | ↓ [22] |
| MDA/8-OHdg | mostly ↑ [21] | mostly ↑ [21] | ↑ [24] |
| ***Proteomics and metabolomics – Lipid metabolism*** | | | |
| Clusterin | ↑; unchanged [25] | ↑; unchanged; ↓ [26] | ↑ [27] |

AD, Alzheimer's disease; VaD, vascular dementia; MCI, mild cognitive impairment; OSA, obstructive sleep apnea; CSF, cerebrospinal fluid; Aβ, amyloid-beta; IL-6, interleukin-6; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; hsCRP, high-sensitivity c-reactive protein; ACT, α1-antichymotrypsin; MDA, malondialdehyde; 8-OHdg, 8-hydroxy-2-desoxyguanosine.

References:

[1] (Humpel and Hochstrasser, 2011; Blennow *et al.*, 2012; Llorens *et al.*, 2017);

[2] (Blennow *et al.*, 2012);

[3] (Ju *et al.*, 2016; Liguori *et al.*, 2017a; Liguori *et al.*, 2017b; Sharma *et al.*, 2017);

[4] (Humpel and Hochstrasser, 2011; Blennow *et al.*, 2012);

[5] (Ju *et al*., 2016; Liguori *et al*., 2017b);

[6] (Baird *et al.*, 2015);
[7] (Song *et al.*, 2011; Baird *et al.*, 2015);
[8] (Bu *et al.*, 2015; Kheirandish-Gozal *et al.*, 2016; Motamedi *et al.*, 2018);
[9] (Koyama *et al.*, 2012; Baird *et al.*, 2015);
[10] (Baird *et al.*, 2015; Mielke *et al.*, 2017);
[11] (Bu *et al.*, 2015; Motamedi *et al.*, 2018);
[12] (Schmitz *et al.*, 2015; Lai *et al.*, 2017);
[13] (Dziedzic, 2006; Brosseron *et al.*, 2014);
[14] (Nadeem *et al.*, 2013; Li *et al.*, 2017a);
[15] (Lai *et al.*, 2017);
[16] (Dziedzic, 2006);
[17] (Ho *et al.*, 2011; Smith and Refsum, 2016; Lai *et al.*, 2017);
[18] (Seshadri *et al.*, 2002; Smith and Refsum, 2016);
[19] (Niu *et al.*, 2014; Li *et al.*, 2017b);
[20] (Bennett *et al.*, 2009; Garcia-Blanco *et al.*, 2017);
[21] (Garcia-Blanco *et al.*, 2017);
[22] (Zhou *et al.*, 2016b);
[23] (Bennett *et al.*, 2009; Garcia-Blanco *et al.*, 2017);
[24] (He *et al.*, 2016; Zhou *et al.*, 2016b);
[25] (Song *et al.*, 2012; Koch and Jensen, 2016);
[26] (Song *et al.*, 2012; Jongbloed *et al.*, 2015; Koch and Jensen, 2016; Weinstein *et al.*, 2016);
[27] (Peng *et al.*, 2017).

***Summary of promising fluid biomarkers of dementia to investigated in OSA***

Establishing a panel of promising biomarkers linking OSA to dementia has the potential to significantly advance our understanding of the pathophysiological mechanisms involved in neurodegeneration. Moreover, studying large cohorts of older adults with OSA using those biomarkers could also help developing protocols to identify OSA individuals who are at risk of dementia. As reviewed here, there is an important overlap between fluid biomarkers observed in early stages of dementia and those found in OSA (see Table 1), suggesting common pathophysiological mechanisms such as AD neuropathology, inflammation, oxidative stress, and metabolic dysfunctions. Despite many of these biomarkers being shared in dementia and OSA, they were not yet investigated in OSA in relation with prodromal, pre-symptomatic and incident dementia. In addition to candidate biomarkers that

were selected based on the current literature, longitudinal discovery studies investigating hundreds of biomarkers are necessary to identify a specific panel of biomarkers and mechanisms between OSA and dementia.

Combining multiple biomarkers would be a promising approach in OSA-related dementia, since there is little overlap between studies for any single biomarker (Kiddle *et al.*, 2014). For example, the combination of CSF $A\beta_{42}$ and tau proteins are more reliable than any of them individually to identify prodromal AD (Blennow *et al.*, 2012). With the expectation that a biomarkers panel be identified and replicated, individuals at higher risk of incident dementia could be regularly screened with this panel of fluid biomarkers combined with the evaluation of their genetic susceptibility measured with a PS.

***Identifying OSA subjects at risk of dementia with the use of fluid biomarkers***

Because all OSA patients probably do not face the same risk of developing dementia, stratified analyses of OSA subjects as a function of incident dementia could help identify which characteristics and their associated biomarker profile best predict dementia. Factors that may modulate the association between OSA and biomarkers of dementia include demographic factors (age, sex, race), lifestyle (cognitive reserve, physical activity), OSA severity (mild, moderate and severe OSA, hypoxemia, sleep fragmentation, daytime sleepiness), genetic polymorphisms and comorbidities (obesity, cardiovascular risk factors and diseases, depression).

We also need to evaluate whether fluid biomarkers are associated with neuroimaging anomalies and neuropsychological deficits in OSA. This would help clarify how fluid biomarkers predict brain changes in term of its structure and function, and thus, further our understanding of underlying mechanisms. The temporal relationship between dementia biomarkers should also be validated within the OSA population to increase our ability to predict the progression to dementia. Aβ deposition occurs first, followed by tau dysfunction, brain atrophy, cognitive decline and finally, clinical presentation (Bateman *et al.*, 2012). This theoretical model was challenged by data-driven modelling using artificial intelligence where vascular dysregulation and inflammation changes significantly precede Aβ and tau alterations in subjects at risk of conversion to dementia (Iturria-Medina *et al.*, 2016). Moreover, assessing

whether neurodegenerative processes and OSA effects have an additive or interaction effect on fluid biomarkers would help predict cognitive decline and clinical progression.

***Effects of OSA treatment on fluid biomarkers levels***

One of the most important questions is whether an effective treatment for OSA positively impacts the levels of fluid biomarkers and slows or even prevents incident dementia. These results could become strong incentives for patients to comply with OSA treatment, and for clinical care professionals and public health policy makers to promote OSA treatment if other studies confirmed them. Indeed, CPAP may delay age of clinical manifestations (Osorio *et al.*, 2015). Moreover, a few studies reviewed here suggest that abnormal levels of some fluid biomarkers in OSA subjects are reversible with CPAP (Chen *et al.*, 2014; Liguori *et al.*, 2017a; Liguori *et al.*, 2017b). The incidence of dementia should be assessed in treated OSA subjects compared to those who refused treatment, and the effectiveness of the CPAP treatment could be documented with fluid biomarkers.

In patients with dementia, an effective CPAP treatment in those with OSA improved neuropsychological functions or slowed the rate of cognitive decline (Ancoli-Israel *et al.*, 2008; Troussiere *et al.*, 2014). These results suggest that treating OSA in demented patients is beneficial, possibly because the OSA-related mechanisms contributing to neurodegeneration are withdrawn. The treatment effect on fluid biomarker levels in demented OSA patients may explain how OSA contributes to clinical neurodegeneration, but also document short and long-term effects of OSA treatment on brain health. Moreover, combined evaluation of fluid biomarkers with a CPAP treatment could also be applied in subjects at earlier stages of neurodegeneration, including MCI subjects, *APOE4* carriers, or those with a high genetic susceptibility measured with a PS.

***Necessity of large cohort studies to investigate fluid biomarkers of dementia in OSA***

In order to establish a specific biomarker panel and underlying mechanisms in OSA that are associated with neurodegeneration, large longitudinal cohort studies are needed. A long follow-up period as well as a large sample size would allow sufficient dementia cases to emerge for a reliable assessment of the relationships. In addition, large sample sizes are necessary to stratify the population according to demographic characteristics and

comorbidities to establish a clinical portrait of OSA individuals at risk of developing dementia. In OSA treatment studies, long follow-up periods are also necessary to determine the optimal minimum treatment duration for an effect on fluid biomarkers levels and incident dementia. Because techniques for studying fluid biomarkers are fairly inexpensive, investigation of biomarkers in OSA in association with dementia could be implemented in various large cohort studies. Cohort studies on aging, dementia, and cardiovascular risk factors would necessary have a significant proportion of individuals presenting OSA given its high prevalence in these portion of the population. Moreover, international collaborations and networks may be an interesting solution in order to profit from large samples and produce clearer and stronger results.

**PRACTICE POINTS**

- Obstructive sleep apnea is increasingly recognized as a risk factor for dementia and is associated with potential mechanisms that might lead to neurodegeneration;
- There is a large overlap in biomarkers that were evaluated independently in dementia and in obstructive sleep apnea. For most of them, the nature and direction of the changes are strikingly similar;
- Amyloid-β, tau proteins, cytokines, acute-phase proteins, homocysteine, oxidative stress markers, and clusterin seem to be key candidate fluid biomarkers to predict and understand the development of neurodegeneration in patients with obstructive sleep apnea.

**PROPOSED RESEARCH AGENDA**

With large cohort studies and a network approach, the following questions should be investigated:

- Which specific fluid biomarkers panel is associated with incident dementia in individuals with obstructive sleep apnea?
- Which specific biomarker panel is more informative about the mechanisms underlying the link between obstructive sleep apnea and dementia?
- What demographic and biomarker pattern characterize the obstructive sleep apnea adults who are at higher risk of developing dementia?

- Does treatment with continuous positive airway pressure normalize fluid biomarkers levels in subjects with obstructive sleep apnea and, if so, protect or delay the incidence of dementia?

# Chapitre 3. Objectifs et hypothèses

## 3.1. Objectif et hypothèse générale

Puisque l'AOS est un facteur de risque de plus en plus reconnu de déclin cognitif et de démence, il est particulièrement important de comprendre son impact sur le fonctionnement et la structure du cerveau des personnes d'âges moyen et âgées, ce qui peut être fait par le biais de la neuroimagerie. Par contre, à l'exception d'études portant sur les hyperintensités de la matière blanche cérébrale, peu a été accompli dans une population âgée de plus de 55 ans en utilisant des techniques de neuroimagerie. Les changements de fonctionnement cérébral et de structure de la matière grise et blanche observés chez les personnes d'âge moyen avec de l'AOS doivent donc être confirmés dans une population plus âgée.

L'objectif général de cette thèse est d'évaluer l'association entre l'AOS chez des personnes âgées de plus de 55 ans et la santé cérébrale, c'est-à-dire le fonctionnement cérébral et la structure anatomique de la matière grise et blanche cérébrale, mesurée par le biais de la neuroimagerie. L'hypothèse générale de cette thèse est que l'AOS sera associée à des dysfonctions cérébrales et des changements neuroanatomiques pouvant s'apparenter aux changements rapportés dans les stades précliniques de la neurodégénérescence.

## 3.2. Objectifs spécifiques

### *3.2.1. Évaluer la santé cérébrale dans l'AOS par le biais de la neuroimagerie*

L'utilisation de différentes méthodes de neuroimagerie de façon combinée peut nous donner un meilleur portrait des changements cérébraux *in vivo*. Cette évaluation complète a le potentiel de mettre la lumière sur les processus mécanistiques qui sous-tendent l'association entre l'AOS et la santé cérébrale. En effet, en ce qui concerne la structure de la matière grise et blanche, le patron observé dans la littérature reste à clarifier : des augmentations et diminutions de matière grise ont été rapportées, tout comme des augmentations et diminutions de diffusivité des molécules d'eau dans la matière blanche.

Dans cette thèse, plusieurs techniques de neuroimagerie ont été utilisées dans l'objectif d'évaluer le cerveau dans son ensemble. Pour mesurer le fonctionnement cérébral au repos éveillé, la $^{99m}$Tc-HMPAO TEMP a été utilisée afin d'évaluer l'association entre l'activité

neuronale mesurée par le flot sanguin cérébral régional et l'AOS (Article 1 et Article 2). Pour évaluer la structure de la matière grise dans l'AOS, les méthodes de morphométrie basée sur le voxel, mesurant la densité et le volume de matière grise, de volumétrie et d'épaisseur corticale en IRM ont été employées (Article 3). Finalement, pour évaluer l'intégrité de la matière blanche dans l'AOS, les méthodes d'imagerie par tenseur de diffusion, les hyperintensités et la fraction de l'eau libre ont été utilisées (Article 4).

### *3.2.2. Évaluer l'association entre la sévérité de l'AOS et la santé cérébrale*

Les personnes avec de l'AOS légère ont, jusqu'à maintenant, été négligées dans la littérature portant sur les changements cérébraux. Puisque ce niveau de sévérité ne justifie pas toujours une recommandation de traitement en clinique, il est important de comprendre si l'AOS légère affecte le cerveau pour s'assurer que des personnes âgées à risque d'impacts néfastes soient traitées. En effet, une connaissance claire des effets néfastes de l'AOS sur la santé cérébrale peut devenir un incitatif à utiliser un traitement pour la population avec de l'AOS, les cliniciens et les décideurs de la santé publique.

Dans cette thèse, la relation entre la sévérité de l'AOS caractérisée par les groupes basés sur l'IAH (léger, modéré, sévère) et les changements cérébraux en neuroimagerie a été évaluée (Article 1, Article 2, Article 3 et Article 4). Toujours en relation avec la santé cérébrale, d'autres facteurs liés à la sévérité, le phénotype et la présentation clinique de l'AOS ont été évalués, soit l'hypoxémie, la fragmentation du sommeil et les perturbations respiratoires (Article 1 et Article 3); l'obésité (Article 1); l'AOS en sommeil paradoxal (Article 2); la cognition, l'humeur et la somnolence (Article 1, Article 2, Article 3 et Article 4).

# Chapitre 4. Méthodologie

## 4.1. Aperçu du protocole

Les participants de recherche inclus dans cette thèse proviennent du programme de recherche *Obstructive sleep apnea and mild cognitive impairment* subventionné par les Instituts de recherche en santé du Canada entre 2012 et 2017 dont Dre Nadia Gosselin est la chercheure principale. Ce grand projet longitudinal se poursuit dans la nouvelle Subvention Fondation des Instituts de recherche en santé du Canada de Dre Gosselin ayant débuté en 2017 (*Targeting sleep to optimize brain recovery and slow neurodegeneration*).

Le programme de recherche comportait trois temps de mesures et plusieurs volets. Au premier temps, les participants de recherche témoin, sans AOS, et les participants avec AOS nouvellement diagnostiquée et non traitée passaient par le processus de recrutement pour valider leur admissibilité aux critères d'inclusion et d'exclusion. Lors d'une première visite au laboratoire, tous les participants ont rempli des questionnaires, ont été enregistrés à l'aide d'une polysomnographie pour une nuit complète, et ont été évalués en neuropsychologie le matin suivant. De plus, des échantillons de sang ont été collectés le matin pour génotypage et pour des tests sanguins de routine. Lors d'une deuxième et troisième visite, les participants ont été évalués en neuroimagerie TEMP et IRM. Par contre, le volet neuroimagerie étant optionnel, ce n'est pas l'ensemble de la cohorte pour qui des enregistrements en TEMP et IRM ont été collectés. Certains participants ont participé à seulement une des deux méthodes d'imagerie. La thèse présentée ici porte sur les mesures obtenues au premier temps de mesure incluant les questionnaires, la polysomnographie, et la neuroimagerie des participants témoins et des personnes avec AOS non traitées. Entre le premier et le deuxième temps de mesure, les personnes avec AOS ont été vues en pneumologie et le traitement PPC leur a été proposé. Ils étaient libres de l'accepter ou le refuser tout en restant dans l'étude. Le deuxième et le troisième temps de mesures du programme de recherche incluaient les questionnaires, la neuropsychologie et la neuroimagerie.

Ayant débuté mes premiers stages de recherche en 2012 au début du programme de recherche longitudinal, ma contribution personnelle à la collecte des données du programme de recherche a touché toutes les mesures au premier temps incluant le recrutement, les

questionnaires, la polysomnographie, la neuropsychologie et la neuroimagerie. De plus, ma contribution se trouve également au niveau de l'analyse des données de neuroimagerie.

## 4.2. Population et recrutement

Les participants de recherche ont été recrutés par le biais de la liste d'attente de la clinique de pneumologie de l'Hôpital du Sacré-Cœur de Montréal ainsi que par des annonces dans les journaux de la région de Montréal. Le projet complet compte plus de 150 participants à ce jour, mais puisque le volet de neuroimagerie était optionnel, 114 participants ont participé à celui-ci et ont un enregistrement valide en TEMP, en IRM ou les deux. En effet, les conditions empêchant les participants d'être enregistrés en imagerie, telle la claustrophobie déjà connue ou la présence d'implants ferromagnétiques ou de stimulateur cardiaque étaient des causes d'exclusion pour la TEMP, l'IRM ou les deux. De plus, certaines images ont été exclues après la portion d'imagerie du projet. Certains problèmes apparaissent pendant l'enregistrement, tels des mouvements de la tête rendant les images illisibles, des artéfacts, des anomalies non expliquées ou encore l'abandon de l'enregistrement par le sujet pour une question d'inconfort ou de claustrophobie. Sur les 114 participants avec des images valides, 21 (18 %) ont été recrutés par le biais de la clinique de pneumologie tandis que les autres ont été recrutés par des annonces. Puisque certains participants n'ont pas été enregistrés avec une des deux méthodes de neuroimagerie, et puisque le recrutement s'est continué sur toute la période de mes études doctorales, les participants inclus dans les quatre études présentées dans cette thèse ne sont pas identiques. La proportion des participants qui se trouve dans plusieurs études est présentée dans la Figure 1.

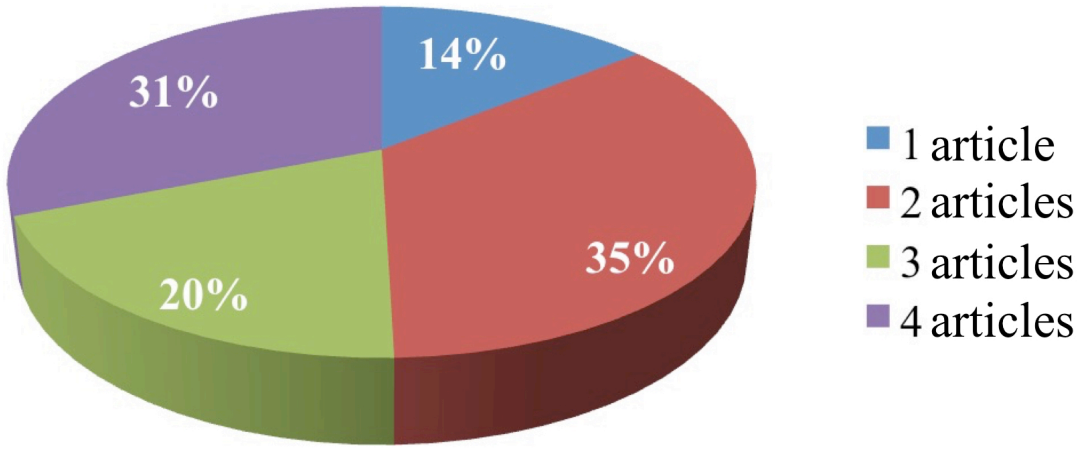


**Figure 1.** Proportion de l'échantillon complet (N=114) qui se retrouve dans les articles scientifiques.

Les personnes incluses dans l'étude devaient avoir entre 55 et 85 ans. Les critères d'exclusion pour l'étude étaient les suivants :

- Traitement pour l'AOS au premier temps de mesure;
- Indice de masse corporelle >40 kg/m$^2$;
- Prise de médication qui peut altérer le sommeil ou le fonctionnement cérébral (antidépresseurs, benzodiazépine, hypnotiques, anxiolytiques, etc.);
- Abus de drogues ou d'alcool;
- Maladie respiratoire (maladie pulmonaire obstructive chronique, asthme, emphysème);
- Maladie neurologique (traumatisme crânien, épilepsie, démence, AVC, encéphalopathie, etc.);
- Maladie psychiatrique (dépression diagnostiquée, troubles anxieux, troubles bipolaires, schizophrénie, etc.);
- Trouble du sommeil autre que l'AOS (trouble comportemental en sommeil paradoxal, insomnie diagnostiquée, syndrome des jambes sans repos, somnambulisme et autres parasomnies, narcolepsie et cataplexie, etc.).

# Chapitre 5. Articles scientifiques

## 5.1. **Article 1 :** Regional cerebral blood flow during wakeful rest in older subjects with mild to severe obstructive sleep apnea

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**Contribution de la candidate :** conception de l'étude, acquisition des données de sommeil et de neuroimagerie en laboratoire, analyses des données, interprétation des données, écriture et révision de l'article suite aux commentaires des co-auteurs, processus de soumission et de révision par les pairs auprès du journal scientifique.

**ABSTRACT**

*Objectives:* To evaluate changes in regional cerebral blood flow (rCBF) during wakeful rest in older subjects with mild to severe obstructive sleep apnea (OSA) and healthy controls, and to identify markers of OSA severity that predict altered rCBF.

*Design:* High-resolution $^{99m}$Tc-HMPAO SPECT images during wakeful rest.

*Setting:* Research sleep laboratory affiliated with a University hospital.

*Participants:* Fifty untreated OSA patients aged between 55 and 85 years divided into mild, moderate and severe OSA and 20 age-matched healthy controls.

*Interventions:* N/A

*Measurements:* Using statistical parametrical mapping, rCBF was compared between groups and correlated with clinical, respiratory and sleep variables.

*Results:* Whereas no rCBF change was observed in mild and moderate groups, participants with severe OSA had reduced rCBF compared to controls in the left parietal lobules, precentral gyrus, bilateral postcentral gyri, and right precuneus. Reduced rCBF in these regions and in areas of the bilateral frontal and left temporal cortex was associated with more hypopneas, snoring, hypoxemia, and sleepiness. Higher apnea, micro-arousal, and body mass indexes were correlated to increased rCBF in the basal ganglia, insula, and limbic system.

*Conclusions:* While older individuals with severe OSA had hypoperfusions in the sensorimotor and parietal areas, respiratory variables and subjective sleepiness were correlated with extended regions of hypoperfusion in the lateral cortex. Interestingly, OSA severity, sleep fragmentation and obesity correlated with increased perfusion in subcortical and medial cortical regions. Anomalies with such a distribution could result in cognitive deficits and reflect impaired vascular regulation, altered neuronal integrity, and/or undergoing neurodegenerative processes.

## INTRODUCTION

Obstructive sleep apnea (OSA) is a respiratory disorder characterized by repetitive pharyngeal collapses during sleep, causing snoring and transitory cessation (apneas) or reduction (hypopneas) of airflow amplitude, which result in intermittent hypoxemia (American Academy of Sleep Medicine Task Force, 1999; Malhotra and White, 2002). During these respiratory events, a profound increase in cerebral blood flow (CBF) is initially observed followed by an important decrease below resting values (Franklin, 2002). Respiratory events generally end with a cortical arousal, which causes sleep fragmentation and further hemodynamic changes through an elevation of sympathetic tone (Chouchou *et al.*, 2014). Hypoxemia and nocturnal CBF fluctuations lead to cerebral hypoxia (Valipour *et al.*, 2002) and neuronal, glial, and endothelial damage (Aviles-Reyes *et al.*, 2010; Lim and Veasey, 2010; Yun *et al.*, 2010). Thus, altered cerebral perfusion, changes in vascular function, sleep fragmentation, and cellular damage may explain why OSA has been linked to excessive daytime sleepiness (American Academy of Sleep Medicine Task Force, 1999), cognitive deficits (Gagnon *et al.*, 2014), and increases risks of cerebrovascular diseases (Lanfranchi and Somers, 2001; Yaggi *et al.*, 2005; Cho *et al.*, 2013).

So far, few neuroimaging studies have been performed in subjects with OSA during wakeful rest to estimate the impact of nocturnal respiratory events on brain function. Among them, studies using transcranial Doppler have shown that OSA individuals have impaired vascular regulation during wakefulness (Placidi *et al.*, 1998; Franklin, 2002; Urbano *et al.*, 2008; Nasr *et al.*, 2009). Studies using magnetic resonance imaging (MRI) and emission tomography techniques have shown that OSA affects brain regions differently. In fact, one study using arterial spin labeling showed reduced regional CBF (rCBF) in several white matter tracts involved in the coordination of respiratory musculature, autonomic regulation and cognition (Yadav *et al.*, 2013). Furthermore, using single photon emission computed tomography or positron emission tomography (PET) combined to a statistical parametrical mapping (SPM) approach, four studies investigated cortical rCBF or glucose metabolism in untreated OSA individuals. All combined, these studies observed hypoperfusion or hypometabolism in the prefrontal cortex, the sensorimotor areas, the limbic system, the parietal lobes, the superior temporal cortex, and the anterior occipital cortex (Joo *et al.*, 2007; Yaouhi *et al.*, 2009; Ju *et al.*, 2012; Shiota *et al.*, 2014).

Nevertheless interesting, these studies show great inconsistencies regarding the cerebral regions affected in OSA, possibly due to methodological variability including the use of different apnea-hypopnea index (AHI) thresholds for OSA diagnosis (varied between 10 to 30 events/hours), different cardiovascular exclusion criteria, sample sizes (≤ 30 subjects in three of the four published SPECT and PET studies), and different statistical thresholds for neuroimaging results. In addition, most neuroimaging studies have focussed on middle-aged adults with severe OSA and therefore, older patients, especially those with mild or moderate OSA, are generally not investigated. Considering that the prevalence of OSA increases from 2-14 % in the middle-aged adult population to 32-42 % in individuals over 60 years of age (Young *et al.*, 2002), studying the impact of OSA in this age group is of utmost importance. In addition to presenting reduction in total CBF (Leenders *et al.*, 1990), findings from an animal study suggest that older individuals could be more vulnerable to intermittent hypoxia (Gozal *et al.*, 2003), which may lead to a more severe impact of OSA on brain function. Accordingly, brain perfusion changes during wakeful rest could be observed not only in severe OSA, but also in milder forms of OSA.

The present study aimed at evaluating rCBF as a measure of brain function during wakeful rest using Technetium-99m Hexa-methyl-amino-propylenamine-oxime ($^{99m}$Tc-HMPAO) high-resolution SPECT in newly diagnosed and untreated mild, moderate and severe OSA patients aged from 55 to 85 years and to compare them to controls without OSA. The novelty of the present study lies in the fact that a large sample was investigated to verify whether the pattern of reduced regional brain perfusion previously described in middle-aged OSA individuals would be observed in older subjects. This large sample size allowed us to divide our groups according to severity, which has not been done in previous studies. Another strength and novelty of this study was the high-resolution NeuroFOCUS SPECT scanner used, which provides 2.5 mm spatial resolution contrary to standard SPECT scanner (spatial resolution of 6-15 mm), enabling perfusion measurement in smaller regions. We hypothesized that OSA of mild or moderate severity in older subjects would be associated with reduced perfusion in cortical regions previously reported as abnormal in middle-aged OSA patients. More specifically, these hypoperfusions could be observed concomitantly in regions sensitive to hypoxemia (prefrontal cortex and hippocampus) (Beebe and Gozal, 2002; Fung *et al.*, 2007) and in regions showing relative hypoperfusion in normal aging (limbic system and association

cortex, especially frontal lobes) (Tumeh *et al.*, 2007). Another novelty of the present study is that we assessed the relationship between rCBF and several markers of OSA severity. We hypothesized that more severe levels of OSA (more respiratory events, lower oxygen saturation, and a more fragmented sleep), daytime sleepiness, and the presence of cardiovascular comorbidities as well as obesity would predict abnormal rCBF.

## METHODS

### *Sample*

Seventy subjects aged between 55 and 85 years (mean age: 64.5 ± 6.7; 15 females) were recruited from the pulmonary department of the *Hôpital du Sacré-Coeur de Montréal* and by ads in local newspapers. Participants with one or more of the following conditions were excluded: 1) central nervous system disorders (e.g. dementia, neurological diseases, traumatic brain injury, epilepsy); 2) uncontrolled diabetes or hypertension; 3) treatment with continuous positive airway pressure or other types of treatment such as a mandibular advancement device; 4) a body mass index (BMI) > 40 $kg/m^2$; 5) use of medication, drugs, or natural products known to influence cognition, cerebral functioning, sleep, and/or affect; and 6) a history of stroke (patients with a history of transient ischemic attacks were not excluded), sleep disorders other than OSA, or any major psychiatric disorders or pulmonary diseases. Written consent was obtained from each participant and the research protocol was approved by the ethics committee of the Hôpital du Sacré-Coeur de Montréal.

### *Questionnaires*

Beck Depression Inventory-II and Beck Anxiety Inventory were used to document depression and anxiety symptoms (Beck *et al.*, 1988; Beck *et al.*, 1996). All participants were assessed for subjective daytime sleepiness using the Epworth Sleepiness Scale (Johns, 1991). Vascular risks factors and comorbidities were assessed using the Vascular Burden Index developed and validated by Villeneuve et al. (Villeneuve *et al.*, 2009; Villeneuve *et al.*, 2011). This questionnaire screen for the presence of hypertension, hypotension, hypercholesterolemia/ dyslipidemia, coronary disease (angina pectoris, myocardial infarction, coronary artery bypass), transitory ischemic attacks, diabetes, arrhythmias, and carotid

stenosis, with a maximum total score of 8 points. Presence of these risk factors was based on previous medical observations.

***Polysomnography recording***

All participants underwent a polysomnography recording that used measurements from thoraco-abdominal strain gauges, an oronasal canula, and a transcutaneous finger pulse oximeter to measure oxygen saturation. Electroencephalographic sleep recordings were performed using an 18 electroencephalogram channel montage accompanied by an electrooculogram, electromyograms on the chin and legs, and electrocardiogram. An apneic episode was defined as a total cessation of airflow lasting 10 s or more. A hypopneic episode was defined as a reduction in airflow of at least 30 % from baseline lasting 10 s or more and accompanied by an oxygen desaturation of at least 3 % or accompanied with an episode of arousal (Berry *et al.*, 2012). The sum of apnea and hypopnea episodes divided by the number of hours of sleep provides the AHI. Sleep was recorded and scored by an experienced electrophysiology technician according to standard methods (Iber *et al.*, 2007). For comparison purposes, based on published criteria (American Academy of Sleep Medicine Task Force, 1999), participants were categorized in three groups consisting of mild (AHI >5 and ≤15), moderate (AHI >15 and ≤30) and severe OSA (>30). Participants with an AHI ≤5 were considered as controls. Polysomnographic results are shown in Table 1 for all groups.

***$^{99m}$Tc-HMPAO SPECT image acquisition***

All participants underwent a daytime $^{99m}$Tc-HMPAO SPECT study during wakeful rest with a high-resolution brain-dedicated scanner (*NeuroFOCUS, NeuroPhysics, Shirley, MA, USA*) providing a 2.5 mm full-width half-maximum (FWHM) spatial resolution. This resolution allows accurate evaluation of perfusion distribution in much smaller brain regions than with conventional 2- or 3-headed gamma camera-based SPECT scanners. A dose of 750 MBq of $^{99m}$Tc-HMPAO prepared in the morning of the testing was administered followed by a saline flush of 30 cc while the subject lied awake on a stretcher with their eyes closed. A static, 30-min acquisition was performed 20 minutes later. Thirty-two slices were reconstructed on a 128 x 128 matrix using a filtered back projection and an attenuation correction was performed using Chang's method with a coefficient of 0.01 $cm^{-1}$.

Reconstructed voxel size was 1.56 mm. This SPECT system does not allow for recording of the whole cerebellum in most subjects, and the cerebellar region was excluded from analysis. SPECT acquisitions were performed between 10:15 and 15:00 hours and were on average obtained 25.2 ± 23.1 days after the polysomnographic recording.

***Image analysis***

All SPECT images were evaluated visually for abnormalities. Using SPM8 (*Statistical Parametric mapping 8, Wellcome Department of Imaging Neurosciences, Institute of Neurology, University College London, UK*) with MatLab (*version 7.3, The MathWorks, Natick, MA, USA*), individual SPECT studies were registered and spatially normalized to the standard SPECT template included in the SPM8 software. Then, normalized images were smoothed using a 14-mm FWHM Gaussian filter. A proportional scaling normalization was used during analyses between images for their individual global mean signal. Thus, final regional results are relative to the mean global signal of CBF. Voxel size of the final images was 2.0 x 2.0 x 2.0 mm.

***Statistical analysis***

Descriptive statistics were performed for all study variables with STATISTICA 10.0 *(Statsoft Inc., Tulsa, USA)*. Chi-square and *t*-tests were used with a statistical significance of $p<0.05$ to compare controls to OSA subjects in relation to their demographic, clinical, and polysomnographic variables. For the first research objective, group differences in rCBF distribution were assessed using SPM8 (two-sample *t*-tests between healthy controls and each OSA group), corrected for multiple comparisons using false discovery rate (FDR) (Genovese *et al.*, 2002) at $p<0.05$ with an extent threshold of 50 contiguous significant voxels across all grey matter, as previously described in Joo and al. (Joo *et al.*, 2007). In order to compare our results with other published imaging studies performed in subjects with OSA (Yaouhi *et al.*, 2009; Ju *et al.*, 2012), a less stringent significance level with a height threshold of $p<0.001$ uncorrected was also used. However, we then increased the extent requirement to 200 contiguous significant voxels in order to reduce the false positive rate. For the second objective, rCBF was correlated with all participants' respiratory events (AHI, apnea index, hypopnea index), oxygen saturation (minimum, mean, total sleep time spent under 90 %),

proportion of sleep time spent snoring, sleep efficiency, micro-arousal index, Epworth Sleepiness Score, BMI and vascular burden index. All correlations (multiple regression design) were done with age as a nuisance covariant and the same two statistical threshold mentioned before were used. The creation of a grey matter mask and the identification of significant regions (ICBM atlas) were performed with the software PickAtlas (*version 3.0, ANSIR Laboratory, Wake Forest University School of Medicine, NC, USA*). Resulting regions were superimposed on the SPECT template available in the SPM8 package. Figures were realized with the MRIcron software (*Analyze viewer, Chris Rorden, PhD, Neuropsychology Lab, Columbia, SC, USA*).

## *RESULTS*

### *Demographic, clinical and polysomnographic variables across groups*

Twenty-three subjects had mild OSA, 14 subjects had moderate OSA, and 13 subjects had severe OSA – for a total of 50 OSA subjects who were compared to 20 controls (see Table 1 for group's demographic, clinical and polysomnographic characteristics and statistics). No differences in age, levels of subjective daytime sleepiness, depression, anxiety, vascular burden and sleep efficiency were found between groups.

### *Group difference for rCBF*

Compared to controls, participants of the severe OSA group had decreased rCBF within a large cluster of voxels of the left hemisphere that includes the precentral and postcentral gyri and the superior and inferior parietal lobules ($p<0.05$ corrected with FDR, see Table 2 and Figure 1). Additional regions of hypoperfusion were found in severe OSA patients compared to controls using uncorrected threshold of $p<0.001$, namely the right postcentral gyrus and the right precuneus. Mild and moderate OSA groups showed no significant differences in rCBF with either statistical threshold when compared to controls. No regions of increased rCBF were found in OSA groups in comparison to healthy controls.

**Table 1.** Demographic, clinical, and polysomnographic variables for control subjects and OSA groups

| Variables | Control (A) | Mild OSA (B) | Moderate OSA (C) | Severe OSA (D) | p | | |
|---|---|---|---|---|---|---|---|
| | n = 20 | n = 23 | n = 14 | n = 13 | AvsB | AvsC | AvsD |
| Gender | 8F; 12M | 5F; 18M | 1F; 13M | 1F; 12M | ns | <0.05 | <0.05 |
| Age (years) | 64.1 (7.1) | 64.5 (7.0) | 63.9 (4.8) | 65.8 (8.0) | ns | ns | ns |
| BMI ($kg/m^2$) | 25.6 (3.3) | 27.3 (3.3) | 28.1 (3.3) | 27.6 (2.5) | ns | <0.05 | ns |
| Epworth Sleepiness Scale score | 9.0 (5.9) | 7.0 (4.2) | 11.5 (4.6) | 9.2 (7.1) | ns | ns | ns |
| Beck Depression Inventory score | 5.9 (5.2) | 6.7 (6.0) | 8.7 (5.2) | 6.8 (5.4) | ns | ns | ns |
| Beck Anxiety Inventory score | 4.8 (4.8) | 3.7 (4.2) | 6.0 (6.4) | 5.0 (4.5) | ns | ns | ns |
| Vascular burden index | 0.9 (1.0) | 1.5 (1.3) | 1.1 (1.0) | 1.6 (1.6) | ns | ns | ns |
| Subjects with a vascular burden >2/8 ( %) | 20 | 52 | 43 | 39 | ns | ns | ns |
| ***Polysomnographic variables*** | | | | | | | |
| AHI (events/h) | 2.8 (2.0) | 10.1 (2.7) | 23.0 (4.3) | 40.9 (11.1) | <0.001 | <0.001 | <0.001 |
| Apnea Index (events/h) | 0.7 (1.1) | 3.3 (3.0) | 10.7 (6.0) | 26.9 (11.7) | <0.001 | <0.001 | <0.001 |
| Hyponea Index (events/h) | 2.1 (1.7) | 6.8 (2.8) | 12.3 (5.6) | 14.1 (5.9) | <0.001 | <0.001 | <0.001 |
| Minimal SpO2 ( %) | 89.5 (2.9) | 87.8 (5.3) | 82.4 (6.0) | 82.0 (5.5) | ns | <0.001 | <0.001 |
| Mean SpO2 ( %) | 94.9 (0.9) | 95.4 (1.2) | 94.2 (0.8) | 94.5 (0.6) | ns | <0.05 | ns |
| TST with SpO2<90 % (min) | 0.5 (1.0) | 1.0 (1.5) | 6.5 (5.7) | 15.4 (19.1) | ns | <0.001 | <0.001 |
| Snoring ( % of TST) | 8.6 (14.5) | 14.5 (15.5) | 34.4 (24.4) | 15.5 (12.9) | ns | <0.001 | ns |
| Micro-arousal index (number/h) | 11.4 (3.7) | 11.9 (4.6) | 15.8 (7.5) | 21.6 (6.9) | ns | <0.05 | <0.001 |
| Sleep efficiency ( %) | 78.9 (12.4) | 77.5 (13.1) | 78.6 (12.7) | 76.1 (11.3) | ns | ns | ns |

Results are presented as mean (standard deviation). OSA, obstructive sleep apnea; F, females; M, males; ns, non significant; BMI, body mass index; AHI, apnea-hypopnea index; SpO2, oxygen saturation; TST, total sleep time.

**Table 2.** Hypoperfused regions in severe OSA compared to control subjects

| Cluster size (*k*) | Location | *p* | Side | BA | Peak t-values | MNI coordinates | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | x | y | z |
| 729 | Postcentral gyrus | 0.05 corrected | L | 2 | 4.54 | -55 | -28 | 54 |
| | Superior parietal lobule | | L | 7 | 4.20 | -30 | -60 | 67 |
| | Precentral gyrus | | L | 4,6 | 4.19 | -41 | -16 | 68 |
| | Inferior parietal lobule (angular gyrus) | | L | 40 | 4.07 | -58 | -50 | 46 |
| 244 | Postcentral gyrus | 0.001 uncorrected | R | 2 | 5.54 | 14 | -50 | 78 |
| 274 | Precuneus | 0.001 uncorrected | R | 7 | 4.67 | 7 | -78 | 52 |
| 236 | Inferior parietal lobule (supramarginal gyrus) | 0.001 uncorrected | L | 40 | 3.77 | -67 | -32 | 32 |
| | Postcentral gyrus | | L | 3 | 3.63 | -68 | -16 | 29 |

MNI, Montreal Neurological Institute; BA, Brodmann area; L, left; R, right.

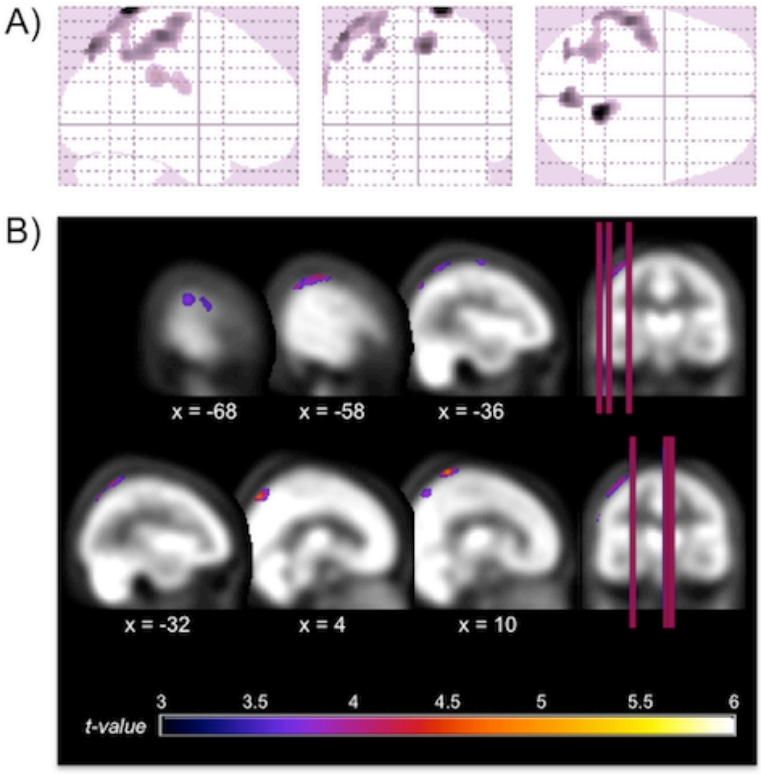


**Figure 1.** Location of the significant reductions in regional cerebral blood flow (rCBF) in severe obstructive sleep apnea (OSA) subjects compared with controls.

A) Glass view of the significant clusters and B) overlays of significant regions on the SPECT template. Hypoperfusions were found in the left superior and inferior parietal lobules, the left precentral gyrus, bilateral postcentral gyri and right precuneus gyrus. Left side of images represents the left hemisphere of the brain.

***Correlation analyses between rCBF and OSA-related variables***

In the correlational analysis including all subjects with or without OSA, several hypoperfusion foci were associated with increased disease severity (See Table 3 and Figure 2). Among the significant correlations observed, we found that higher AHI and higher hypopnea index were associated with hypoperfusions in the lateral portions of the left frontal (inferior and middle frontal gyri), sensorimotor (precentral and postcentral gyri), temporal (middle temporal gyrus) and parietal lobes (inferior parietal lobule) in addition to the right precuneus. A higher proportion of sleep spent snoring was associated with hypoperfusions in the left anterior parahippocampal gyrus, the anterior pole of the temporal lobe, as well as the inferior frontal gyrus. Hypoxemia, and more specifically the time spent with oxygen saturation below 90 %, was correlated with reduced rCBF in the left dorsolateral prefrontal cortex, while subjective sleepiness measured by the Epworth Sleepiness Scale was associated with hypoperfused bilateral dorsomedial prefrontal cortex.

OSA severity (higher AHI, apnea index and micro-arousal index) was also associated with hyperperfusions. Contrary to hypoperfusions (mostly in the lateral portion of the frontal, temporal and parietal cortex), hyperperfusions were all observed in the subcortical or medial cortical regions, including the caudate nucleus, the putamen, the amygdala, the hippocampus, the insula and the parahippocampal gyrus (see Table 4 and Figure 3), mostly in the right hemisphere. No correlation was found between rCBF and sleep efficiency.

For cardiovascular comorbidities, no correlation was found between rCBF and the vascular burden index with either statistical threshold. However, higher BMI representing obesity was associated with both modest hypoperfusion in the postcentral gyrus and hyperperfusions in the hippocampi and the left parahippocampal gyrus extending to the globus pallidus (See Table 3 and 4, Figure 2 and 3).

**Table 3.** Location of hypoperfused regions associated with OSA-related variables.

| Cluster size (*k*) | Location | *p* | Side | BA | Peak t-values | MNI coordinates | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | x | y | z |
| ***Apnea-Hypopnea Index*** | | | | | | | | |
| 848 | Postcentral gyrus | 0.05 corrected | L | 3 | 4.41 | -58 | -38 | 50 |
| | Precentral gyrus | | L | 6 | 3.64 | -64 | -16 | 44 |
| | Inferior parietal lobule (angular gyrus) | | L | 40 | 3.56 | -56 | -42 | 52 |
| 288 | Precuneus | 0.001 uncorrected | R | 7 | 4.85 | 7 | -78 | 52 |
| 212 | Inferior frontal gyrus | 0.001 uncorrected | L | 47 | 4.62 | -54 | 30 | 0 |
| ***Hypopnea Index*** | | | | | | | | |
| 683 | Inferior parietal lobule (supramarginal gyrus) | 0.05 corrected | L | 40 | 4.44 | -70 | -28 | 26 |
| | Middle temporal gyrus | | L | 21 | 3.86 | -67 | -6 | -6 |
| | Postcentral gyrus | | L | 40 | 3.69 | -58 | -28 | 54 |
| 389 | Inferior frontal gyrus | 0.001 uncorrected | L | 47 | 4.31 | -56 | 28 | -2 |
| 340 | Middle frontal gyrus | 0.001 uncorrected | L | 6 | 4.09 | -58 | 6 | 46 |
| ***Proportion of time spent snoring ( %)*** | | | | | | | | |
| 2442 | Parahippocampal gyrus | 0.05 corrected | L | 34 | 4.86 | -14 | -4 | -26 |
| | Medial temporal pole | | L | 38 | 4.83 | -34 | 16 | -32 |
| | Lateral temporal pole | | L | 38 | 4.22 | -54 | 14 | -26 |
| | Inferior frontal gyrus | | L | 45 | 3.61 | -56 | 34 | 4 |
| ***Time spent with oxygen saturation <90 %*** | | | | | | | | |
| 297 | Superior frontal gyrus | 0.001 uncorrected | L | 8 | 4.82 | -16 | 28 | 54 |
| 219 | Middle frontal gyrus | 0.001 uncorrected | L | 9 | 4.41 | -48 | 28 | 36 |
| ***Epworth Sleepiness Scale*** | | | | | | | | |
| 580 | Superior medial frontal gyrus | 0.05 corrected | L | 9 | 4.25 | -8 | 48 | 40 |
| | Superior medial frontal gyrus | | L | 8 | 3.85 | -6 | 34 | 44 |
| | Superior medial frontal gyrus | | R | 8 | 3.76 | 4 | 20 | 50 |
| ***Body mass index*** | | | | | | | | |
| 218 | Postcentral gyrus | 0.001 uncorrected | R | 2 | 4.44 | 64 | -18 | 28 |

MNI, Montreal Neurological Institute; BA, Brodmann area; L, left; R, right.

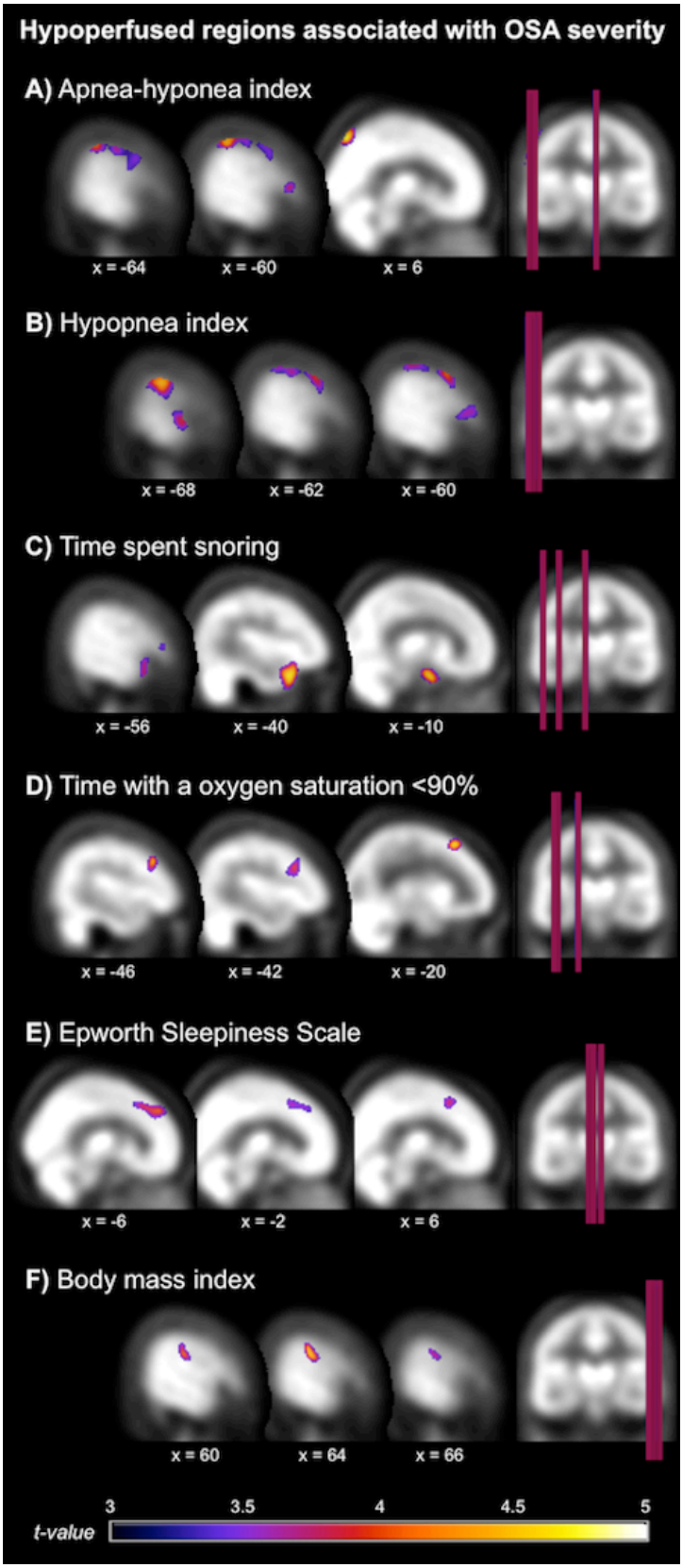


**Figure 2.** Location of hypoperfusions that correlated with variables representing more severe obstructive sleep apnea (OSA). Regions showing hypoperfusions were as follow: A) and B) left inferior and middle frontal, precentral, postcentral, and middle temporal gyri, inferior parietal lobule, and right precuneus; C) left parahippocampal, anterior temporal pole, and inferior frontal gyri; D) left dorsolateral prefrontal cortex; E) bilateral dorsomedial prefrontal cortex; F) right postcentral gyrus. Results are overlays on the SPECT template and left side of images represent the left hemisphere of the brain.

**Table 4.** Location of hyperperfused regions associated with OSA-related variables

| Cluster size (*k*) | Location | *p* | Side | Peak t-values | MNI coordinates | | |
|---|---|---|---|---|---|---|---|
| | | | | | x | y | z |
| ***Apnea-Hypopnea Index*** | | | | | | | |
| 470 | Amygdala, Hippocampus | 0.001 uncorrected | R | 4.45 | 30 | -6 | -16 |
| | Caudate nucleus, Putamen | | R | 3.83 | 10 | 10 | -4 |
| ***Apnea Index*** | | | | | | | |
| 501 | Amygdala, Hippocampus | 0.05 corrected | R | 4.53 | 30 | -6 | -16 |
| | Caudate nucleus, Putamen | | R | 3.88 | 10 | 8 | -2 |
| ***Micro-arousal index*** | | | | | | | |
| 585 | Parahippocampal gyrus | 0.05 corrected | R | 4.38 | 26 | 2 | -14 |
| | Insula | | R | 3.73 | 32 | 18 | -6 |
| 249 | Putamen | 0.001 uncorrected | L | 3.99 | -28 | 2 | -6 |
| ***Body mass index*** | | | | | | | |
| 397 | Hippocampus | 0.001 uncorrected | L | 3.82 | -26 | -20 | -12 |
| | Parahippocampal gyrus | | L | 3.61 | -18 | -25 | -16 |
| | Globus pallidus (lentiform nucleus) | | L | 3.46 | -18 | -9 | 5 |
| 208 | Hippocampus | 0.001 uncorrected | R | 3.82 | 32 | -14 | -16 |

MNI, Montreal Neurological Institute; L, left; R, right

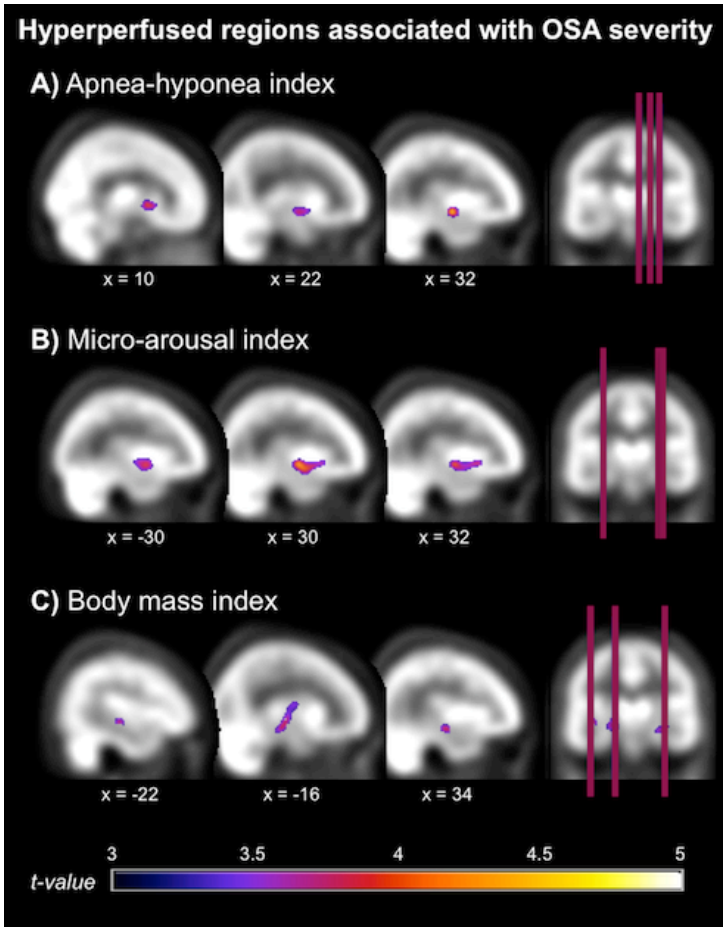


**Figure 3.** Locations of hyperperfusions that correlated with variables representing more severe obstructive sleep apnea (OSA).

Regions showing hyperperfusions were as follow: A) right basal ganglia, amygdala, and hippocampus; B) right parahippocampal gyrus, insular cortex, and left putamen; C) bilateral hippocampi, left parahippocampal gyrus, and globus pallidus. Results are overlays on the SPECT template and left side of images represent the left hemisphere of the brain.

## DISCUSSION

In the present study, we investigated rCBF using a high-resolution SPECT scanner in a large sample of older subjects with mild, moderate and severe OSA during wakeful rest in order to evaluate brain function impairment in this population. Group comparisons showed that only severe OSA subjects had reduced rCBF in sensorimotor areas and parietal lobes, especially on the left side of the brain. Additionally, correlational analyses showed that higher levels of respiratory disturbances during sleep, greater daytime sleepiness, and obesity were

associated to lateral cortical hypoperfusion of the parietal, temporal and frontal lobes. On the other hand, more respiratory events, fragmented sleep, and obesity were associated with hyperperfusion of subcortical and medial cortical structures, namely the basal ganglia, the limbic system, and the insula.

***Reduced rCBF in older subjects with severe OSA***

The parietal hypoperfusion found in the present study could be a particularity of older OSA subjects. A recent SPECT study performed in 15 middle-aged subjects with severe OSA showed reduced rCBF only in the prefrontal areas (Shiota *et al.*, 2014). Another SPECT study investigating a relatively large sample of middle-aged men (27 controls and 27 severe OSA) found reduced rCBF in the parahippocampal and lingual gyri, but not in the parietal cortex (Joo *et al.*, 2007). Even though SPECT studies in middle-aged OSA subjects failed to observed parietal hypoperfusion, two studies using PET in older middle-aged OSA subjects (54.8 ± 5.7 and 49.8 ± 7.0 years old respectively) reported reduced glucose metabolism in the parietal cortex (Yaouhi *et al.*, 2009; Ju *et al.*, 2012). This either suggests that PET is more sensitive than SPECT in detecting parietal anomalies in middle-aged subjects or that changes in the parietal cortex tend to occur after the age of 50. Parietal hypoperfusion is a well-documented marker of early Alzheimer's disease (Masterman *et al.*, 1997; Farid *et al.*, 2010; Alexopoulos *et al.*, 2012; Jacobs *et al.*, 2012), especially on the left side (Warkentin *et al.*, 2004). Considering that OSA has been identified as a risk factor for mild cognitive impairment and dementia (Yaffe *et al.*, 2011; Chang *et al.*, 2013; Pan and Kastin, 2014), a proportion of our severe OSA subjects may have underlying neurodegenerative processes. Indeed, hypoxia increases both the accumulation of amyloid-β and tau phosphorylation (Daulatzai, 2013), which are pathological markers of Alzheimer's disease. Additional longitudinal cohort studies of OSA patients are definitely needed to understand how OSA contributes to abnormal cognitive decline in older subjects and whether parietal hypoperfusion is an early marker of subsequent dementia in OSA.

Other mechanisms combined or not with the hypothetical neurodegenerative process may explain the regional cerebral hypoperfusion observed in older OSA individuals, namely a vascular dysfunction and/or a neuronal injury. First, during respiratory events, intermittent hypoxemia in combination with fast fluctuations in CBF and variations in blood pressure can

lead to oxidative stress, inflammation, endothelial dysfunction, and atherosclerosis (Khayat *et al.*, 2009; Yun *et al.*, 2010; Daulatzai, 2013). Then, endothelial dysfunction and atherosclerosis directly reduce the diameter of blood vessels in addition to affect vasoreactivity, leading to hypoperfusion even during wakefulness (de la Torre, 2012; Daulatzai, 2013). Concordant with this hypothesis, several studies have shown that OSA severity is associated with impaired cerebrovascular reactivity during wakefulness (Placidi *et al.*, 1998; Urbano *et al.*, 2008; Nasr *et al.*, 2009; Reichmuth *et al.*, 2009; Prilipko *et al.*, 2014). More specifically, subjects with OSA have reduced cerebrovascular autoregulation at rest, during hypoxia and hypercapnia, and during orthostatic hypotension.

The second mechanism that could be responsible for decreased rCBF in OSA is neuronal injuries occurring as a consequence of nocturnal hypoxia, fluctuations in blood pressure and perfusion during respiratory events. Other processes secondary to respiratory events, including endothelial dysfunction, proteasomal activity, reactive gliosis, inflammation, reduced dendritic branching, impaired neurotransmitters production, and oxidative stress may also lead to neuronal function impairment and/or death (Gozal *et al.*, 2003; Xu *et al.*, 2004; Veasey, 2009; Aviles-Reyes *et al.*, 2010; Yun *et al.*, 2010). Since regional brain perfusion is closely correlated with local neuronal activity (Paemeleire, 2002), altered neuronal function following injuries or even loss could lead to hypoperfusion. Accordingly, several regions showing hypoperfusions in the present study were reported to have altered resting-state connectivity (Santarnecchi *et al.*, 2013; Zhang *et al.*, 2013; Peng *et al.*, 2014a) as well as cortical thinning or reduced grey matter density in middle-aged OSA individuals (Macey *et al.*, 2002; Yaouhi *et al.*, 2009; Canessa *et al.*, 2011; Joo *et al.*, 2013).

Although mechanisms underlying the vulnerability of some brain regions to vascular dysfunction or neuronal loss in the context of OSA are not fully understood, some characteristics of these regions may explain their susceptibility. In fact, during hypoxia, cortical associative regions, which are phylogenically newer, are less protected in comparison to subcortical structures (Binks *et al.*, 2008). Moreover, a study with severe OSA subjects using SPECT during sleep found reduced left parietal rCBF (Ficker *et al.*, 1997), which suggests an increased risk of vascular and neuronal impairment leading to daytime hypoperfusion. Finally, the inferior parietal lobe and the precuneus are part of the default mode network (Buckner *et al.*, 2008), as well as several regions found as impaired in

association with OSA severity markers in our correlation analysis. It has been hypothesized that the default mode network could be particularly vulnerable to various injuries occurring in aging and in Alzheimer's disease (Fjell *et al.*, 2015) and this network has been shown to be impaired in previous functional MRI studies in OSA (Sweet *et al.*, 2010; Prilipko *et al.*, 2011; Prilipko *et al.*, 2012; Zhang *et al.*, 2013).

***Normal rCBF in mild and moderate OSA***

Based on previous empirical evidence from an animal model of OSA in aging rats (Gozal *et al.*, 2003) and on the reduction of global CBF with age (Leenders *et al.*, 1990), we expected that older subjects with mild and moderate OSA would show regional hypoperfusions, but our results did not confirm this hypothesis. The absence of brain anomalies among older subjects with mild OSA corroborates previous results in middle-aged patients, where a higher level of OSA severity was necessary to observe neuroimaging findings, namely silent lacunar infarctions and periventricular hyperintensities (Nishibayashi *et al.*, 2008), as well as altered metabolite concentrations representing reduced neuronal integrity (Kamba *et al.*, 1997; Alkan *et al.*, 2013). Our results are also consistent with those found in neuropsychological studies of middle-aged and elderly subjects, which showed that cognitive deficits are more likely to be observed in individuals with moderate and severe OSA than in those with mild OSA or in healthy controls (Sforza *et al.*, 2010; Chen *et al.*, 2011a). These studies, combined with our results, suggest that a certain level of OSA severity, as measured with the AHI, is necessary to observe changes in brain function and metabolism, independently of age.

***Hypoperfusion and markers of OSA severity***

We found that OSA-related variables including hypopneas, proportion of time spent snoring, hypoxemia and subjective sleepiness were also associated with hypoperfusions in lateral portions of the parietal, temporal and frontal lobes, especially in the left hemisphere. While hypopnea episodes were associated with reduced perfusion, apneas were not. Since apneas and hypopneas are characterized by different levels of hypoxemia, arousals and heart rate increases (Ayappa *et al.*, 2005), further studies will be needed to understand the differential effect of cessations (apneas) and reductions (hypopneas) of airflow amplitude on

brain perfusion and neuronal function. In addition to AHI and hypopnea index, snoring was also associated with reduced rCBF in the left anterior temporal pole extending to the frontal lobe. Habitual snoring in children without OSA increases the risk for cognitive problems and poorer academic performances (Biggs *et al.*, 2014), but the relation between brain function and snoring is not well understood in adults. It is possible that respiratory disturbances provoking snoring without reaching criteria to be considered apneas or hypopneas could affect the brain differently that apnea and hypopnea events. Although correlational analyses with markers of OSA severity are of particular importance in OSA studies, our group analyses leaded to two regions of hypoperfusion that were not observed in the correlational analyses (left parietal lobule, right postcentral gyrus), which could be caused by a non-linear relationship between markers of OSA severity and rCBF.

We also found that hypoxemia and sleepiness were associated with abnormal perfusion in the prefrontal cortex. Consistent with our findings, previous SPECT and PET studies, that investigated OSA subjects with higher levels of hypoxemia and subjective sleepiness than in our study, showed reduced prefrontal perfusion or metabolism (Ju *et al.*, 2012; Shiota *et al.*, 2014), a region that seems particularly sensitive to hypoxemia and sleep deprivation (Beebe and Gozal, 2002). However, the prefrontal regions were not found to be altered in our group comparisons, suggesting that hypoxemia and subjective sleepiness should be considered as contributing factors to brain dysfunction independently of level of OSA severity as measured by the AHI in older individuals.

***Association between hyperperfusions and OSA-related variables***

Also of interest, significant higher rCBF in several subcortical areas (i.e. putamen, caudate nucleus, globus pallidus, amygdala and hippocampus) and medial cortical regions (i.e. insula and parahippocampal gyrus) were associated with higher AHI, apnea and micro-arousal indexes. To our knowledge, hyperperfusions have not been previously reported in SPECT and PET studies in middle-aged OSA subjects (Joo *et al.*, 2007; Yaouhi *et al.*, 2009; Ju *et al.*, 2012; Shiota *et al.*, 2014). However, a resting-state fMRI study in OSA reported increased connectivity in the basal ganglia and insula (Peng *et al.*, 2014a). These hyperperfusions may be specific to the older OSA population, but it is also possible that our large sample size used for the correlation analysis and the high spatial resolution of our SPECT scanner allowed the

observation of small but significant changes in rCBF that were not previously found in emission tomography studies. In addition, hyperperfusions observed in the present study were not found in our group analysis, suggesting that increased rCBF is a more subtle change in brain functioning that occurs with increasing OSA severity and sleep fragmentation. This pattern of lateral cortical hypoperfusion and subcortical hyperperfusion may be explained by preferential protection of critical brain regions during apneic events and sleep deprivation. In fact, subcortical structures show marked increases in perfusion during hypoxia as compared to cortical regions (Binks *et al.*, 2008), which may explain why subcortical regions could maintain higher perfusion values during wakefulness in subjects with OSA. On the other hand, some studies showed anatomical changes in subcortical structures in middle-aged OSA individuals (Yaouhi *et al.*, 2009; Joo *et al.*, 2010; Torelli *et al.*, 2011; Kumar *et al.*, 2014a), which could suggest neuronal injuries. Thus, despite altered structure, increased perfusion during hypoxia could partially protect those regions compared to lateral cortical regions, represented by a hyperperfusion and increased connectivity during wakeful rest.

However, our analysis is scaled in function of the individual global signal of rCBF. It has been shown that OSA subjects have reduced mean CBF velocity (Urbano *et al.*, 2008), and we found reduction in rCBF in lateral cortical regions. This may result in reduced global rCBF, and in comparison, subcortical rCBF could be represented as hyperperfused with increased OSA severity, as it has been previously suggested in the aging population (Pagani *et al.*, 2002). Therefore, our hyperperfusion results may be a representation of either subcortical preservation of perfusion or compensatory increases in perfusion.

Although BMI was associated with a reduction in rCBF of the left parietal cortex, it was mostly correlated with increased perfusion in central structures including the hippocampus and parahippocampal gyrus, which were also increased in perfusion in association with the AHI, apneas and micro-arousals. The hippocampus and parahippocampal gyrus have been widely studied in the context of OSA and several studies showed reduced volume or density (Macey *et al.*, 2002; Morrell *et al.*, 2003; Gale and Hopkins, 2004; Yaouhi *et al.*, 2009; Joo *et al.*, 2010; Canessa *et al.*, 2011; Torelli *et al.*, 2011; Dusak *et al.*, 2013; Joo *et al.*, 2013), changes in neuronal function assessed by fMRI (Santarnecchi *et al.*, 2013) and alteration in metabolites ratios (Bartlett *et al.*, 2004; O'Donoghue *et al.*, 2012; Alkan *et al.*, 2013). In animal studies, it was shown that apneas induce excitotoxicity in hippocampal

neurons (Fung *et al.*, 2007), that sleep fragmentation affects hippocampal synaptic plasticity (Tartar *et al.*, 2006), and that a diet with excess fat and refined carbohydrate enhances symptoms associated with hypoxic insult to the hippocampus (Goldbart *et al.*, 2006). Thus, obesity could increase vulnerability to intermittent hypoxia and sleep fragmentation in OSA, and these alterations could be linked to increased daytime perfusion. Furthermore, early stage of Alzheimer's disease may be characterized by hippocampus hyperactivity, thus suggesting again an underlying neurodegenerative process (Leal and Yassa, 2013).

***Impact of neuroimaging statistical thresholding***

In the current study, we used corrected and uncorrected statistical thresholds for neuroimaging analyses. It has been suggested that the vast differences in regions found in imaging studies on OSA could be attributed in part to the use of different statistical thresholds (Morrell and Glasser, 2011). Some variables were associated with rCBF changes only with the uncorrected threshold, such as the time spent with low oxygen saturation and BMI, which suggests that their effect could be less pronounced than other parameters. This is consistent with the fact that our subjects were not severely hypoxic nor morbidly obese. In addition, regions that were found to be significant with the less stringent statistical threshold were generally observed to be significantly affected by similar variables with the corrected threshold. Therefore, we suggest that the uncorrected threshold with a larger extent threshold could justifiably be used in the context of resting-state metabolic or perfusion tomography while the use of a corrected threshold could hide some modest changes in OSA, especially in studies with small sample sizes.

***Limitations***

Some limitations in our study should be acknowledged. First, our scanning system did not allow for consistent evaluation of cerebellar perfusion changes. Although it has been often overlooked in OSA, the cerebellum seems to be vulnerable to intermittent hypoxia in an animal model and in humans (Pae *et al.*, 2005; Harper *et al.*, 2013). Thus, further studies should specifically investigate cerebellar function in OSA and its role in cognition in this population. Another limitation is that our OSA subjects were not severely hypoxic, with minimal oxygen saturation drops in the severe OSA group to an average of 82 ± 5.5 %. It is

possible that more hypoxic patients were not recruited in our study because they presented exclusion factors, such as a history of stroke or BMI > 40. Thirdly, our groups were not matched for sex. Although results concerning sex differences in regional brain perfusion are highly inconsistent (Cosgrove *et al.*, 2007), a study performed in older subjects showed that females have reduced rCBF in regions that were reported as hypoperfused in our study, including parietal areas (Li *et al.*, 2004). This suggests that our un-matched groups could have lead to increased risk of false negatives, since most of the females in our study were in the control group. Finally, the lack of relationship between vascular disease burden and regional perfusion could be due to the low number of concomitant comorbidities and risk factors in our subjects. Therefore, we could not eliminate the possibility that OSA and vascular risk factors interact to affect the brain.

## CONCLUSIONS

Our results show that older individuals with newly diagnosed severe OSA show rCBF anomalies at rest, mostly in sensorimotor areas and the left parietal cortex. Considering that AHI is known to increase up to 53 % in 17 months in older apneic patients without significant weight gain (Pendlebury *et al.*, 1997), particular attention should be given to individuals with mild or moderate OSA in order to reduce their risk of eventually presenting brain/cognitive dysfunction linked to their condition. In addition, different variables representing OSA severity should be taken into account since they could independently contribute to abnormal brain and neuronal function. While most markers of respiratory disturbances, sleepiness, and obesity are associated with regional reductions of brain perfusion in lateral frontal, temporal and parietal areas, other factors such as respiratory events, sleep fragmentation, and obesity are associated with increased perfusion in subcortical and medial cortical areas including the limbic system, the insula and basal ganglia. These changes in regional perfusion could underlie vascular impairment and neuronal injuries, and be associated with deficits in several cognitive domains. The perfusion pattern observed in our study is similar to what is observed in early stage of Alzheimer's disease, which suggests the presence of undergoing neurodegenerative processes. Indeed, hypoperfusion in Alzheimer's disease is observed before clinical symptoms and is implicated in the progression of the disease (Daulatzai, 2013). Thus,

the role of OSA in neurodegeneration should be investigated as well as whether these functional changes are reversible or not with an appropriate treatment in future studies.

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## 5.2. **Article 2 :** Obstructive sleep apnea during REM sleep and daytime cerebral functioning : A regional cerebral blood flow study using high-resolution SPECT

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**Contribution de la candidate :** conception de l'étude, acquisition des données de sommeil et de neuroimagerie en laboratoire, analyses des données, interprétation des données, écriture et révision de l'article suite aux commentaires des co-auteurs, processus de soumission et de révision par les pairs auprès du journal scientifique.

**ABSTRACT**

Obstructive sleep apnea (OSA) events predominantly during rapid eye movement (REM) sleep may have impacts on brain health, even in milder OSA cases. We evaluated whether REM sleep OSA is associated with abnormal daytime cerebral functioning using high-resolution single-photon emission computed tomography (SPECT). We tested 96 subjects (25 women, age: 65.2 ± 6.4) with a wide range of OSA severity from no to severe OSA (apnea-hypopnea index [AHI]: 0-97). We found that apneas and hypopneas during REM sleep (REM-AH) were associated with reduced daytime regional cerebral blood flow (rCBF) in the bilateral ventromedial prefrontal cortex and in the right insula extending to the frontal cortex (peak $p<0.001$ in clusters ≥100 voxels). Apneas and hypopneas during non-REM sleep (NREM-AH) were associated with reduced daytime rCBF in the left sensorimotor and temporal cortex. In subjects that did not feature moderate to severe OSA (AHI<15) or NREM sleep OSA (NREM-AHI<15), REM-AH was associated with reduced daytime rCBF in the insula and extending to the frontal cortex. Similar but smaller daytime rCBF changes were observed with REM-AHI. Obstructive respiratory events that occurred in NREM versus REM sleep are associated with distinct patterns of daytime cerebral perfusion. OSA during REM could be more detrimental to brain health, as evidenced by reduced daytime rCBF in milder forms of OSA or in REM sleep OSA exclusively.

## INTRODUCTION

Previous studies using quantitative neuroimaging techniques have shown that obstructive sleep apnea (OSA) is associated with altered daytime cerebral functioning over many different cortical and subcortical regions (Joo *et al.*, 2007; Shiota *et al.*, 2014; Baril *et al.*, 2015; Innes *et al.*, 2015; Chen *et al.*, 2017; Kim *et al.*, 2017). Impacts of OSA on brain function also include daytime sleepiness and altered mood (Sanchez *et al.*, 2009). Recent studies showed that OSA increases the risk of accelerated cognitive decline and dementia (Leng *et al.*, 2017). Improving our understanding of how OSA causes daytime cerebral dysfunctions, particularly in older individuals, is needed to identify patients at risk of adverse long-term neurocognitive consequences.

The sleep stage in which apneas and hypopneas occur might significantly affect how OSA will impact daytime cerebral functioning. About 14 to 37 % of individuals with OSA have most of their apneas and hypopneas during rapid-eye movement (REM) sleep, and this proportion is higher for milder OSA cases (Haba-Rubio *et al.*, 2005; Pamidi *et al.*, 2011; Conwell *et al.*, 2012; Alzoubaidi and Mokhlesi, 2016; Lee *et al.*, 2016). Because REM sleep represents only a small proportion of total sleep duration, many respiratory events predominantly during REM sleep may still result in a low overall apnea-hypopnea index (AHI), leading to a milder OSA diagnosis. This poses a clinical dilemma as to whether we should treat milder OSA cases with OSA predominantly during REM sleep (Ganguly, 2012). This can only be resolved if we understand the specific impact of OSA during REM versus non-REM (NREM) OSA on general health. Aiming at answering this question, previous studies have shown that obstructive respiratory events during REM sleep are generally longer, more hypoxic and cause higher blood pressure elevation than those during NREM sleep (Garpestad *et al.*, 1995; Muraki *et al.*, 2008). OSA during REM sleep was also repeatedly associated with cardiovascular and metabolic consequences, including a higher incidence of hypertension (Mokhlesi *et al.*, 2014; Appleton *et al.*, 2016), loss of nighttime blood pressure dipping (Mokhlesi *et al.*, 2015), poor glycemic control in type 2 diabetes patients (Grimaldi *et al.*, 2014), and insulin resistance (Chami *et al.*, 2015). Because all these conditions may affect brain functioning, these recent discoveries suggest that REM sleep OSA may be especially detrimental to brain health.

The present study aimed at determining how respiratory events, apneas and hypopneas, during REM sleep are associated with abnormal daytime cerebral functioning. To achieve this goal, the association between OSA during REM versus NREM sleep was investigated with single photon emission computed tomography (SPECT) during wakefulness to measure regional cerebral blood flow (rCBF), as this technique was shown to be particularly sensitive to OSA (Baril *et al.*, 2015). Resting-state cerebral perfusion is considered a marker of brain functioning because it is closely related to neuronal and astroglial activity via neuro-vascular coupling (Sestini, 2007). We hypothesized that 1) the severity of OSA during REM versus NREM sleep would be characterized by distinct daytime rCBF patterns, and that 2) OSA during REM sleep would be associated with daytime rCBF anomalies even in milder cases for whom there is a clinical dilemma. Additional daytime functioning measurements were used to assess sleepiness, mood, and cognition.

## MATERIAL AND METHODS

### *Recruitment*

We recruited subjects aged between 55 and 85 years old with a wide range of OSA severities from ads in media, although some subjects (n=21) were recruited from a waiting list for OSA screening in a pulmonary clinic. Recruitment continued until all OSA severity groups (from healthy controls to severe OSA individuals) were represented. Exclusion criteria were psychiatric (e.g., diagnosed depression and anxiety disorders), neurologic (e.g., dementia, stroke) and pulmonary diseases (e.g. chronic obstructive pulmonary disease); sleep disorders other than OSA (e.g., restless leg syndrome, insomnia, rapid-eye movement sleep behavior disorder, parasomnias); morbid obesity ($\geq$ 40 kg/m$^2$); drug and alcohol abuse; and medications known to influence sleep or cerebral functioning (e.g., antidepressants, benzodiazepines, opioids, antiepileptics, antipsychotics). Cardiovascular risk factors and diseases were assessed with the Index of Vascular Burden (Villeneuve *et al.*, 2009). Participants with controlled diabetes or hypertension were not excluded, but their conditions were documented in that index. All OSA subjects included in our study were newly diagnosed and none of them were treated for OSA. The Hôpital du Sacré-Coeur de Montréal Ethics' Committee approved the research protocol (#2012-697). Written informed consent was obtained from each participant.

***Overview of the protocol***

In order to characterize our sample, we used questionnaires, namely Epworth Sleepiness Scale (ESS) (Johns, 1991); Beck Depression Inventory-II (BDI-II) (Beck *et al.*, 1996); Beck Anxiety Inventory (BAI) (Beck *et al.*, 1988), and a cognitive screening test, the Montreal Cognitive Assessment (MoCA) (Nasreddine *et al.*, 2005). Participants were evaluated with a polysomnographic recording and a SPECT imaging session. Questionnaires were administered the evening before polysomnography, except for the MoCA that was performed the morning after by a trained neuropsychologist. The daytime SPECT imaging was performed a month on average after the polysomnographic recording (26.2 ± 30.2 days).

***Polysomnographic recording***

The full-night polysomnographic recording was performed in a sleep laboratory and included an 18-channel electroencephalogram, an electrooculogram, chin and anterior tibialis electromyogram, and an electrocardiogram. Apneas and hypopneas were recorded with thoracic-abdominal strain gauges, oronasal cannula and thermal sensors, and a transcutaneous finger pulse oximeter. Sleep stages as well as apneas and hypopneas were scored by a medical electrophysiology technologist with extensive training in sleep according to the 2007 American Academy of Sleep Medicine Manual for the scoring of sleep (Iber *et al.*, 2007) and their 2012 update for the scoring of respiratory events (Berry *et al.*, 2012). Apneas and hypopneas were scored if they lasted >10 s. An airflow reduction of ≥90 % and ≥30 % defined an apnea and a hypopnea, respectively. A hypopnea had to be accompanied by either an oxygen desaturation of ≥3 % or an arousal.

Apneas and hypopneas that occurred either completely or partially during REM sleep were computed in the REM-AH and REM-AHI, while others were computed in the NREM-AH and NREM-AHI. The REM-AH was computed by adding the total number of apneas and hypopneas during REM sleep (and vice versa for NREM-AH). The REM-AHI was calculated as follows: apneas+hypopneas during REM sleep / REM sleep duration in hours (and vice versa for NREM-AHI). Although these variables include central events, all OSA participants had mostly obstructive rather than central events (9.8 ± 15.0 % of the AHI were central events).

***SPECT image acquisition, processing, and data analysis***

To assess rCBF during wakefulness, all subjects underwent technetium-99m-hexamethylpropyleneamine oxime ($^{99m}$Tc-HMPAO) SPECT scanning using a high-resolution brain-dedicated scanner (NeuroFOCUS, NeuroPhysics, Shirley, USA). This procedure was described in a previous study by our group (Baril *et al*., 2015). While subjects lay awake with their eyes closed, an average dose of 750 MBq of $^{99m}$Tc-HMPAO was administered intravenously followed by a saline flush. $^{99m}$Tc-HMPAO uptake in the brain takes about a minute. This fast uptake allows reducing to a maximum the potential effect of drowsiness on scanning. Twenty minutes later, projections were acquired statically for 30 minutes.

Individual images were reconstructed in a 128 x 128 matrix to achieve 32 slices with a filtered back projection and an attenuation correction (Chang's absorption coefficient: 0.01 $cm^{-1}$). Because this SPECT scanner does not record the whole cerebellum, this region was excluded from analyses. All acquired individual images were visually inspected for gross abnormalities. Individual SPECT images were registered and spatially normalized (co-registered and warped) to the standard SPECT template included in SPM8 (*http://www.fil.ion.ucl.ac.uk/spm/software/spm8/*). Normalized images were smoothed using a 14-mm full-width half-maximum filter and proportionally scaled with a grand mean scaling of 50 ml/min/100g for individual global mean signals. Final individual images were thus equally smoothed and normalized into the same common space in order to performed voxel-based statistical comparisons.

***Statistical analyses***

Statistics were performed with SPSS 19 (IBM SPSS Statistics, New York, USA), except for rCBF analyses that were performed within SPM. Comparisons between control, mild, moderate and severe OSA groups were performed with one-way ANOVA for continuous variables and chi-square for categorical variables. These variables included clinical, demographic, polysomnographic and cognitive data (see Table 1).

***Use of a regression approach in REM sleep OSA***

We assessed the relationship between REM sleep OSA and daytime cerebral functioning mostly using regression models. Although groups are clinically important, there is many different criteria that exist in the current literature with arguably arbitrary cut-offs to define the presence of REM sleep OSA (Alzoubaidi and Mokhlesi, 2016). Moreover, some studies showed a dose-response relationship between various physiological functions and respiratory events during REM sleep (Grimaldi *et al.*, 2014; Mokhlesi *et al.*, 2014; Chami *et al.*, 2015; Mokhlesi *et al.*, 2015). Regression models are not limited by arbitrary cut-offs and may represent more closely the physiopathology compared to a group analysis. Regressions models used in the present study were based on those performed in large cohort studies that have investigated the effect of REM sleep OSA on hypertension, glucose metabolism as well as sleepiness and quality of life (Chami *et al.*, 2010; Mokhlesi *et al.*, 2014; Chami *et al.*, 2015; Mokhlesi *et al.*, 2015).

***Independent variables for statistical models***

Here, we constructed five statistical models (4 regression models and one group analysis, presented below). REM sleep OSA was assessed with REM-AHI or REM-AH. Because REM sleep duration is the denominator to compute the REM-AHI, a very short duration may lead to an overestimation of REM OSA. Therefore, for analyses using the REM-AHI, subjects with very short REM sleep duration (<30 minutes) during their polysomnographic recording were excluded. This threshold was used in previous studies investigating the impacts of REM sleep OSA (Mokhlesi *et al.*, 2014; Appleton *et al.*, 2016). Because the REM-AHI is limited by the REM sleep duration to accurately assessed OSA during REM sleep, we also use the REM-AH in models. With models performed with the REM-AH, all subjects were included regardless of REM sleep duration since there is no denominator effect. However, total sleep time was included as a covariate in regression models to adjust the number of apneas and hypopneas for sleep duration. Indeed, because total sleep time and REM sleep duration are highly correlated, including total sleep time in models partially adjust for REM sleep duration.

Respiratory variables representing OSA were negatively skewed, did not have a normal distribution, and contained at least one value equal to zero. Thus, the formula "$\log_{10}$(variable +

1)" was used. Similar data transformation for regression models was used in previous studies investigating the impacts of REM sleep OSA (Chami *et al.*, 2010; Grimaldi *et al.*, 2014; Mokhlesi *et al.*, 2014; Chami *et al.*, 2015; Mokhlesi *et al.*, 2015). Statistics that were performed between variables included in regression models suggested no multicollinearity (variance inflation factor <1.1).

Age was included as a covariate in all models. Because the prevalence of REM sleep OSA is reported to be closely associated with sex (Pamidi *et al.*, 2011), we did not include it as a covariate upfront since it could have removed an REM sleep OSA effect. We, however, performed supplementary analyses that included both age and sex as covariates.

***Model 1: Regression between REM sleep OSA and daytime rCBF in all subjects***

To assess whether OSA during REM versus NREM sleep is associated with distinct patterns of daytime cerebral functioning, linear regressions were used across all subjects from controls to severe OSA individuals. Since both REM and NREM OSA variables were included in the same model simultaneously, significant regressions with REM OSA were controlled for NREM OSA, and vice versa. This allowed investigating OSA effect during each sleep type independently on daytime rCBF as a dependent variable.

***Model 2: Regression between REM sleep OSA and daytime rCBF in subjects with an AHI<15***

OSA that is predominantly during REM sleep can result in a low overall OSA severity. To assess whether REM sleep OSA affects daytime functioning in milder OSA severity, REM and NREM OSA variables were included simultaneously in a regression model with daytime rCBF as a dependent variable in subjects with an AHI<15 only, thus excluding subjects with a overall moderate and severe OSA.

***Model 3: Regression between REM sleep OSA and daytime rCBF in subjects with an NREM-AHI<15***

Although regression models 1 and 2 are adjusted statistically for NREM sleep OSA, we performed an additional analysis specifically in subjects with an NREM-AHI<15, which

correspond to either no or mild NREM sleep OSA. This model allowed investigating daytime rCBF as a dependent variable in relationship with REM sleep OSA in subjects that do not present NREM sleep OSA. Thus, this analysis highlights the impacts of REM sleep OSA when it is present exclusively.

***Model 4: daytime rCBF changes between REM sleep OSA quartiles***

We divided the complete sample into quartiles according to REM sleep OSA variables. These four groups were compared between them regarding their daytime rCBF as a dependent variable with NREM sleep OSA as a covariate. This analysis was performed in previous studies (Mokhlesi *et al.*, 2014; Chami *et al.*, 2015; Mokhlesi *et al.*, 2015) and allowed investigating the effects of the severity of REM sleep OSA independently of NREM sleep OSA in a group design.

***Model 5: Regression between REM sleep OSA and symptomatology***

To investigate whether REM sleep OSA (or NREM sleep OSA) is associated with global cognitive performance, depressive and anxious symptoms or with daytime sleepiness, we performed regression analyses across all subjects including both REM sleep and NREM sleep OSA variables simultaneously in regression models with MoCA, BDI-II, BAI and ESS as dependent variables.

***Statistical thresholds***

For daytime rCBF analyses performed within SPM, models were applied with the voxel-based technique. Final processed individual SPECT images have thousands of rCBF values: one single rCBF value for every voxel (2 $mm^3$). This type of neuroimaging technique applies the statistical models on all voxels specified. We used a mask covering gray matter in the cerebrum to apply constructed models on these voxels only, thus excluding the cerebellum, the white matter and cerebrospinal fluid. Significance was set at $p$ <0.001 for voxel peaks combined with an extent threshold of clusters containing ≥100 contiguous voxels. This specific combination of a liberal p-value uncorrected for multiple comparisons combined with a restrictive cluster size was shown to better find and localizes regions with changed metabolism, without increasing false positives (Mayoral *et al.*, 2016). Significant regions were

identified using PickAtlas with the Automated Anatomical Labeling (AAL) atlas (*http://fmri.wfubmc.edu/software/pickatlas*; version 3.0). For exploratory analyses with sleepiness, mood, and cognition as dependent variables, a threshold of $p$ <0.05 was chosen.

## RESULTS

### *Sample characteristics*

The sample included 96 subjects (25 females; 71 males; mean age: 65.2 ± 6.4 years; age range: 55-82 years). In order to describe our sample, we divided the sample into four groups according to their AHI: control group (17 % of the sample) and mild (38 %), moderate (21 %), and severe (24 %) OSA groups. Detailed participant characteristics are presented in Table 1. At study entry, 44 % of the final sample reported an OSA-related complaint, including snoring, daytime sleepiness or bed partner witnessing respiratory disturbances. The average apnea and hypopnea duration as well as mean and minimal oxygen saturation did not differ significantly between REM and NREM sleep in the full sample or in any OSA severity groups (results not shown).

No difference was found between controls and OSA groups for sleepiness, mood, or cognition. In our sample, around a third presented daytime sleepiness (33 % with Epworth Sleepiness Scale ≥10), whereas about a fifth presented cognitive deficits (21 % with the Montreal Cognitive Assessment <26). Low levels of depression and anxiety (9 % with Beck Depression Inventory ≥14 and 16 % with Beck Anxiety Inventory ≥10) were observed. No difference between groups was found for the vascular burden as well.

**Table 1.** Clinical, polysomnographic, and respiratory variables for healthy control subjects and OSA groups.

| Variables | Controls [A] | Mild OSA [B] | Moderate OSA [C] | Severe OSA [D] | p-value | Post-hoc tests |
|---|---|---|---|---|---|---|
| AHI criteria for groups | <5 | ≥5 to <15 | ≥15 to <30 | ≥30 | n/a | |
| Number of subjects | 16 | 37 | 20 | 23 | n/a | |
| Sex (#; %Male) | 10; 62.5 % | 24; 64.9 % | 17; 85.0 % | 20; 87.0 % | ns | |
| Age (years) | 64.4 (6.7) | 64.4 (5.9) | 64.6 (6.3) | 67.0 (7.0) | ns | |
| Body Mass Index (kg/m$^2$) | 25.9 (3.4) | 26.7 (3.6) | 28.9 (3.6) | 28.6 (2.5) | <0.05 | A <C |

| | | | | | | |
|---|---|---|---|---|---|---|
| Vascular Burden Index | 0.9 (1.1) | 1.3 (1.4) | 1.3 (1.0) | 1.4 (1.3) | ns | |
| Hypertension (%) | 31.3 % | 48.6 % | 60.0 % | 56.5 % | ns | |
| Epworth Sleepiness Scale | 7.8 (5.7) | 7.5 (4.6) | 9.1 (5.2) | 8.4 (4.8) | ns | |
| Daytime sleepiness ≥10 (%) | 31.3 % | 29.7 % | 45.0 % | 30.4 % | ns | |
| Beck Depression Inventory II | 5.4 (5.4) | 6.4 (5.4) | 7.1 (5.4) | 7.0 (5.2) | ns | |
| Mild depression ≥14 (%) | 6.3 % | 11.1 % | 10.5 % | 8.7 % | ns | |
| Beck Anxiety Inventory | 4.7 (4.7) | 4.0 (4.0) | 5.2 (5.7) | 4.1 (4.1) | ns | |
| Mild anxiety ≥10 (%) | 12.5 % | 16.2 % | 20 % | 13.0 % | ns | |
| Montreal Cognitive Assessment | 27.4 (2.2) | 27.6 (2.0) | 27.2 (2.4) | 26.5 (3.0) | ns | |
| Cognitive deficits <26 (%) | 12.5 % | 16.7 % | 20.0 % | 36.4 % | ns | |
| ***Polysomnographic variables*** | | | | | | |
| TST (min) | 367.0 (54.9) | 358.7 (74.0) | 347.1 (49.1) | 370.5 (62.6) | ns | |
| Sleep efficiency (%) | 78.4 (8.8) | 79.1 (12.5) | 78.7 (11.2) | 79.2 (11.0) | ns | |
| Micro-arousal index (/hour) | 11.1 (4.0) | 13.5 (5.4) | 17.0 (6.6) | 23.8 (10.8) | <0.001 | A, B, C <D |
| NREM 1 (min) | 58.5 (28.1) | 62.4 (23.3) | 78.3 (30.5) | 121.0 (51.7) | <0.001 | A, B, C <D |
| NREM 2 (min) | 209.7 (44.2) | 197.7 (61.6) | 196.7 (47.6) | 180.8 (57.5) | ns | |
| NREM 3 (min) | 40.3 (31.7) | 41.4 (39.0) | 21.1 (24.5) | 16.3 (18.7) | <0.01 | B >D |
| NREM (min) | 308.5 (52.9) | 301.4 (60.1) | 296.0 (42.7) | 318.1 (54.6) | ns | |
| NREM (%) | 83.9 (4.6) | 84.5 (5.5) | 85.5 (5.7) | 86.0 (5.7) | ns | |
| REM (min) | 58.5 (16.5) | 57.2 (24.0) | 51.0 (20.5) | 52.3 (24.3) | ns | |
| REM duration <30 (%) | 0.0 % | 13.5 % | 20.0 % | 13.0 % | ns | |
| REM (%) | 16.1 (4.6) | 15.5 (5.5) | 14.5 (5.7) | 14.0 (5.7) | ns | |
| ***Respiratory variables*** | | | | | | |
| AHI (AH/hour) | 2.0 (1.3) | 9.3 (2.8) | 22.3 (4.6) | 46.6 (17.9) | <0.001 | A <B <C <D |
| NREM-AHI (AH/hour) | 1.4 (1.2) | 7.5 (3.5) | 20.3 (5.9) | 46.5 (18.2) | <0.001 | A, B <C <D |
| #NREM-AH | 6.8 (5.5) | 37.0 (18.8) | 101.1 (37.1) | 246.0 (107.7) | <0.001 | A, B <C <D |
| REM-AHI (AH/hour) | 5.4 (5.1) | 22.7 (22.2) | 40.1 (28.2) | 49.5 (30.2) | <0.001 | A <C, D; B <D |
| #REM-AHI | 5.3 (5.4) | 18.0 (14.1) | 28.2 (17.0) | 38.0 (22.4) | <0.001 | A <B, C, D; B<D |
| Minimal $SpO_2$ (%) | 90.4 (2.9) | 87.0 (4.5) | 82.9 (5.6) | 82.5 (5.5) | <0.001 | A, B >C, D |
| Minimal NREM $SpO_2$ (%) | 91.3 (2.9) | 88.2 (4.6) | 84.1 (5.8) | 83.9 (4.8) | <0.001 | A, B >C, D |
| Minimal REM $SpO_2$ (%) | 91.4 (2.3) | 89.6 (3.5) | 85.2 (6.3) | 84.7 (6.1) | <0.001 | A, B >C, D |
| TST $SpO_2$ <90 % (min) | 0.1 (0.2) | 2.1 (5.1) | 6.0 (5.1) | 16.1 (18.9) | <0.001 | A, B, C <D |

Results are presented as mean (standard deviation). OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; N/A, not applicable; TST, Total sleep time; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; AH, apneas and hypopneas; $SpO_2$, oxygen desaturation.

***Model 1: Regression between REM sleep OSA and daytime rCBF in all subjects***

In all subjects (n=96), the REM-AH and NREM-AH were independently associated with distinct patterns of reduced daytime rCBF (see Figure 1 and Table 2). Reduced daytime rCBF was observed in association with REM-AH in the bilateral ventromedial prefrontal cortex and the right insula extending to the inferior frontal gyrus. Reduced daytime rCBF with NREM-AH was present in the left sensorimotor cortex and left lateral temporal cortex. No region of increased daytime rCBF was observed. When sex was added as a covariate, a similar pattern of hypoperfusion was observed with REM-AH whereas no daytime rCBF changes were observed with NREM-AH (see Table 2).

We performed the same model with REM-AHI and NREM-AHI (instead of REM-AH and NREM-AH) in subjects with an REM sleep duration ≥30 minutes (n=84). Of the 96 subjects recruited, 12 subjects had <30 minutes of REM sleep during their in-laboratory polysomnographic recording. As stated earlier, a very short REM sleep duration led to a very high REM-AHI and therefore, an overestimation of OSA during REM. These subjects with short REM sleep duration had a higher AHI ($p$ <0.05), shorter total sleep time ($p$ <0.001) and more hypertension (91.7 %, $p$ <0.01) than subjects with more than 30 minutes of REM sleep. Unsurprisingly, subjects with short REM sleep duration had a higher REM-AHI compared to other subjects (64.6 events/hour versus 24.9 events/hour respectively, $p$ <0.001).

As for REM-AH and NREM-AH, distinct patterns of daytime rCBF were also associated with REM-AHI and NREM-AHI. Reduced daytime rCBF in the right medial orbitofrontal cortex was associated with REM-AHI, and reduced daytime rCBF in the left postcentral gyrus was correlated with NREM-AHI. Therefore, the same regions of hypoperfusion were found with the absolute amount of AHs than with the AHIs. However, less and smaller clusters were found with REM-AHI and NREM-AHI compared to analyses performed in the complete sample with REM-AH and NREM-AH (see Table 2). The REM-AHI seems to be less sensitive to daytime rCBF changes than the absolute number of apneas and hypopneas observed in REM sleep (REM-AH) while adjusting for total sleep duration. Therefore, for the following models 2 through 5, we used the REM-AH and NREM-AH in the complete sample while still adjusting for total sleep duration.

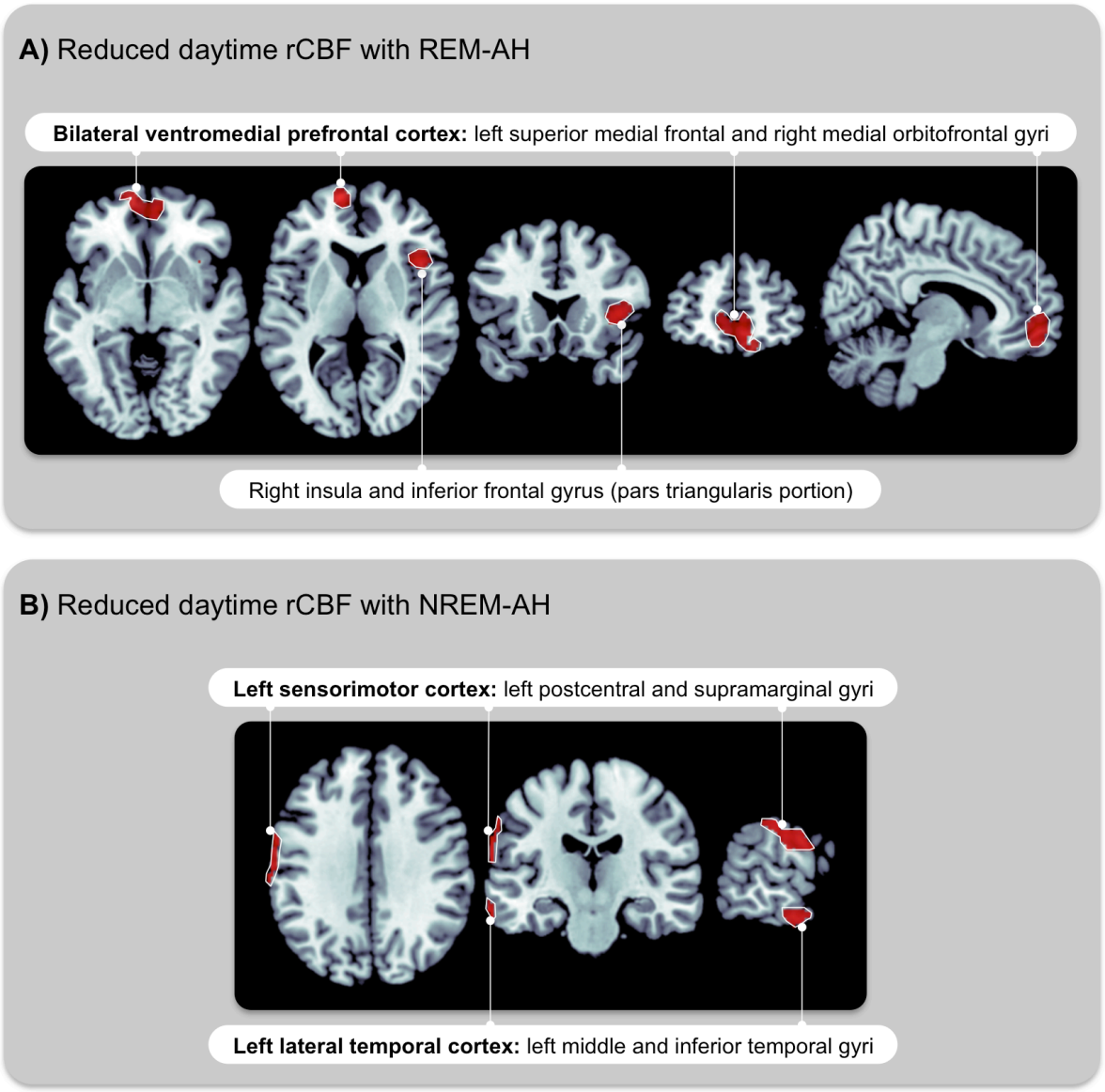


**Figure 1.** Daytime brain hypoperfusion patterns associated with OSA during REM versus NREM sleep.

In the complete sample representing all OSA severities (n=96, AHI from 0 to 97, model 1), reduced daytime rCBF is associated with A) a higher REM-AH in the bilateral ventromedial prefrontal cortex and right insula extending to the frontal cortex; B) a higher NREM-AH in the left sensorimotor and lateral temporal cortex. Regression models were between REM-AH and daytime rCBF, adjusted for age, total sleep duration and NREM-AH (A); and between NREM-AH and daytime rCBF, adjusted for age, total sleep duration and REM-AH (B). Significant regions of rCBF associated with either REM-AH or NREM-AH were obtained with the following threshold: $p$ <0.001 uncorrected for peaks voxels found within a cluster of >100 continuous voxels. rCBF, regional cerebral blood flow; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; AH, apneas + hypopneas; AHI, apnea-hypopnea index; OSA, obstructive sleep apnea.

**Table 2.** Significant clusters of reduced daytime rCBF with REM-AH and NREM-AH in all subjects

| Cluster size (k) | T | MNI coordinates | | | Peak location with AAL atlas |
|---|---|---|---|---|---|
| | | x | y | z | |
| *Model 1: Reduced daytime rCBF with REM-AH* | | | | | |
| 647*† | 4.6 | -12 | 62 | 2 | L superior frontal medial |
| | 4.0 | 6 | 54 | -8 | R medial orbitofrontal |
| 221* | 4.1 | 42 | 20 | 4 | R inferior frontal pars triangularis (extending to the R insula) |
| *Model 1: Reduced daytime rCBF with NREM-AH* | | | | | |
| 140 | 4.1 | -68 | -16 | -20 | L middle temporal |
| | 3.8 | -68 | -26 | -20 | L inferior temporal |
| 225† | 3.9 | -66 | -14 | 22 | L postcentral (parietal) |
| | 3.9 | -66 | -16 | 30 | L postcentral (parietal) |
| | 3.9 | -64 | -20 | 38 | L supramarginal (parietal) |

Regression models included both REM-AH and NREM-AH as well as age and total sleep duration as covariates. Clusters marked with (*) were still significant when sex was added as a covariate (cluster size: 146 and 133 voxels). Clusters marked with (†) were still significant with REM-AHI or NREM-AHI instead of REM-AH and NREM-AH in subjects with REM sleep duration ≥ 30 minutes (cluster size: 207 and 193 voxels). Significant regions of daytime rCBF were obtained with the following threshold: $p$ <0.005 uncorrected for peaks voxels found within a cluster of >200 continuous voxels. rCBF, regional cerebral blood flow; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; AH, apneas + hypopneas; AHI; apnea-hypopnea index; MNI, Montreal Neurological Institute; AAL, Automated Anatomical Labeling; OSA, obstructive sleep apnea; L, left; R, right.

### *Model 2: Regression between REM sleep OSA and daytime rCBF in subjects with an AHI<15*

In subjects with an overall OSA severity considered as no or mild OSA (n=54), the REM-AH was associated with reduced daytime rCBF in the bilateral insula extending to the inferior frontal gyrus on the right hemisphere, adjusted for NREM-AH, age and total sleep duration (see Figure 2A and Table 3). Similar results on the right hemisphere were observed when sex was entered as a covariate or when the REM-AHI was used instead in subjects with a REM sleep duration ≥30 minutes (see Table 3). No region of increased daytime rCBF was found, and no association was observed between daytime rCBF and NREM-AH.

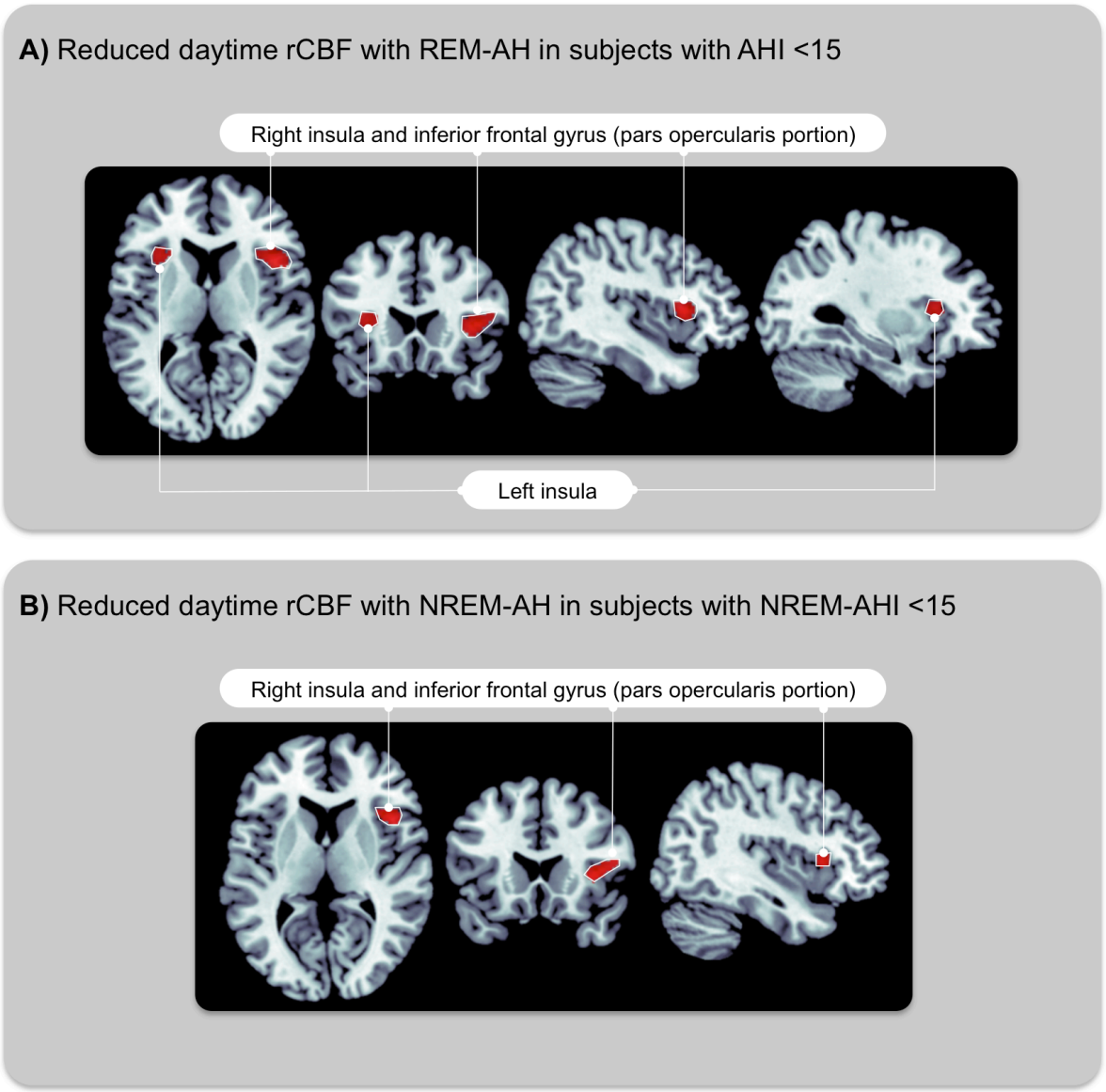


**Figure 2.** Daytime brain perfusion patterns associated with OSA during REM sleep subjects in specific subsamples.

A) In subjects with either no or mild OSA (n=54, AHI<15, model 2), a higher REM-AH was associated with reduced daytime rCBF in the right insula extending to the frontal cortex as well as the left insula. B) In subjects with either no or mild NREM sleep OSA (n=55, NREM-AHI<15, model 3), a higher REM-AH was associated with reduced daytime rCBF in the right insula extending to the frontal cortex. Regressions model were between REM-AH and daytime rCBF, adjusted for age, total sleep duration and NREM-AH (A); and between REM-AH and daytime rCBF, adjusted for age and total sleep duration. Significant regions of rCBF associated with either REM-AH were obtained with the following threshold: $p$ <0.001 uncorrected for peaks voxels found within a cluster of >100 continuous voxels. rCBF, regional cerebral blood flow; NREM, non-rapid eye movement sleep;

REM, rapid eye movement sleep; AH, apneas + hypopneas; AHI, apnea-hypopnea index; OSA, obstructive sleep apnea.

**Table 3.** Significant clusters of reduced daytime rCBF with REM-AH and NREM-AH specific subsamples

| Cluster size (k) | T | MNI coordinates | | | Peak location with AAL atlas |
|---|---|---|---|---|---|
| | | x | y | z | |
| *Model 2: Reduced daytime rCBF with REM-AH in subjects with AHI<15* | | | | | |
| 271*† | 4.4 | 40 | 18 | 6 | R inferior frontal pars opercularis (extending to the R insula) |
| 100 | 3.9 | -30 | 22 | 10 | L insula |
| *Model 3: Reduced daytime rCBF with REM-AH in subjects with NREM-AHI<15* | | | | | |
| 192*† | 3.9 | 36 | 20 | 4 | R insula |
| | 3.8 | 46 | 16 | 10 | R inferior frontal pars opercularis |
| *Model 4: Daytime rCBF in REM-AH quartile 1 > quartile 2* | | | | | |
| 166 | 3.7 | 30 | 14 | -2 | R putamen |
| | 3.5 | 22 | 6 | 0 | R putamen |
| | 3.3 | 22 | 0 | 10 | R putamen (extending to the R insula) |
| *Model 4: Daytime rCBF in REM-AH quartile 1 > quartile 4* | | | | | |
| 109 | 3.8 | -12 | 64 | 4 | L superior frontal medial |

Regression model 2 included both REM-AH and NREM-AH as well as age and total sleep duration as covariates. Regression model 3 included REM-AH as well as age and total sleep duration as covariates. Group analysis (model 4) in quartiles was adjusted for total sleep duration and NREM-AH. Clusters marked with (*) were still significant when sex was added as a covariate (cluster size: 200 and 121 voxels). Clusters marked with (†) were still significant with REM instead of REM-AH in subjects with REM sleep duration ≥ 30 minutes (cluster size: 185 and 192 voxels). Significant regions of daytime rCBF were obtained with the following threshold: $p$ <0.005 uncorrected for peaks voxels found within a cluster of >200 continuous voxels. rCBF, regional cerebral blood flow; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; AH, apneas + hypopneas; AHI; apnea-hypopnea index; MNI, Montreal Neurological Institute; AAL, Automated Anatomical Labeling; OSA, obstructive sleep apnea; L, left; R, right.

### *Model 3: Regression between REM sleep OSA and daytime rCBF in subjects with an NREM-AHI<15*

In subjects with either no or mild NREM sleep OSA (n=55), REM-AH was associated with reduced daytime rCBF in the right insula extending to the inferior frontal (see Figure 2B and Table 3). The same cluster of reduced daytime rCBF was observed in association when

sex was entered as a covariate or when the REM-AHI was used instead in subjects with a REM sleep duration ≥30 minutes (see Table 3). No region of increased daytime rCBF was found.

***Model 4: daytime rCBF changes between REM sleep OSA quartiles***

The quartiles were adjusted for total sleep time by computing the REM-AH by hours of total sleep in the complete sample (n=96). The first quartile included subjects between 0 and 1.2 REM-AH by hours of sleep; the second between 1.3 and 3.4; the third between 3.5 and 5.6; and the fourth with subjects with 5.7 and over (range: 5.7 – 14.2). The second REM-AH quartile was associated with reduced daytime rCBF in the right putamen extending to the right insula compared to the first quartile. The fourth REM-AH quartile had reduced daytime rCBF in the left superior medial frontal cortex compared to the first quartile. These group differences were not significant, however, when sex was entered as a covariate or when the REM-AHI was used to separate quartiles instead in subjects with a REM sleep duration ≥30 minutes. No region of increased daytime rCBF was observed.

***Model 5: Regression between REM sleep OSA and symptomatology***

In the complete sample (n=96), only a trend was observed: a higher REM-AH was associated with a worse MoCA (r=-0.197, p=0.06) when adjusting for NREM-AH, age and total sleep time. When sex was entered as a covariate, the same trend remained (r=-0.206, p=0.05). No association was found with the BDI-II, BAI and ESS scores with REM-AH, and no association was found between any questionnaire score and the NREM-AH.

In the sample corresponding to either no or mild OSA (AHI<15, n=54) and in the sample without NREM sleep OSA (NREM-AHI<15, n=55), trends were found with a higher REM-AH associated with more depressive symptoms (r=0.261, p=0.07; r=0.269, p=0.05). However, these trends were not present when adjusted for sex in the AHI<15 sample, but was still present in the NREM-AHI<15 sample (r=0.256, p=0.07). In subjects with either no or mild OSA with an AHI<15, no association were found between NREM-AH and any questionnaire score. In these subsamples, no association was found with the MoCA, BAI and ESS scores.

None of these trends were observed with the REM-AHI in subjects with a REM sleep duration ≥30 minutes instead of the REM-AH.

In ANCOVA group analyses, the fourth REM-AH quartile had a lower MoCA score when compared to the first quartile (p=0.03) adjusted for total sleep duration, age and NREM-AH, which was still observed when sex was entered as a covariate (p=0.04). No other difference between REM sleep OSA severity quartiles was observed for ESS, BDI-II and ESS scores.

## DISCUSSION

### *Summary of the cerebral perfusion findings*

In this study, we aimed to clarify the impacts of OSA during REM sleep on daytime cerebral functioning. We found that more respiratory events during REM or NREM sleep are associated with different patterns of daytime brain perfusion. In fact, the presence of more apneas and hypopneas during REM sleep was associated with daytime hypoperfusion in the ventromedial prefrontal and fronto-insular regions, whereas more respiratory events during NREM sleep was associated with daytime hypoperfusion in the left sensorimotor and temporal cortex. Another significant finding is that reduced daytime brain perfusion was also observed in fronto-insular regions in association with REM sleep OSA among subjects without moderate to severe OSA or without NREM sleep OSA. This result suggests that when the overall OSA severity is low, REM sleep OSA can still affect daytime cerebral functioning, a finding that was not observed for NREM sleep OSA. This also suggests that the presence of REM sleep OSA exclusively can affect daytime cerebral functioning. The novelty of our study lies in the use of neuroimaging to investigate whether REM sleep OSA affects daytime cerebral functioning in a large sample of participants, including subjects with milder forms of OSA.

### *SPECT as a sensitive tool to detect cerebral dysfunctions in OSA*

Resting-state cerebral perfusion is considered as a marker of brain functioning because it is closely related to neuronal and astroglial activity (Sestini, 2007), although other contributing factors to cerebral perfusion include vascular reactivity and cerebral autoregulation (Macey, 2015). Because neurovascular coupling was reported to be preserved

in OSA individuals (Tekgol Uzuner and Uzuner, 2016), we can hypothesize that altered daytime rCBF represent, in part at least, metabolic demands of neurons and astrocytes. Hypoperfusions in the ventral, medial and orbital prefrontal cortex, as well as in the insula were found in previous OSA studies (Shiota *et al.*, 2014; Baril *et al.*, 2015; Innes *et al.*, 2015; Chen *et al.*, 2017; Kim *et al.*, 2017). Similarly, reduced rCBF in temporal and sensorimotor regions were also reported in OSA subjects (Joo *et al.*, 2007; Baril *et al.*, 2015; Innes *et al.*, 2015; Chen *et al.*, 2017; Kim *et al.*, 2017). Therefore, our study brings new insight into the discrepancies across brain regions that have been reported as hypoperfused in previous OSA studies: differences in the numbers of apneas and hypopneas during REM and NREM sleep could explain why different brain locations show abnormal daytime rCBF in different studies.

***Characteristics of OSA during REM sleep and daytime cerebral functioning***

During REM sleep, upper airway muscle activity is reduced and their collapsibility increases (Moszczynski and Murray, 2012; Mokhlesi *et al.*, 2014; Alzoubaidi and Mokhlesi, 2016), which may lead to more apneas and hypopneas during REM sleep, even in milder OSA cases. The literature is scarce on the consequences of REM sleep OSA with a mild overall severity. In addition, it is unclear whether these patients should they be treated or not (Ganguly, 2012). Our results showed that REM sleep OSA could be more harmful to brain functioning than NREM sleep OSA. Previous authors have suggested that the armful impact of REM sleep OSA could be due to the fact that respiratory events during REM sleep last longer and provoke more hypoxemia (Muraki *et al.*, 2008). In the present study, however, it was not the case. Apneas and hypopneas duration as well as mean and minimal saturation did not differ statistically between REM and NREM sleep in our sample. Instead, another hypothesis could be that the impact of REM sleep OSA could be related to the physiological response to apneas and hypopneas rather than their characteristics like duration and oxygen saturation. Compared to NREM sleep, REM sleep is characterized by a high level of brain activity, higher sympathetic activity, and irregular heart rate (Moszczynski and Murray, 2012; Chouchou and Desseilles, 2014). These REM sleep particularities could put the brain in a state that is more vulnerable to the effects of OSA. In fact, blood pressure fluctuations are higher for apneas and hypopneas during REM sleep than NREM sleep (Garpestad *et al.*, 1995). Moreover, increased activity during REM sleep has been previously reported for the ventral and orbital prefrontal

cortex as well as for the anterior portion of the insula (Hobson *et al.*, 1998). Areas with increased metabolic requirements during apneas and hypopneas could be more susceptible to injury provoked by oxygen shortage, arousals, and hemodynamic fluctuations. These areas of high activity during REM sleep could show neuronal dysfunction that can then be manifested during daytime as reduced activity. Thus, OSA during REM sleep could lead to vascular and metabolic consequences to which the brain is especially vulnerable. Consistently, OSA during REM sleep was recently associated with impaired cardiovascular and metabolic function (Grimaldi *et al.*, 2014; Mokhlesi *et al.*, 2014; Chami *et al.*, 2015; Mokhlesi *et al.*, 2015; Appleton *et al.*, 2016).

Because we observed larger and more regions of reduced rCBF, our analyses were stronger when using the absolute number of apneas and hypopneas during REM sleep rather than the REM-AHI and NREM-AHI. This could be due to the exclusion of subjects with very short REM sleep duration in order to accurately compute the REM-AHI: indeed, subjects with very short REM sleep duration may be the ones that are most affected by OSA during REM sleep, which could be characterized by a perturbed and short REM sleep. Moreover, stronger results may also suggest that the absolute amount (AH) rather than the density (AHI) of apneas and hypopneas during REM sleep is more representative of underlying processes that may be detrimental to brain health. Overall, although the AHI is the standard measurement of OSA severity, REM-AH may not be the best variable to assess the REM sleep OSA giving the high influence of REM sleep duration on its value.

***Clinical significance of REM sleep OSA***

While some previous studies did not observe any association between OSA symptomatology and REM sleep OSA (Haba-Rubio *et al.*, 2005; Liu *et al.*, 2011; Khan *et al.*, 2013), others found that OSA during REM sleep was associated with depression (Conwell *et al.*, 2012; Lee *et al.*, 2016), and OSA during NREM sleep was associated with sleepiness (Punjabi *et al.*, 2002; Chami *et al.*, 2010; Pamidi *et al.*, 2011). Moreover, a study used a unique design in OSA individuals by applying CPAP during NREM sleep and removing it during REM sleep. They found that spatial navigation memory was impaired after this specific REM sleep disruption by OSA (Varga *et al.*, 2014).

In the present study, we found associations at a trend level between REM sleep OSA and worse cognitive performance in the complete sample and more depressive symptoms in subjects without moderate to severe OSA or without NREM sleep OSA. Moreover, when we used a group analysis with REM sleep OSA quartiles, subjects with more severe REM sleep OSA had a worse global cognitive performance than those with the lower REM sleep OSA severity level. Interestingly, worse cognitive performance with REM sleep OSA was observed only in analyses that included the complete sample with all levels of OSA severity, where reduced rCBF in the ventromedial prefrontal cortex was also observed. This suggests that the ventromedial prefrontal cortex may be involved in cognitive deficits associated with REM sleep OSA, and that a certain level of OSA severity may be necessary to observe clinically measurable cognitive deficits. In fact, the ventromedial prefrontal cortex is involved in various cognitive functions, including executive functions and memory (Zald and Andreotti, 2010). On the other hand, in subjects with REM sleep OSA exclusively, and thus, lower overall severity, reduced fronto-insular perfusion was observed concomitantly with a trend for more depressive symptoms. The insula is structurally included in the limbic system and plays a role in emotional behavior and feelings (Gasquoine, 2014). Therefore, the abnormal functioning in the insula during daytime may explain the trend for more depressive symptoms in relationship with REM sleep OSA in milder forms of OSA.

Only a fifth and a tenth of our sample showed cognitive deficits and mild depression levels, which may explain why trends were observed. These trends obviously need to be replicated in a sample that is more symptomatic. Indeed, compared to previous studies, our sample could be composed of OSA individuals with less clinical dysfunctions since a prevalence as high as 87 % for daytime sleepiness and 59 % for cognitive deficits were reported in other samples (Seneviratne and Puvanendran, 2004; Pierobon *et al.*, 2008).

As other authors have suggested (Grimaldi *et al.*, 2014; Mokhlesi *et al.*, 2014; Mokhlesi *et al.*, 2015; Alzoubaidi and Mokhlesi, 2016), we propose that individuals with several apneas and hypopneas during REM sleep, even with milder OSA forms, could benefit from treatment to reduce harmful effects to brain health. Consistently, continuous positive airway pressure (CPAP) was previously shown to be effective in reversing at least partially daytime rCBF changes in OSA individuals (Shiota *et al.*, 2014; Kim *et al.*, 2017). Moreover, many OSA patients treated with CPAP remove their mask before the end of the night, which is

where most REM sleep occurs. This could lead to up to 60 % of REM sleep untreated with an average CPAP use (Grimaldi *et al.*, 2014). A poor CPAP adherence near the morning could make these treated patients vulnerable to the effects of OSA during REM sleep. This is problematic since subjects with OSA exclusively during REM sleep have a lower adherence to CPAP than other OSA patients (Almeneessier *et al.*, 2017).

***Strengths and limitations***

To our knowledge, this is the first study to assess the specific effects of REM sleep OSA on brain health using neuroimaging. Our study adds to the current literature that underlines the detrimental effects of REM sleep OSA on physiological processes. The large sample investigated in this study, which included subjects with all levels of OSA severity, allowed us to investigate the specific effects of REM sleep OSA in milder cases.

REM sleep OSA was shown to be more prevalent in younger individuals and women (Pamidi *et al.*, 2011), two populations that are either not or only poorly represented in the present study. Nevertheless, sex was entered as a covariate in our additional analyses, and we found less but similar results.

***Conclusions***

We found that apneas and hypopneas during REM versus NREM sleep were associated with distinct patterns of daytime regional cerebral perfusion, with a hypoperfused ventromedial prefrontal and fronto-insular distribution associated with REM sleep OSA as well as a hypoperfused left sensorimotor and temporal cortex associated with NREM sleep OSA. Only REM sleep OSA was independently associated with altered rCBF during wakefulness in subjects with a milder OSA forms. Our results suggest that OSA during REM sleep could be more detrimental to brain health, as evidence by trends observed for worse cognitive performance and more depressive symptoms with more REM sleep OSA. Therefore, subjects with OSA predominantly during REM sleep, but with low overall OSA severity could benefit from treatment. As suggested by others (Grimaldi *et al.*, 2014; Mokhlesi *et al.*, 2014; Mokhlesi *et al.*, 2015; Alzoubaidi and Mokhlesi, 2016), prolonged use of CPAP therapy throughout the night may also be beneficial, as most REM sleep occurs near morning. However, before justifying treatment for all REM sleep predominant OSA patients, our results

need to be replicated in longitudinal treatment studies to obtain a more complete understanding of the impacts of REM sleep OSA on the brain.

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## 5.3. **Article 3 :** Gray matter hypertrophy and thickening with obstructive sleep apnea in middle-aged and older adults

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**Contribution de la candidate :** conception de l'étude, acquisition des données de sommeil et de neuroimagerie en laboratoire, analyses des données, interprétation des données, écriture et révision de l'article suite aux commentaires des co-auteurs, processus de soumission et de révision par les pairs auprès du journal scientifique.

## AT A GLANCE COMMENTARY

***Scientific Knowledge on the Subject***: Older individuals with obstructive sleep apnea are at risk of presenting cognitive decline and dementia. While previous studies investigated cerebral gray matter structure in obstructive sleep apnea, inconsistencies exist regarding the presence of changes and their specific locations in the brain. Furthermore, there is a lack of understanding regarding gray matter integrity in the aging population with obstructive sleep apnea since very few studies specifically evaluated this age group.

***What This Study Adds to the Field***: This study assessed the relationship between intrinsic markers of obstructive sleep apnea severity and multiple measures of cerebral gray matter structure in a large sample of middle-aged and older individuals. We found that the main markers of obstructive sleep apnea severity are related to increased thickness and/or volume of the frontal, parietal, and cingulate regions of the cortex as well as the amygdala. These results suggest that obstructive sleep apnea in the aging and mostly presymptomatic population is associated with underlying cerebral adaptive/reactive mechanisms.

**ABSTRACT**

**Rationale:** Obstructive sleep apnea causes intermittent hypoxemia, hemodynamic fluctuations, and sleep fragmentation, all of which could damage cerebral gray matter that can be indirectly assessed with neuroimaging.

**Objectives:** To investigate whether markers of obstructive sleep apnea severity are associated with gray matter changes among middle-aged and older individuals.

**Methods:** Seventy-one subjects (ages: 55 to 76; apnea–hypopnea index: 0.2 to 96.6 events/h) were evaluated with magnetic resonance imaging. Two techniques were used: *1)* voxel-based morphometry, which measures gray matter volume and concentration; *2)* FreeSurfer automated segmentation, which estimates the volume of predefined cortical/subcortical regions and cortical thickness. Regression analyses were performed between gray matter characteristics and markers of obstructive sleep apnea severity (hypoxemia, respiratory disturbances, sleep fragmentation).

**Measurements and Main Results:** Subjects had few symptoms, i.e. sleepiness, depression, anxiety and cognitive deficits. While no association was found with voxel-based morphometry, FreeSurfer revealed increased gray matter with obstructive sleep apnea. Higher levels of hypoxemia correlated with increased volume and thickness of the left lateral prefrontal cortex as well as increased thickness of the right frontal pole, the right lateral parietal lobules, and the left posterior cingulate cortex. Respiratory disturbances positively correlated with right amygdala volume while more severe sleep fragmentation was associated with increased thickness of the inferior frontal gyrus.

**Conclusions:** Gray matter hypertrophy and thickening were associated with hypoxemia, respiratory disturbances, and sleep fragmentation. These structural changes in a group of middle-aged and older individuals may represent adaptive/reactive brain mechanisms attributed to a presymptomatic stage of obstructive sleep apnea.

## INTRODUCTION

Repetitive airway collapses in obstructive sleep apnea (OSA) lead to chronic cycles of hypoxemia/reoxygenation and hypercapnia, hemodynamic fluctuations, and sleep fragmentation (Daulatzai, 2015). According to animal models, these pathophysiological processes have consequences on the brain by provoking oxidative stress, cellular death and cellular morphological modifications (Aviles-Reyes *et al.*, 2010; Almendros *et al.*, 2011; Nair *et al.*, 2011). Consequently, OSA may lead to structural cerebral gray matter changes. Considering that OSA is particularly common in the aging population (Daulatzai, 2015) and is a risk factor for accelerated cognitive decline (Osorio *et al.*, 2015) and dementia (Chang *et al.*, 2013), the relation between gray matter integrity and OSA severity in the older population must be assessed to deepen our understanding of its contribution to neurodegeneration.

In OSA, gray matter volume has been investigated predominantly in middle-aged adults using voxel-based morphometry (VBM). A recent meta-analysis showed that OSA correlates with a smaller parahippocampal and fronto-temporal cortex (Weng *et al.*, 2014). However, due to variations between studies (e.g. VBM pipeline, apnea-hypopnea index [AHI] thresholds), others argue that there is currently no clear evidence of gray matter atrophy (Celle *et al.*, 2016).

Since the sole use of VBM resulted in inconsistencies, its combination with alternative morphometric techniques could lead to a clearer picture of gray matter integrity in OSA. Few studies used other analysis techniques and gray matter characteristics. Regional cortical thinning and reduced gray matter concentration were reported in middle-aged individuals with OSA (Joo *et al.*, 2010; Joo *et al.*, 2013). Moreover, segmentation of predefined subcortical structures in OSA individuals showed gray matter atrophy (hippocampi, mammillary bodies, caudate nuclei) (Kumar *et al.*, 2008; Torelli *et al.*, 2011; Dusak *et al.*, 2013) but also hypertrophy (hippocampi, putamen) (Rosenzweig *et al.*, 2013; Kumar *et al.*, 2014a).

It is unclear whether OSA leads to altered structural gray matter integrity. This is especially true in the older population with OSA for whom gray matter integrity has not been assessed thoroughly. The present study focuses on late middle-aged and older individuals, and investigates the association between OSA severity and gray matter characteristics estimated with different analysis techniques: volume and concentration measured with VBM; and cortical thickness and cortical/subcortical volume assessed with FreeSurfer automated

segmentation. Instead of groups based on an arbitrary criterion to define OSA, we used a regression approach on a large sample with varying levels of OSA severity. The novelty of the study resides in the fact that it combines multiple analysis techniques and gray matter characteristics in association with multiple markers of OSA severity (hypoxemia, respiratory disturbances, and sleep fragmentation).

We hypothesized that all markers of OSA severity, but more particularly hypoxemia, would be linked to reduced gray matter in regions known to be sensitive to pathological processes observed in OSA (e.g. hippocampus and surrounding structures, prefrontal cortex) (Daulatzai, 2015). We also hypothesized that an alternative method to VBM, namely FreeSurfer automated segmentation, could be more sensitive to reveal how OSA affects specific brain regions. Preliminary results have been previously reported in abstract form (Baril *et al.*, 2016).

**METHODS**

An online supplement describes the protocol in detail. The study included 71 subjects who were either healthy controls or newly diagnosed and untreated individuals with OSA. Thirty-seven of them (52 %) participated in a previous study on cerebral perfusion in OSA (Baril *et al.*, 2015). Ten subjects were recruited from a clinic for suspected OSA while the remaining subjects were recruited through newspapers advertisements. Exclusion criteria were neurological, pulmonary, and major psychiatric diseases; sleep disorders other than OSA; OSA treatment including continuous positive airway pressure; uncontrolled diabetes and hypertension; morbid obesity; and medication affecting cerebral functioning. The Ethics Committees (#2012-697 and #12-13-008) approved the research protocol and written consent was obtained from each subject.

Subjects were evaluated with an all-night in-laboratory polysomnographic recording and 3-Tesla magnetic resonance imaging (MRI). Although the AHI is generally thought to represent OSA severity, its sole use has been challenged (Asghari and Mohammadi, 2013). Indeed, other variables related to oxygen saturation and sleep quality are also recognized as correlates of OSA severity. A principal component analysis was therefore used to extract independent markers of OSA severity, to reduce the number of statistical tests, and to prevent the multi-collinearity problem of highly correlated variables in a regression. Respiratory and

sleep variables that strongly correlated with the AHI ($p$ <0.001) were included in the principal component analysis. Although less-correlated variables could be of interest, they may not fully reflect OSA pathophysiology and are not as well suited for a principal component analysis. Resulting rotated and uncorrelated components represented hypoxemia, respiratory disturbances, and sleep fragmentation (see Table 1).

**Table 1.** Markers of OSA severity obtained with a principal component analysis of respiratory and sleep variables.

| **Respiratory and sleep variables** | **Components** | | |
|---|---|---|---|
| | Hypoxemia | Respiratory disturbances | Sleep fragmentation |
| Minimal $SpO_2$ (%) | **-0.867** | -0.330 | -0.188 |
| TST with $SpO_2$ <90 % (min) | **0.815** | 0.408 | 0.175 |
| Apnea–Hypopnea Index (events/h) | 0.389 | **0.877** | 0.221 |
| TST in apnea–hypopnea (%) | 0.401 | **0.852** | 0.265 |
| Micro-arousal index (events/h) | -0.002 | 0.404 | **0.816** |
| Number of stage transitions to NREM1 and wakefulness | 0.437 | 0.050 | **0.803** |
| Accounted variance (%) | 32.0 % | 32.3 % | 24.9 % |

Bold variables show how variable loads on each rotated component. Loadings >0.5 were considered to be variables that contribute the most to the component. OSA, obstructive sleep apnea; $SpO_2$, oxygen saturation; TST, total sleep time; NREM1, non-rapid eye movement sleep stage 1.

Figure 1 depicts the neuroimaging analysis techniques used, i.e., VBM and FreeSurfer automated segmentation. VBM was performed in accordance with published recommendations (Celle *et al.*, 2016). T1-weighted MRI images were processed with the VBM8 toolbox (http://www.neuro.uni-jena.de/) within SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Default processing options were used to run the pipeline, including a spatial normalization that deformed every subject into a common space. The pipeline was run once with and once without modulation, which rescales images and transforms gray matter concentration into volume (Mechelli *et al.*, 2005). A multiple regression design within SPM8 was performed between markers of OSA severity (hypoxemia, respiratory disturbances, and sleep fragmentation) and both gray matter volume and

concentration, adjusted for age, sex, body mass index, and intracranial volume. Level of significance was set at $p$ <0.05, clusters corrected for multiple comparisons with topological false-discovery rate.

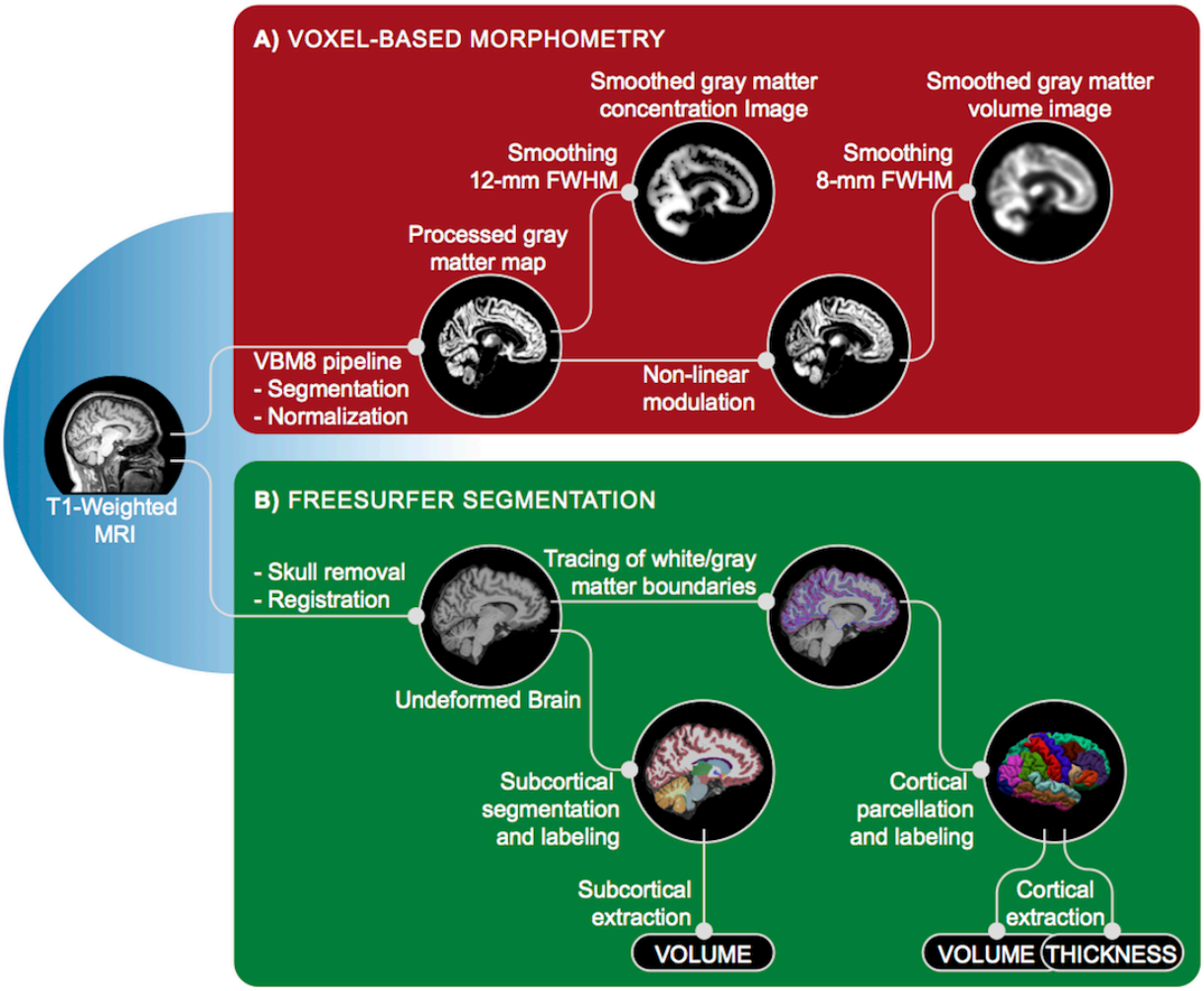


**Figure 1.** Processing steps for estimating gray matter characteristics using VBM (A) and FreeSurfer (B).
T1-weighted MRI images were used for both VBM and FreeSurfer analyses. In order to conduct VBM analyses (A), images were first segmented and normalized into a common space. A non-linear modulation was performed to obtain volume and final volume and concentration images were smoothed. In summary, the VBM processing pipeline segments and deforms gray matter to allow inter-subject comparisons for both gray matter concentration and volume in every voxel. For FreeSurfer analyses (B), non-brain tissues were first removed and a registration was performed. The brain was segmented according to voxel intensities and a probabilistic atlas to extract subcortical volumes. White- and gray matter boundaries were traced and the cortex was parcelled and labeled based on folding pattern and a probabilistic atlas. Thus, FreeSurfer outputs are undeformed cortical/subcortical volume as well as cortical thickness of regions predefined by built-in atlases. Overall, both analysis techniques

work differently to estimate gray matter characteristics: with VBM, the brain was deformed and gray matter was compare at each voxel. With FreeSurfer automated segmentation, gray matter values are averaged over regions labeled in the undeformed brain according to built-in atlases. VBM images and FreeSurfer extracted values correspond to final processed variables used in multiple regression analyses with markers of OSA severity. FWHM, full-width half maximum; MRI, magnetic resonance imaging; VBM, voxel-based morphometry; OSA, obstructive sleep apnea.

MRI images were also processed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/), which features the volumetric segmentation of subcortical structures (Fischl *et al.*, 2002) and the parcellation of the cortical surface (Fischl *et al.*, 2004) without a deforming spatial normalization. Cortical/subcortical volume and cortical thickness values from predefined brain regions were extracted for each subject. Hierarchical linear regressions for extracted FreeSurfer values were performed with age, sex, body mass index, and intracranial volume as covariates (Step 1) and with markers of OSA severity (hypoxemia, respiratory disturbances, and sleep fragmentation; Step 2). Level of significance was set at $p < 0.01$ for $R^2$ changes, i.e., the increase in variance explained by adding OSA variables to covariates, and $p < 0.01$ for predicting markers of OSA severity.

## RESULTS

### *Clinical characteristics of the sample*

Seventy-eight subjects were evaluated with an MRI. A neuroradiologist inspected the MRI images, which led to the exclusion of six subjects for major abnormalities such as silent infarcts or large arachnoid cysts. Another subject was excluded due to a processing problem, for a total of seven exclusions after the MRI.

**Table 2.** Clinical and polysomnographic characteristics of healthy control, mild, moderate and severe OSA groups.

| Variables | Groups | | | | One-way ANOVA | |
|---|---|---|---|---|---|---|
| | Control **(A)** AHI <5 | Mild OSA **(B)** AHI ≥5 to <15 | Moderate OSA **(C)** AHI ≥15 to <30 | Severe OSA **(D)** AHI ≥30 | $F/X^2$ | **Post-hoc tests** |
| Number of subjects | n = 12 | n = 30 | n = 11 | n = 18 | | |
| Sex* (#F; %F) | 2F; 16.7 % | 10F; 33.3 % | 1F; 9.1 % | 3F; 16.7 % | 3.7 | |
| Age (years) | 62.3 (4.7) | 65.8 (5.9) | 65.9 (5.1) | 66.1 (5.7) | 1.4 | |
| Body mass index ($kg/m^2$) | 26.5 (3.9) | 26.5 (3.1) | 27.9 (2.1) | 28.7 (2.6) | 2.6 | |
| Epworth Sleepiness Scale | 6.5 (4.8) | 7.2 (4.8) | 9.7 (4.8) | 8.2 (4.6) | 0.6 | |
| Beck Depression Inventory | 3.2 (3.7) | 5.3 (4.9) | 6.2 (5.2) | 7.6 (5.9) | 1.8 | |
| Beck Anxiety Inventory | 4.3 (5.3) | 3.1 (3.3) | 3.2 (4.5) | 4.0 (4.1) | 0.2 | |
| Montreal Cognitive Assessment | 27.4 (2.4) | 27.5 (2.0) | 27.5 (2.4) | 26.9 (2.6) | 0.3 | |
| Mini-Mental State Examination | 28.1 (2.3) | 29.0 (1.0) | 28.2 (1.8) | 29.2 (1.0) | 2.6 | |
| Index of Vascular Burden | 0.8 (0.8) | 1.0 (1.1) | 1.0 (0.9) | 0.9 (0.8) | 0.1 | |
| % hypercholesterolemia* | 25.0 | 36.7 | 36.4 | 44.4 | 1.2 | |
| % hypertension* | 41.7 | 40.0 | 54.6 | 39.0 | 0.8 | |
| ***Respiratory variables*** | | | | | | |
| AHI (events/h) | 2.1 (1.5) | 9.2 (2.5) | 22.2 (4.8) | 45.1 (19.5) | 180.8‡ | A<B<C<D |
| TST in apnea–hypopnea (%) | 1.2 (1.1) | 5.7 (2.0) | 12.8 (1.9) | 31.5 (15.5) | 147.8‡ | A<B<C<D |
| Mean $SpO_2$ (%) | 95.5 (0.6) | 94.6 (1.2) | 93.7 (0.7) | 94.2 (1.2) | 6.1† | A>C, D |
| Minimal $SpO_2$ (%) | 90.5 (3.3) | 88.5 (3.3) | 83.6 (3.8) | 81.5 (5.9) | 16.3‡ | A, B>C, D |
| TST with $SpO_2$ <90 % (min) | 0.1 (0.1) | 2.0 (5.7) | 5.5 (3.8) | 17.6 (18.6) | 26.2‡ | A, B<C, D |
| ***Sleep variables*** | | | | | | |
| TST (min) | 369.2 (60.7) | 341.5 (64.5) | 370.9 (43.9) | 368.5 (46.0) | 1.4 | |
| Wake duration (min) | 100.8 (44.6) | 101.3 (57.5) | 80.2 (46.4) | 91.6 (54.0) | 0.6 | |
| Sleep efficiency (%) | 78.5 (9.0) | 77.2 (12.6) | 82.6 (9.1) | 80.6 (10.0) | 0.8 | |
| Micro-arousal index (events/h) | 12.0 (3.9) | 14.3 (6.1) | 14.3 (5.7) | 25.2 (11.2) | 8.8‡ | A, B, C<D |
| # of stage transitions to NREM1 and wakefulness | 56.9 (19.2) | 55.1 (15.0) | 66.8 (19.0) | 97.8 (41.8) | 9.6‡ | A, B<D |

Results are presented as mean (standard deviation). OSA, obstructive sleep apnea; AHI, apnea–hypopnea index; F, females; TST, total sleep time; $SpO_2$, oxygen saturation; NREM1, non-rapid eye movement sleep stage 1. * $X^2$ tests were performed between groups; † $p < 0.05$; ‡ $p < 0.001$.

The final sample was composed of 71 subjects ranging in age from 55 to 76 (mean age: 65.3 ± 5.6 years). Although the objective of the study was answered with a regression design across the complete sample, subjects were divided into four groups based on their AHI and one-way ANOVAs were performed to better characterize our sample' characteristics (see Table 2). Healthy control subjects (AHI <5) represented 17 % of the sample, 42 % were included in the mild OSA group (AHI between ≥5 and <15), 16 % were included in the moderate OSA group (AHI between ≥15 and <30), and 25 % were individuals considered to have severe OSA (AHI ≥30). The AHI varied from 0.2 to 96.6 events/h and 35 % of the final sample had an OSA-related complaint and/or had suspected OSA before joining the study (e.g., snoring, daytime sleepiness, lack of energy, bed partner witnessing respiratory disturbances).

Groups were statistically comparable for the Epworth Sleepiness Scale, the Beck Depression and Anxiety Inventories, the Montreal Cognitive Assessment, the Mini-Mental State Examination, and the Index of Vascular Burden (see Table 2). Markers of OSA severity extracted with the principal component analysis (see Table 1) did not correlate with any of these questionnaires and tests. In fact, a minority of mild to severe OSA subjects had excessive daytime sleepiness (33 % with Epworth Sleepiness ≥10), depressive symptoms (26 % with Beck Depression Inventory II ≥10), anxiety symptoms (12 % with Beck Anxiety Inventory ≥10) and cognitive deficits (16 % with Montreal Cognitive Assessment <26). In summary, this suggests that our participants were not highly symptomatic in terms of sleepiness, mood, and global cognition, and that this symptomatology was not related to OSA severity. Moreover, a minority of OSA subjects was obese (25 % with a body mass index ≥30 $kg/m^2$) or had more than one cardiovascular risk factor and disease (31 % with an Index of Vascular Burden >1).

***Gray matter hypertrophy and thickening with OSA severity***

VBM revealed no significant association between OSA severity and clusters of gray matter volume or concentration at a false-discovery rate corrected threshold ($p$ <0.05).

Conversely, with FreeSurfer automated segmentation, significant regression models revealed increases, but no decrease, in cortical thickness and volume associated with markers of OSA severity (see Table 3, Figure 2, and Figure E1 of the online supplement). The majority

of significant models were of increased cortical thickness in relation to the level of hypoxemia. More severe hypoxemia was associated with increased thickness of the left rostral middle frontal gyrus, the right frontal pole, the right superior and inferior parietal lobules, and the left posterior cingulate cortex. Hypoxemia levels were also positively correlated with the volume of the left pars orbitalis portion of the inferior frontal gyrus. Moreover, higher levels of respiratory disturbances were associated with a hypertrophic right amygdala whereas an increased level of sleep fragmentation was correlated with a thicker pars triangularis region of the right inferior frontal gyrus.

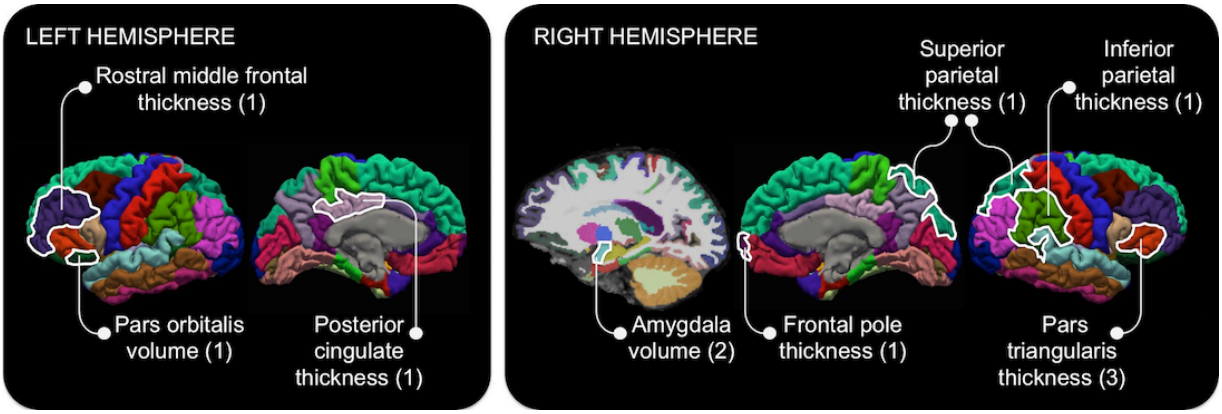


**Figure 2.** Locations of increased gray matter estimated with FreeSurfer automated segmentation in association with markers of OSA severity.

Hypoxemia [1] was positively correlated with the volume of the left pars orbitalis of the inferior frontal gyrus and the thickness of the left rostral middle frontal gyrus, the left posterior cingulate cortex, and the right frontal pole, as well as the right superior and inferior parietal lobules. Moreover, higher levels of respiratory disturbances [2] were associated with a larger right amygdala while more severe sleep fragmentation [3] was correlated with an increased thickness of the right pars triangularis of the inferior frontal gyrus. Regression analyses included age, sex, body mass index, and intracranial volume as nuisance covariates. OSA, obstructive sleep apnea.

**Table 3.** Significant hierarchical linear regressions between markers of OSA severity and regions of increased gray matter volume and thickness segmented automatically with FreeSurfer.

| Brain regions | | Step 1: Nuisance covariates | Age | Sex | BMI | ICV | Step 2: OSA severity | Hypoxemia | Respiratory disturbances | Sleep fragmentation |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Subcortical volume*** | | | | | | | | | | |
| R amygdala | $R^2$ | 31.9 %† | | | | | 47.9 %† | | | |
| | $\Delta R^2$ | | | | | | 16.0 %† | | | |
| | β | | -0.07 | 0.01 | 0.05 | 0.52† | | -0.06 | **0.39†** | 0.16 |
| ***Cortical volume*** | | | | | | | | | | |
| L pars orbitalis (inferior frontal) | $R^2$ | 11.8 % | | | | | 30.0 %† | | | |
| | $\Delta R^2$ | | | | | | 18.3 %† | | | |
| | β | | -0.03 | 0.05 | -0.08 | 0.30 | | **0.44†** | -0.02 | -0.12 |
| ***Cortical thickness*** | | | | | | | | | | |
| L rostral middle frontal gyrus | $R^2$ | 8.9 % | | | | | 29.4 %† | | | |
| | $\Delta R^2$ | | | | | | 20.5 %† | | | |
| | β | | -0.24 | -0.02 | 0.11 | -0.23 | | **0.47†** | 0.13 | 0.02 |
| R frontal pole | $R^2$ | 0.0 % | | | | | 19.1 % | | | |
| | $\Delta R^2$ | | | | | | 18.8 %† | | | |
| | β | | 0.00 | -0.00 | 0.03 | -0.06 | | **0.45†** | 0.11 | 0.03 |
| R pars triangularis (inferior frontal) | $R^2$ | 6.5 % | | | | | 22.9 % | | | |
| | $\Delta R^2$ | | | | | | 16.5 %* | | | |
| | β | | -0.16 | 0.11 | 0.18 | -0.15 | | 0.23 | 0.17 | **0.32*** |
| R superior parietal lobule | $R^2$ | 7.7 % | | | | | 24.3 % | | | |
| | $\Delta R^2$ | | | | | | 16.7 %* | | | |
| | β | | -0.11 | 0.03 | 0.22 | 0.04 | | **0.40†** | 0.17 | 0.09 |
| R inferior parietal lobule | $R^2$ | 3.8 % | | | | | 20.8 % | | | |
| | $\Delta R^2$ | | | | | | 17.0 %* | | | |
| | β | | -0.17 | 0.00 | 0.09 | -0.08 | | **0.43†** | 0.13 | -0.08 |
| L posterior cingulate cortex | $R^2$ | 5.9 % | | | | | 23.7 % | | | |
| | $\Delta R^2$ | | | | | | 17.8 %† | | | |
| | β | | -0.08 | -0.18 | 0.15 | -0.03 | | **0.36†** | 0.29 | 0.08 |

Bold variables show the predicting OSA component for each region of increased gray matter. OSA, obstructive sleep apnea; BMI, body mass index; ICV, intracranial volume; $\Delta R^2$; $R^2$ change; R, right; L, left. *p <0.01; †p <0.005.

***Complementary results of gray matter hypertrophy and thickening with OSA severity***

Interestingly, similar positive associations were observed at a trend level with FreeSurfer ($R^2$ change between $p$ <0.05 and $p$ >0.01; predicting OSA components $p$ <0.01; β values between 0.24 and 0.40) for contralateral cortical regions in relation to hypoxemia levels (thickness of the right rostral middle frontal gyrus, left inferior parietal lobule, and right posterior cingulate cortex) as well as for subcortical regions in association with more respiratory disturbances (volume of the left amygdala, hippocampus, and thalamus).

To assess whether gray matter structure is associated with markers of OSA severity even in milder forms of OSA, analyses were conducted among control subjects and mild to moderate groups (AHI <30). With FreeSurfer, increased gray matter was found in relation to hypoxemia in several fronto-parietal regions and respiratory disturbances in left thalamus and precuneus (see online supplement).

## DISCUSSION

This study investigated the association between markers of OSA severity and gray matter integrity in untreated individuals aged 55 and over. We found that higher levels of hypoxemia during sleep were associated with increased volume and/or thickness of the prefrontal, parietal, and cingulate regions of the cortex. Moreover, a higher number of respiratory disturbances was associated with an enlarged amygdala whereas a more fragmented sleep was correlated to a thicker frontal cortex. Our hypothesis was only partially confirmed since we predicted that atrophied gray matter would be associated with increased OSA severity. The novelty of this study lies not only in its results, but also in the use of specific markers of OSA severity in relation with multiple cerebral gray matter characteristics.

***Potential mechanisms underlying gray matter increases with OSA severity***

It would be surprising that gray matter increases underlie better neuron viability or neurogenesis. Indeed, neurogenesis in the adult brain is less probable outside the hippocampus, the subventricular zone and the olfactory bulb (Riddle and Lichtenwalner, 2007). Gray matter hypertrophy and thickening may instead result from cerebral edema, a well-known effect of hypoxemia that can be observed after only 16 h in protocols imitating

altitude in humans (Kallenberg *et al.*, 2007). Consistently, a diffusion MRI study in individuals with newly diagnosed OSA suggested the presence of vasogenic edema in subcortical structures (Emin Akkoyunlu *et al.*, 2013). In addition to edema, hypoxia causes changes in cellular size or quantity with the potential to enlarged gray matter. In fact, studies on rodents subjected to intermittent hypoxia during their sleep (1 to 10 days and 5 weeks respectively) showed increased brain water content, branching of surviving neurons, as well as astroglial hyperplasia and/or hypertrophy (i.e., reactive gliosis) (Aviles-Reyes *et al.*, 2010; Baronio *et al.*, 2013). Increased gray matter in relation to hypoxemia levels could also be representative of early neurodegeneration processes. Multiple animal models of hypoxic exposure (from few hours to several days) consistently showed increased β-amyloid generation (Daulatzai, 2015), a pathogenic mechanism of Alzheimer's disease. β-amyloid deposition in the absence of abnormal tau levels was recently reported to correlate with increased cortical thickness (Fortea *et al.*, 2014).

Overall, intermittent hypoxemia is probably a key mechanism leading to cerebral edema, cellular responses and early neurodegeneration in gray matter. This is consistent with our findings since most regions with increased gray matter were associated with hypoxemia levels. Similarly, hypoxemia strongly correlated with gray matter increases even when subjects with severe OSA were removed from the analysis, confirming that milder forms of OSA are also associated with gray matter changes in our sample. At the clinical level, it suggests that intermittent hypoxemia may be particularly important to consider when making decision for treatment, even in patients with AHI below 30.

In addition to the relationship between hypoxemia and gray matter characteristics, respiratory disturbances and sleep fragmentation were also associated with gray matter hypertrophy or thickening in the present study. Changes in breathing pattern due to obstructions and sleep fragmentation were shown to be both independently associated with blood pressure fluctuations (Orban *et al.*, 2008; Chouchou *et al.*, 2013), which could lead to cerebral edema (Skalidi *et al.*, 2013). Furthermore, experimental obstructive apneas and sleep fragmentation may distinctly provoke cellular responses through various mechanisms, such as cerebral oxidative stress (Almendros *et al.*, 2011; Nair *et al.*, 2011). However, the specific effects of respiratory disturbances and sleep fragmentation are less understood than the effects of intermittent hypoxemia.

***Increases versus decreases of gray matter structure in OSA***

Although the existing literature mostly reports gray matter losses among individuals with OSA (Kumar *et al.*, 2008; Joo *et al.*, 2010; Torelli *et al.*, 2011; Dusak *et al.*, 2013; Joo *et al.*, 2013; Weng *et al.*, 2014; Celle *et al.*, 2016), gray matter hypertrophy has also been observed (Rosenzweig *et al.*, 2013; Fatouleh *et al.*, 2014; Kumar *et al.*, 2014a; Lundblad *et al.*, 2014; Lin *et al.*, 2016). The same pattern is shown with the effect of OSA treatment on gray matter. In one set of studies, treatment led to gray matter hypertrophy, suggesting a recovery from atrophic processes (Canessa *et al.*, 2011; Rosenzweig *et al.*, 2016), while others showed that OSA treatment reduced either regional gray matter or whole brain volume (O'Donoghue *et al.*, 2005; Lin *et al.*, 2016), suggesting reversal of hypertrophic processes such as brain edema.

Increased gray matter may represent a presymptomatic stage of the OSA disease process where its severity is characterized by reactive and adaptive brain mechanisms, such as cerebral edema, reactive gliosis, neuronal branching, and increased β-amyloid deposition. Later in the disease progression, gray matter atrophy could represent predominantly neuronal damage due to chronic OSA and lead to cognitive decline. Both adaptive and maladaptive effects on the brain have consistently been described for processes that follow cycles of airway obstructions and reoxygenation (Rosenzweig *et al.*, 2015). Our sample had low levels of symptoms, namely sleepiness, mood and cognitive deficits, which reflect that most subjects were in a presymptomatic stage of OSA that may be characterized by more adaptive brain responses and thus, increased gray matter. Obviously, these hypotheses must be confirmed.

OSA duration might affect the balance between adaptive and maladaptive mechanisms, but it is generally unknown. In hypoxic rodent and human protocols that observed mechanisms that could underlie increased gray matter, exposure to hypoxia was relatively short (from a few hours to several days) (Kallenberg *et al.*, 2007; Aviles-Reyes *et al.*, 2010; Baronio *et al.*, 2013; Daulatzai, 2015). Gray matter hypertrophy and thickening could therefore be present in an earlier stage of the disease, although duration of hypoxic exposure in rodent and human protocols is difficult to translate to OSA in a clinical setting.

Age could also determine whether atrophy or hypertrophy is observed in reaction to OSA. In fact, OSA in older adults is possibly different in terms of mechanisms, comorbidities,

consequences, and symptoms compared to younger patients. Age is associated with partially protective mechanisms against OSA, such as reduced production of oxidative stress following apneas (Dalmases *et al.*, 2014) and decreased blood pressure and heart rate responses following arousals (Goff *et al.*, 2008). Adaptive effects of hypoxia on the brain could lead to relative cerebrovascular protection and reduced mortality risk in subjects over age 50 with OSA compared to their younger counterparts (Lavie and Lavie, 2006). Therefore, a different response to OSA could occur with age and its severity may be correlated with increases in gray matter structure. Very few studies have specifically evaluated gray matter in subjects over age 50. These had very different designs and objectives, and thus, diverging results (Celle *et al.*, 2009; Dalmases *et al.*, 2015b; Sforza *et al.*, 2016). Therefore, how OSA impacts the aging brain must be clarified.

***Vulnerability of specific brain regions to OSA***

In the present study, markers of OSA severity were associated with increased thickness or volume in the lateral prefrontal cortex, the parietal lobules, and posterior cingulate cortex as well as the amygdala. Interestingly, previous studies on OSA showed both increased and decreased gray matter volume and/or thickness in the same or adjacent regions as those reported in the present study (Macey *et al.*, 2002; Torelli *et al.*, 2011; Dusak *et al.*, 2013; Joo *et al.*, 2013; Rosenzweig *et al.*, 2013; Zhang *et al.*, 2013; Fatouleh *et al.*, 2014; Kumar *et al.*, 2014a; Lundblad *et al.*, 2014; Lin *et al.*, 2016). Therefore, these regions may be especially vulnerable to OSA and be preferentially affected by both swelling and atrophic processes. It is also important to highlight that we found trends for association between OSA markers of severity and increased gray matter in contralateral brain regions. It would be interesting to follow this cohort in order to verify whether these trends will reach significance over time.

Hypoxemia and sleep fragmentation correlated with the structure of the lateral prefrontal cortex in our study. It has been suggested that the prefrontal cortex is vulnerable to both hypoxemia and sleep disruption in OSA (Beebe and Gozal, 2002). In addition, our results showed that hypoxemia was associated with core constituents of the default mode network, namely the parietal and posterior cingulate regions of the cortex. The metabolic activity of these highly connected regions fluctuates together (Passow *et al.*, 2015) and their elevated oxygen demand could make them more vulnerable to hypoxemia (Raichle *et al.*, 2001).

Finally, we found that amygdala volume was linked to respiratory disturbances, which is consistent with its altered activity during a respiratory challenge in OSA subjects (Harper *et al.*, 2003).

***Utility of complementary gray matter analysis techniques and characteristics***

While the most widely used technique for gray matter analysis is VBM, we observed no changes with this method, a result supported by previous studies on OSA (O'Donoghue *et al.*, 2005; Innes *et al.*, 2015). VBM has limitations including misregistration and reduced accuracy of region location (Mechelli *et al.*, 2005). This might be exacerbated by ventricular expansion caused by global atrophy in normal aging, in which processing errors could lead to false results in regions surrounding the ventricles. FreeSurfer automated segmentation may be more sensitive in detecting early changes in OSA than a voxel-based approach, since volume and thickness are computed by region without a prior spatial normalization. Instead, the brain is labeled and segmented in an automated manner similar to manual volumetry (Fischl *et al.*, 2002; Fischl *et al.*, 2004), which probably represent more closely the real structure. However, FreeSurfer automated segmentation is time-consuming and depends on predefined atlases.

VBM and FreeSurfer segmentation show results on different scales. While VBM investigates the brain voxel by voxel (1.5 $mm^3$), the predefined regions extracted with FreeSurfer are much larger. This suggests that increases in gray matter with OSA severity are subtle and diffuse across a given brain structure, which could have been missed in some previous VBM studies. In addition, more regions of increased thickness than volume were observed with FreeSurfer, a result that may also have been missed with VBM. Overall, FreeSurfer automated segmentation and its measurement of cortical thickness seems to be more sensitive to detect gray matter increases with OSA severity than VBM. However, our results must be replicated by further studies in the older population with OSA.

***Strengths and limitations***

Our large sample size of 71 subjects with an AHI varying from 0.2 to 96.6 events/h represent the entire spectrum of OSA severity, which allowed a regression approach. This eliminated the need for an arbitrary criterion to define the presence of the condition that is necessary for a between-group design, leading to inconsistencies between studies. A

regression design also allowed us to investigate different markers of OSA severity. Moreover, the use of different analysis techniques and gray matter characteristics yielded a more complete evaluation of gray matter in OSA.

Nonetheless, the fact that most of our subjects were not severely hypoxic (see Table 2) and were mostly presymptomatic restricts the generalization of our results to other individuals with OSA. Although our strict exclusion criteria facilitate the interpretation of our findings by excluding many confounding conditions, they could limit the generalization of our results to individuals presenting OSA and comorbidities.

Although we included sex as a nuisance covariate, women with OSA may present more maladaptive than adaptive cerebral processes. In fact, compared to males with comparable OSA severity, females have impaired white matter integrity (Macey *et al.*, 2012). Since we investigated only 16 females (23 % of our sample), this could explain the difference between our results and the study by Celle et al. (Celle *et al.*, 2009), which showed brainstem atrophy among mostly women (64 %) in a similar age group.

### *Conclusions*

Our study revealed that markers of OSA severity, i.e. hypoxemia, respiratory disturbances, and sleep fragmentation, are linked to increases in cortical thickness and gray matter volume that are more sensitively detected with a technique alternative to VBM, namely FreeSurfer automated segmentation. OSA severity, especially hypoxemia, could contribute to gray matter hypertrophy and thickening through local edema and reactive cellular responses. These structural changes in frontal, parietal, and cingulate regions of the cortex and in the amygdala may be possible in presymptomatic and/or older subjects with OSA, among whom more adaptive than maladaptive mechanisms may occur. Longitudinal investigations are needed to determine whether increased gray matter structure will later show atrophy and be associated with cognitive decline in order to deepen our understanding of the link between OSA and neurodegeneration in the aging population.

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## SUPPLEMENTARY MATERIAL

## DETAILED METHODS

### *Overview of the protocol*

Individuals with obstructive sleep apnea (OSA) and healthy control subjects were either recruited from a Sleep apnea clinic's waiting list for suspected OSA or by advertisements in local newspapers. During a phone interview, subjects who fulfilled our study criteria and were within our age group of interest were invited to the laboratory for the screening process that included questionnaires and a polysomnographic recording. Subjects' medical history was evaluated using a homemade structured questionnaire. Weight and height were measured to calculate body mass index. All subjects filled out the Epworth Sleepiness Scale (Johns, 1991), the Beck Depression Inventory-II (Beck *et al.*, 1996), and the Beck Anxiety Inventory (Beck *et al.*, 1988) for levels of sleepiness, depression, and anxiety respectively. The Index of Vascular Burden (Villeneuve *et al.*, 2009) was completed to document vascular risk factors as well as cardiovascular and cerebrovascular diseases, i.e., hypertension or hypotension, hypercholesterolemia and dyslipidemia, diabetes, carotid stenosis, coronary diseases, angina pectoris, myocardial infarction, coronary artery bypass, arrhythmia, and transitory ischemic attacks. The Montreal Cognitive Assessment (Nasreddine *et al.*, 2005) and the Mini-Mental State Examination (Folstein *et al.*, 1983) were also completed. Subjects that were not excluded after this screening process were invited to a magnetic resonance imaging (MRI) acquisition. Written consent was obtained from each participant. The research protocol was approved by the *Hôpital du Sacré-Coeur de Montréal* (#2012-697) and by the *Institut universitaire de Gériatrie de Montréal* (#12-13-008) ethics committees.

### *Sample*

Exclusion criteria were: 1) diseases affecting the brain (e.g., neurological and psychiatric diseases, dementia, epilepsy, clinical history of stroke, traumatic brain injury); 2) a Montreal Cognitive Assessment score <23 and a Mini-Mental State Examination score <25 (Wang *et al.*, 2013); 3) any pulmonary diseases (e.g., asthma, chronic obstructive pulmonary disease); 4) sleep disorders other than OSA (e.g., restless leg syndrome, rapid-eye movement sleep behavior disorder, parasomnias, diagnosed insomnia); 5) uncontrolled diabetes or

hypertension; 6) morbid obesity (body mass index ≥40 kg/m$^2$); 7) OSA treatment with continuous positive airway pressure or a mandibular advancement device; and 8) the use of medication and/or drugs known to influence cognition, sleep, or cerebral functioning. Exclusion criteria were investigated with the phone interview and during the screening process that included questionnaires and the in-laboratory polysomnography (see below).

Eighty-four subjects were invited to the screening process after the phone interview. Six subjects were excluded at the screening process for early dementia, asthma, chronic obstructive pulmonary disease, rapid-eye movement sleep behavior disorder, or central sleep apnea. Seventy-eight subjects were therefore invited to the MRI procedure (see below). In order to exclude major brain abnormalities, a neuroradiologist visually inspected T1-weighted images (see below) in addition to T2-weigthed and Fluid Attenuated Inversion Recovery sequences (not described). Following this inspection, six subjects were excluded for major brain abnormalities: extensive white matter damage or extensive atrophy that is uncharacteristic and abnormal for the subject's age; silent infarcts; meningioma, and large arachnoid cyst. During neuroimaging processing steps, another subject had processing problems impossible to fix and was excluded from all analyses. In summary, a total of 13 subjects were excluded either at screening or after the MRI acquisition. These subjects were excluded from all analyses and are not represented on any table and figure.

The final sample was composed of 71 subjects. Among them, 10 subjects were recruited from a Sleep apnea clinic's waiting list for suspected OSA while 61 subjects were recruited by advertisements in local newspapers. Fifteen of the 61 subjects recruited by advertisements (25 %) had an OSA-related complaint (e.g., snoring, daytime sleepiness, lack of energy, bed partner witnessing respiratory disturbances). Overall, 25 of the 71 included subjects (35 %) had an OSA-related complaint and/or suspected OSA before joining the study. All subjects with OSA were newly diagnosed and untreated. Thirty-seven subjects (52 %) were also included in a previously published paper by our group that investigated regional cerebral perfusion in OSA subjects (Baril *et al.*, 2015). Parts of the present method is also reported in our previous study (Baril *et al.*, 2015), namely exclusion criteria, questionnaires and polysomnographic recording details.

***Polysomnographic recording***

The polysomnography protocol was published previously (Baril *et al.*, 2015). Briefly, all subjects underwent an in-laboratory all-night polysomnographic recording with an 18-electroencephalogram channel montage that also included electrooculograms, electromyograms, and an electrocardiogram. Respiratory events were recorded using thoraco-abdominal strain gauges, an oronasal canula, a thermal sensor, and a transcutaneous finger pulse oximeter to measure oxygen saturation. Sleep and respiratory events were scored according to the rules of the American Academy of Sleep Medicine by an experienced medical electrophysiology technologist (Iber *et al.*, 2007; Berry *et al.*, 2012). An apneic episode was defined as a reduction in airflow of ≥90 % from baseline lasting ≥10 s. A hypopneic episode was defined as a reduction in airflow of ≥30 % from baseline lasting ≥10 s accompanied either by an oxygen desaturation ≥3 % or by an electroencephalogram arousal.

***MRI acquisition parameters***

With a Magnetom TRIO 3 Tesla MRI scanner (*Siemens Healthcare, USA*), a three-dimensional T1-weighted Turbo Flash multi-echo Magnetization-prepared rapid gradient-echo (MPRAGE) was acquired with a 32-channel head coil using the parameters from the Massachusetts General Hospital (*Boston, Massachusetts, USA*). Acquisition parameters were: repetition time=2530 ms / root mean square of 4 echo times=1.64 ms, 3.50 ms, 5.36 ms, 7.22 ms; matrix size=256x256; field of view=256x256 mm; voxel size=1.0 mm isotropic, flip angle=7 º; and 176 sagittal orientations, pixel bandwidth=651 Hz/Px. Subjects were instructed to stay awake and the T1-weighted sequence was performed first before other sequences (not described). Overall, the T1 acquisition lasted 6 minutes and 13 seconds.

***Overview of analysis techniques and processing steps to assess gray matter***

Figure 1 of the published paper shows processing steps for both techniques, namely voxel-based morphometry (VBM) and FreeSurfer automated segmentation. While the aim of both analysis techniques is to estimate gray matter characteristics, they achieved that goal through different processing steps. For VBM, the two main steps are segmentation and normalization. Segmentation attributes a gray matter probability to each brain voxel based on MRI signal intensity, from 0 (no gray matter) to 1 (exclusively gray matter). VBM use these

gray matter probability values to perform statistical analyses at each brain voxel. However, in order to be able to compare voxels in a group of individuals, we performed a spatial normalization that deforms (stretch or compress) every voxel to make the brain of each subject fit a common space. This procedure allowed inter-subject comparisons in every voxel for both gray matter concentration and volume.

The FreeSurfer automated segmentation works differently. Based on both MRI signal intensity and a built-in probabilistic atlas, FreeSurfer attributes an anatomic label to each subcortical voxel. The summation of all voxels with the same label gives the gray matter volume of each subcortical structure. For the cortex, FreeSurfer works by tracing boundaries (gray matter, white matter, cerebrospinal fluid) based on the MRI signal. Based on a built-in probabilistic atlas and how the cortex is folded, FreeSurfer can then label all portions of these gray and white matter boundaries. Gray matter volume and averaged cortical thickness are calculated for each brain region that has the same label. Overall, FreeSurfer outputs correspond to undeformed volume and thickness of brain regions predefined by built-in atlases.

***Detailed voxel-based morphometry processing steps***

MRI T1-weighted images were processed with the VBM8 toolbox (http://www.neuro.uni-jena.de; *Christian Gaser, Departments of Psychiatry and Neurology, University of Jena, Germany)* integrated in SPM8 (http://www.fil.ion.ucl.ac.uk/%20spm/software/spm8/; *Statistical Parametric mapping 8, Wellcome Department of Imaging Neurosciences, Institute of Neurology, University College London, UK*) and MatLab R2014a (*version 8.3, The MathWorks, Natick, MA, USA*). The VBM8 toolbox is an update on the so-called "optimized VBM". Default processing options were used to run the VBM8 pipeline for every subject. Briefly, the processing pipeline includes the removal of non-brain tissues using "New Segment" and the segmentation of images into gray matter, white matter and cerebrospinal fluid according to probability maps. An affine registration to the Montreal Neurological Institute (MNI) is performed followed by a high-dimensional Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) spatial normalization (Ashburner, 2007). This step deforms every subject to the Template 6 (IXI 550-MNI 152) provided in the VBM8 toolbox, which is already in the

stereotactic space of the MNI152 template. The pipeline was run twice for each subject: once with and once without a non-linear modulation applied to the gray matter images, which result in volume and concentration maps respectively (Mechelli *et al.*, 2005). Gray matter concentration corresponds to the probability between 0 and 1 that there is gray matter in any given voxel. The non-linear modulation rescales voxels' values with the Jacobian determinants that represent the number of deformation voxels underwent during the spatial normalization, and thus transforming gray matter concentration into volume. Finally, processed unmodulated gray matter concentration maps were smoothed with a 12-mm full width half maximum Gaussian kernel while modulated gray matter volume maps were smoothed with an 8-mm full width half maximum Gaussian kernel. Sizes of these kernels were chosen to achieve similar final smoothing between concentration and volume images. These kernels were used in a previous OSA study that investigated both concentration and volume (Joo *et al.*, 2010). An absolute threshold masking of 0.1 was applied and thus, voxels with low probability of gray matter (<0.1) were ignored in the analyses.

***Detailed FreeSurfer processing steps and automated segmentation/parcellation***

MRI T1-weighted images were also processed using FreeSurfer image analysis suite version 5.3.0. (http://surfer.nmr.mgh.harvard.edu/; *Laboratory for Computational Neuroimaging, Center for Biomedical Imaging, Charlestown, MA, USA*). FreeSurfer processing stream has been described extensively and the image analysis suite is documented and available online. The complete processing pipeline named "recon-all" (all cortical reconstructions) was run. This pipeline includes an automated affine Talairach registration to the MNI305 atlas followed by the removal of non-brain tissues (Segonne *et al.*, 2004). Then, volumetric segmentation and labeling of subcortical structures are performed in the undeformed brain of each subject, which are based on voxel intensities and a registered probabilistic atlas (Fischl *et al.*, 2002). Afterward, an intensity normalization is performed (Sled *et al.*, 1998) followed by the tracing of the white- gray matter boundary and the gray matter- cerebrospinal fluid boundary using triangular meshes. The resulting cortical surface is labeled and parcelled based on a probabilistic atlas of cortical folding rather than voxel intensities (Fischl *et al.*, 2004). In order to assess the quality of the segmentation and parcellation, all individual images were visually inspected and modifications were applied

manually to remove residual meninges and skull if necessary. Finally, segmented subcortical and intracranial volumes were extracted from the aseg.stats file of every subject, and individual parcelled cortical volume and thickness were extracted from rh.aparc.stats and lh.aparc.stats files. These files compute gray matter measurements of predefined regions included in the built-in atlases without being deformed into a common space (Fischl *et al.*, 2002; Fischl *et al.*, 2004).

Overall, the volume of 19 subcortical regions was extracted and entered as dependent variables in statistical analyses: brainstem and bilateral accumbens area, amygdala, caudate, cerebellum, hippocampus, pallidum, putamen, thalamus, and ventral diencephalon. As for cortical regions, each hemisphere was subdivided in 33 regions, for which both volume and thickness were extracted and entered in statistical analyses. These regions were distributed in the frontal lobe (frontal pole, lateral and medial orbitofrontal gyri, subdivisions of the inferior frontal gyrus [pars opercularis, pars triangularis, pars orbitalis], caudal and rostral middle frontal gyri, superior frontal gyrus and precentral gyrus), parietal lobe (inferior and superior parietal gyri, supramarginal and postcentral gyri, precuneus, paracentral lobule), temporal lobe (inferior, middle and superior temporal gyri, temporal pole, entorhinal cortex, transverse temporal area and parahippocampal gyrus), occipital lobe (fusiform, lateral occipital, lingual and pericalcarine gyri, cuneus,), cingulate cortex (caudal and rostral anterior cingulate cortex, posterior cingulate cortex, isthmus of the cingulate), and insula.

***Statistical analyses***

Statistics were performed with SPSS 19 *(IBM SPSS Statistics, New York, USA)*, except for VBM statistics that were performed within SPM8. For all variables not normally distributed, we used their logarithm in all statistical analyses.

***Principal component analysis for markers of OSA severity***

Variables that strongly correlated with the apnea-hypopnea index (AHI, r varying from 0.452 to 0.981, $p$ <0.001) were entered in the principal component analysis with a varimax rotation in order to preserve the independence of resulting components. The number of components to be extracted (i.e. 3 components) was chosen after examining the nature/origin of variables that strongly correlated with the AHI (scoring of oxygen saturation recording;

apneas and hypopneas; polysomnographic scoring). Variables with a loading >0.5 were considered as the most contributing variables to the component and are shown in the Table 1 of the published paper. The most contributing variables were used to name components and facilitated the interpretation.

***Multiple linear regressions***

For VBM analysis performed within SPM8, multiple linear regressions with components representing OSA severity (i.e., hypoxemia, respiratory disturbances, and sleep fragmentation) were performed for both gray matter concentration and volume, with age, sex, body mass index, and intracranial volume as nuisance covariates. VBM analysis is based on the General Linear Model, and thus T-contrasts were evaluated for both positive [1] and negative [-1] regressions for each OSA component. The level of significance was set at $p$ <0.05, corrected for multiple comparisons at the cluster level with topological false-discovery rate (Chumbley *et al.*, 2010). The multiple comparison correction was applied on results obtained with an uncorrected height threshold of $p$ <0.001 and an extent threshold of 50 contiguous voxels. The processing stream and statistical inferences for VBM analyses were performed according to published recommendations made by Celle and al. (Celle *et al.*, 2016) in their recent methodological review of OSA studies.

Moreover, hierarchical linear regression analyses were performed with extracted values from FreeSurfer automated segmentation as dependent variables. Hierarchical linear regressions are multilevel models in which a linear regression is performed with more than one model (or step) that include a given set of chosen independent variables. This statistical test assesses the amount of variance accounted by our variables of interest (step 2), while adjusting first for covariates (step 1). Age, sex, body mass index and intracranial volume were entered as nuisance covariates in the first step. The three OSA components (i.e., intermittent hypoxemia, respiratory disturbances and sleep fragmentation) were added in the second step. Nuisance variables and independent variables were all mean-centered. Associations were considered significant at a $R^2$ change of $p$ <0.01, i.e., when a significant increase in variance explained was observed between the first and second steps, and $p$ <0.01 for the predicting markers of OSA severity. These statistical thresholds were chosen in order to partially reduce

the risk of Type I errors while maximizing statistical power. Results are shown in Table 3 and Figure 2 of the published paper as well as in Figure E1 of the present supplement.

***Supplementary analyses among milder forms of OSA***

In order to assess if gray matter integrity is associated with markers of OSA severity among subjects with milder forms of OSA, all regression analyses (VBM and FreeSurfer automated segmentation) were performed again without subjects with severe OSA (AHI ≥30), i.e. within the control group and mild and moderate OSA groups (53 subjects).

**SUPPLEMENTARY RESULTS**

***Gray matter hypertrophy and thickening with OSA severity among milder forms of OSA***

With VBM, no significant association was found between OSA severity and clusters of gray matter volume or concentration were observed when subjects with severe OSA were excluded from the analysis.

With FreeSurfer automated segmentation, two of the eight brain regions that were found as enlarged in the full sample were still significantly associated with OSA severity when individuals with severe OSA were removed (R2 changes of $p < 0.01$, $p < 0.01$ for the predicting markers of OSA severity). More severe hypoxemia was still significantly associated with increased thickness of the right frontal pole and the left rostral middle frontal gyrus. Moreover, new significant associations were found with increased gray matter when severe OSA individuals were removed. Higher levels of hypoxemia correlated with an increased right inferior parietal volume and a thicker left precuneus. The left precuneus thickness and the left thalamus volume were also significantly associated with more respiratory disturbances. No region of reduced gray matter was found in association with OSA severity when subjects with severe OSA were excluded from the analyses.

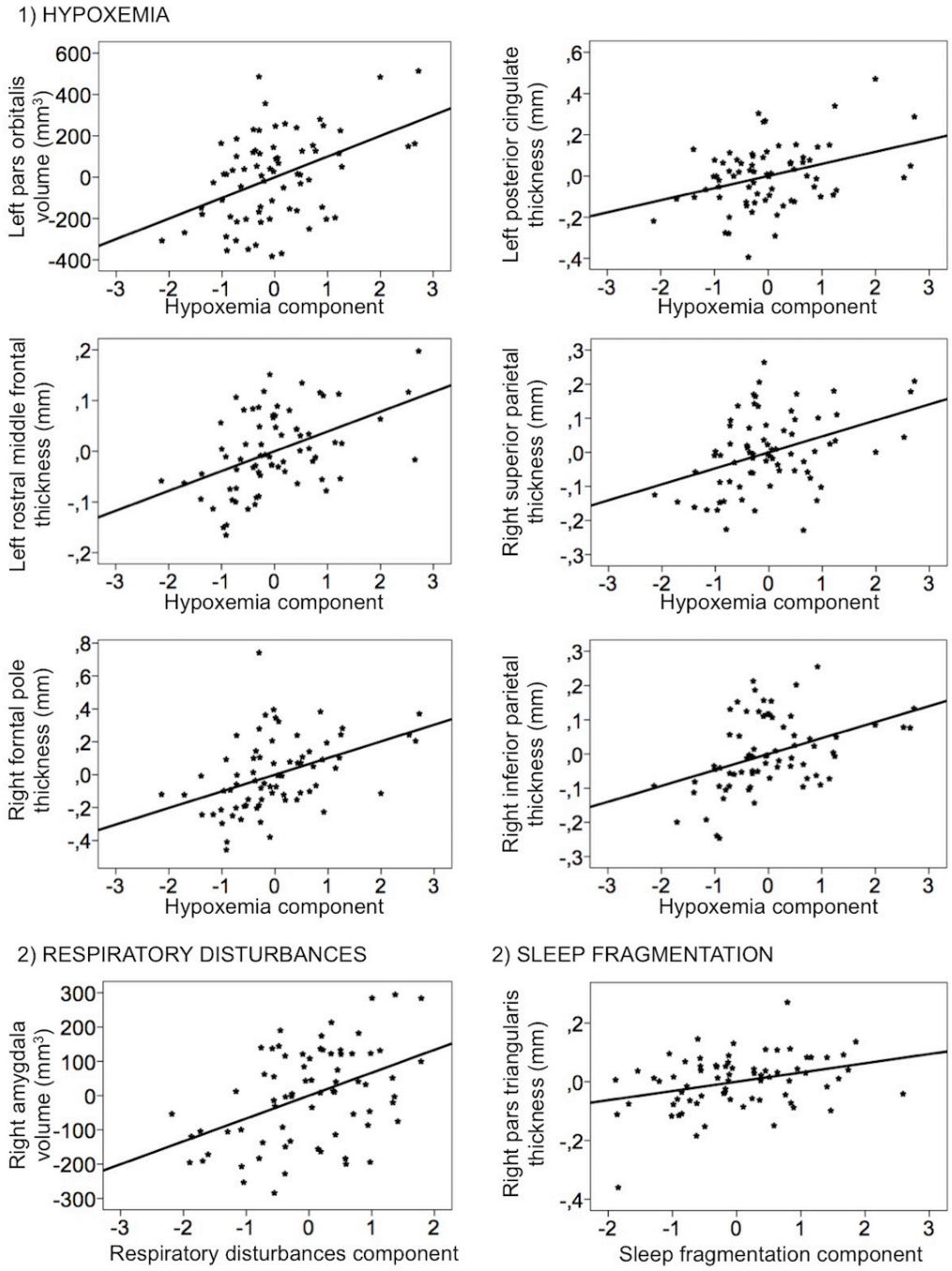


**Figure E1.** Significant hierarchical linear regressions between markers of OSA severity obtained with the principal component analysis and regions of increased gray matter estimated with FreeSurfer automated segmentation.

Regressions of increased gray matter volume or cortical thickness in association to 1) hypoxemia; 2) respiratory disturbances; and 3) sleep fragmentation are shown as centered residuals, with nuisance covariates being age, sex, body mass index and intracranial volume.

## 5.4. **Article 4 :** Cerebral white matter diffusion characteristics and free-water with obstructive sleep apnea

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**Soumis à :** American Journal of Respiratory and Critical Care Medicine

**Contribution de la candidate :** conception de l'étude, acquisition des données de sommeil et de neuroimagerie en laboratoire, analyses des données, interprétation des données, écriture et révision de l'article suite aux commentaires des co-auteurs, processus de soumission auprès du journal scientifique.

## AT A GLANCE COMMENTARY

**Scientific Knowledge on the Subject:** Obstructive sleep apnea in the elderly is increasingly recognized as a modifiable risk factor for cognitive decline and dementia. An altered pattern of white matter diffusion characteristics has the potential to predict cognitive decline. Studies performed in middle-aged individuals with obstructive sleep apnea reported the presence of white matter diffusion changes. However, how obstructive sleep apnea of different severity affects white matter diffusion characteristics in older adults was not investigated before.

**What This Study Adds to the Field:** How water molecules diffuse provides information about the cellular microstructure that restricts their movement and about water displacements between intracellular and extracellular spaces. We found that mild obstructive sleep apnea was associated with widespread reductions in white matter diffusivities, while moderate-severe obstructive sleep apnea was associated with a focal axial diffusivity reduction in the corpus callosum. Mild obstructive sleep apnea may cause mechanisms restricting water diffusion such as cytotoxic edema and reactive gliosis, while moderate-severe obstructive sleep apnea might be characterized with competing mechanisms, including reactive gliosis, cellular loss, cytotoxic and vasogenic edema.

**ABSTRACT**

**Rationale:** Characterizing the effects of obstructive sleep apnea on the aging brain could be key in understanding the transition between normal aging and dementia in this population. White matter diffusion changes are observed before clinical manifestations of cognitive decline and yet, it remains unknown whether obstructive sleep apnea in late-life affects white matter.

**Objectives:** To assess white matter diffusion characteristics in newly diagnosed and untreated individuals aged 55 or older with different severity of obstructive sleep apnea.

**Methods:** Three groups were evaluated with polysomnography and magnetic resonance imaging: controls (n=18) and mild (n=27) and moderate-severe obstructive sleep apnea (n=20) groups. Diffusion tensor imaging metrics (fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity) were compared between groups with Tract-Based Spatial Statistics. Complementary techniques were used: free-water imaging, regional volumetry and white matter hyperintensities.

**Main Results:** Compared to controls, the mild obstructive sleep apnea group showed widespread white matter diffusivities reductions and reduced free-water fraction while the moderate-severe obstructive sleep apnea group showed reduced axial diffusivity in the corpus callosum. Both groups had hypertrophied white matter and subcortical structures compared to controls. No fractional anisotropy or hyperintensities change was observed between groups.

**Conclusions:** In middle-aged and older adults, altered white matter diffusion characterized by reduced diffusivity was observed in obstructive sleep apnea, especially in the milder form. We hypothesized that while mild obstructive sleep apnea may cause early mechanisms restricting water diffusion, moderate-severe obstructive sleep apnea might be characterized with competing pathological mechanisms leading to apparent partial normalization of diffusion metrics.

## INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep disorder that causes intermittent hypoxemia and repeated arousals (Malhotra and White, 2002). Epidemiological studies have shown an association between OSA and dementia (Leng *et al.*, 2017; Shi *et al.*, 2017a). In fact, OSA in older adults could precipitate neurodegeneration by creating microstructural cerebral changes, especially white matter damage. White matter microstructure changes were shown to be predictive of cognitive decline (Selnes *et al.*, 2013).

With diffusion tensor imaging (DTI), the highly oriented structure of myelinated axons that limits the diffusion of water molecules allows the evaluation of white matter microstructure. Four DTI metrics can be computed: fractional anisotropy (FA), mean, radial, and axial diffusivity (MD, AD, RD). Alzheimer's disease and mild cognitive impairment are associated with widespread decreased FA as well as increased MD, AD and RD (Sexton *et al.*, 2011; Sun *et al.*, 2014). Low FA is considered a marker of poor white matter integrity while increased diffusivities represent many pathological and chronic processes that allow water to diffuse more freely (Pitkonen *et al.*, 2012; Zhang *et al.*, 2012; Winklewski *et al.*, 2018).

A different portrait was found previously in middle-aged adults with OSA (see Table 1) (Macey *et al.*, 2008; Kumar *et al.*, 2012; Macey *et al.*, 2012; Castronovo *et al.*, 2014; Kumar *et al.*, 2014b; Chen *et al.*, 2015). Reduced diffusivities were reported more consistently than increased diffusivities. Decreased diffusivities can be observed with various acute pathologic processes that restrict water movement inside cells (Pitkonen *et al.*, 2012; Zhang *et al.*, 2012; Caverzasi *et al.*, 2014; Winklewski *et al.*, 2018). Yet, no DTI study has investigated white matter diffusion characteristics in older adults, a population at higher risk of ongoing neurodegenerative processes. Moreover, no DTI study evaluated mild OSA, which is prevalent in older adults (Tufik *et al.*, 2010). Although it is not the case for moderate-severe OSA (Sforza *et al.*, 2017), mild OSA tends to worsen over time when left untreated (Sahlman *et al.*, 2007). Mild OSA may represent a temporal window during which treatment could prevent neurodegeneration, although adverse effects on brain health has not been properly demonstrated in mild OSA (Chowdhuri *et al.*, 2016).

**Table 1.** Water diffusivity changes found in previous studies by comparing DTI metrics between OSA and control groups.

| Study | Groups, sex (AHI, events/h) | Age (years/old) | FA | MD | AD | RD | Interpretation by the authors |
|---|---|---|---|---|---|---|---|
| (Macey *et al.*, 2008) | 41 OSA, 7 women (≥15; 35.7 ± 18.1)<br>69 controls, 25 women (n/a) | 46.3 ± 8.9<br>47.5 ± 8.8 | ↓ | n/a | n/a | n/a | Extensive altered white matter diffusion characteristics in OSA, potentially reflecting damage from hypoxia, oxidative stress and inflammation. |
| (Macey *et al.*, 2012) | 20 men OSA (≥15; 25.5 ± 2.9)<br>10 women OSA (≥15; 22.5 ± 4.1)<br>30 men controls (n/a)<br>20 women controls (n/a) | 48.9 ± 1.7<br>52.6 ± 2.4<br>49.2 ± 1.4<br>50.3 ± 1.7 | ↓ | n/a | n/a | n/a | An interaction effect between OSA and sex was reported: Women with OSA showed reduced FA compared to controls, while this difference was not found in men. This could be representative of different psychological symptomatology such as depression and anxiety, and/or cardiovascular symptoms in women with OSA specifically. |
| (Kumar *et al.*, 2012) | 23 OSA, 3 women (≥15; 34.9 ± 24.1)<br>23 controls, 3 women (n/a) | 44.4 ± 9.3<br>45.3 ± 11.0 | n/a | ↓ | n/a | n/a | Reduced global and regional MD with OSA in multiple brain regions suggests acute tissue injury and cytotoxic edema, probably as a result of hypoxia and cardiovascular changes. |
| (Kumar *et al.*, 2014b) | 23 OSA, 3 women (≥15; 34.9 ± 24.1)<br>23 controls, 3 women (n/a) | 44.4 ± 9.3<br>45.3 ± 11.0 | n/a | n/a | ↓ | ↓ | Reduced global and widespread regional AD and RD in OSA may indicate acute axonal and myelin injury respectively that could be the result of axonal and myelin swelling. |
| (Castronovo *et al.*, 2014) | 13 men OSA, before and after 3-month and 1-year of continuous positive airway pressure treatment (≥30; 61.4 ± 9.8)<br>15 men controls (<5; 1.6 ± 1.5) | 43.2 ± 7.6<br>42.2 ± 6.6 | ↓ | ↓ | n/a | n/a | Before treatment, OSA subjects had reductions in FA and MD that were concomitant with cognitive impairments, mood alterations and sleepiness. After 3-month and 1-year treatment, a near complete reversal of white matter altered integrity was progressively shown. This reversal was present with recovery to normal levels of cognitive functions. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (Chen *et al.*, 2015) | 20 OSA, 2 women (≥30; 58.9 ± 14.5) | 38.6 ± 9.9 | ↓ | Ø | Ø | ↑ | Altered white matter diffusion characteristics suggesting demyelination in OSA, were correlated with leukocyte early apoptosis that is a marker of systemic inflammation. |
| | 14 controls, 3 women (<5; 2.9 ± 1.3) | 38.2 ± 9.9 | | | | | |

Results are presented as mean ± standard deviation. DTI, diffusion tensor imaging; OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; n/a, non applicable or non available; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; Ø, no between-group differences.

These previous studies in younger OSA adults offered an overview of the complexity of interpreting diffusion metrics in this population. To clarify underlying pathophysiological processes, it may be necessary to combine multiple neuroimaging techniques. Combined to DTI, the following techniques have the potential to clarify the nature of white matter alterations in OSA: Free-water (FW) imaging, which estimates water in the extracellular space (Pasternak *et al.*, 2009); volumetry, which can identify extensive cell loss; and white matter hyperintensities (WMH), which represent small-vessel ischemic injuries (Brickman *et al.*, 2009).

We aimed to characterize white matter diffusion characteristics in late middle-aged and older adults with different OSA severity levels. We evaluated adults aged 55 and older in groups with mild and moderate-severe OSA compared to non-apneic participants. Our hypotheses were that 1) both mild and moderate-severe OSA groups will show altered white matter diffusion characteristics when compared to controls; and 2) white matter will be more affected by moderate-severe OSA than mild OSA. Preliminary results were presented and publish in an abstract form (Baril *et al.*, 2017a).

## METHODS

### *Sample and protocol*

Sixty-five subjects aged between 55 and 85 years old were recruited and divided according to the apnea-hypopnea index (AHI): controls (AHI ≤5/h), mild OSA (AHI>5 to ≤15/h) and moderate-severe OSA (AHI >15/h). All participants were evaluated using a polysomnographic recording and magnetic resonance imaging (MRI). The complete protocol

is provided in a data supplement available online, which describes exclusion criteria, the polysomnographic recording, and questionnaires. The research protocol was approved by Ethics' Committees of the *Hôpital du Sacré-Coeur de Montréal* and the Functional Neuroimaging Unit of the *Institut Universitaire de Gériatrie de Montréal* (#2012-697 and #12-13-008). Each participant gave written informed consent before starting the study.

***White matter characterization with neuroimaging***

To assess white matter structural integrity, we used Tract-Based Spatial Statistics (TBSS) with the DTI technique acquired on diffusion MRI images. We used the Toolkit for Analysis in Diffusion MRI for pre-processing (www.unf-montreal.ca/toad/html/en/) and FSL for statistical group comparison using TBSS (www.fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/UserGuide). Overall, these steps allowed the creation of a white matter skeleton common for all subjects, on which individual DTI metrics data for every subject is projected for statistical comparisons. Voxel-wise analysis in the white matter skeleton is then performed for FA, MD, AD and RD.

We used complementary neuroimaging analysis techniques. FW imaging is computed using diffusion MRI data to estimate tissue ("bound") and isotropic ("free") water compartments (Pasternak *et al.*, 2009). The latter represents the proportion of water that diffuses mostly in the extracellular space. The average FW fraction brain value was extracted for each subject, and was adjusted in statistical models for the volume of cerebrospinal fluid volume in order to specifically assess tissue FW. For volumetry, we estimated regional white and gray matter volumes with FreeSurfer (www.surfer.nmr.mgh.harvard.edu/) on T1 MRI images. Finally, we estimated the volume of WMH with the Lesion Segmentation Toolbox (www.statistical-modelling.de/lst.html), which thresholds T1 and fluid-attenuated inversion recovery (FLAIR) MRI images to identify regions of hyperintense signal. Regional white matter and gray matter volumes, in addition to WMH volume were extracted for every subject.

In the online data supplement, the complete protocol for MRI acquisition, processing and neuroimaging analysis techniques is presented.

**Table 2.** Demographic, clinical and polysomnographic variables of control, mild OSA and moderate-severe OSA groups.

| Variables | Control [1] | Mild OSA [2] | Moderate to Severe OSA [3] | F or $X^2$ | Post-hoc tests |
|---|---|---|---|---|---|
| Apnea-hypopnea index criteria for groups | ≤5 | >5 to ≤15 | >15 | n/a | |
| Number of subjects | 18 | 27 | 20 | n/a | |
| **Demographic and clinical variables** | | | | | |
| Sex (#; %Men) | 11; 61.1 % | 18; 66.7 % | 19; 95.0 % | 6.9* | 1, 2 <3 |
| Age (years) | 65.2 (7.2) | 64.2 (5.3) | 65.2 (5.5) | 0.2 | |
| Education (years) | 16.6 (3.7) | 14.6 (2.7) | 15.9 (3.0) | 2.3 | |
| Body Mass Index ($kg/m^2$) | 25.0 (3.1) | 26.4 (3.4) | 28.6 (2.5) | 6.5† | 1, 2 <3 |
| Vascular Burden Index | 0.8 (0.9) | 1.0 (1.1) | 1.0 (0.9) | 0.3 | |
| *APOE4* allele carriers (%) | 27.8 % | 23.1 % | 20.0 % | 0.3 | |
| *BDNF* Met allele carriers (%) | 27.8 % | 23.1 % | 20.0 % | 0.3 | |
| Epworth Sleepiness Scale | 7.7 (5.4) | 7.4 (4.9) | 9.4 (4.0) | 1.1 | |
| Beck Depression Inventory II | 4.7 (4.3) | 5.6 (4.9) | 8.6 (5.8) | 3.1 | |
| Beck Anxiety Inventory | 4.3 (5.3) | 3.4 (3.2) | 4.3 (4.8) | 0.4 | |
| Montreal Cognitive Assessment | 27.9 (2.3) | 27.5 (2.2) | 27.2 (2.8) | 0.2 | |
| **Polysomnographic variables** | | | | | |
| Total sleep time (min) | 355.6 (70.5) | 349.7 (66.3) | 372.0 (41.9) | 0.8 | |
| Sleep efficiency (%) | 79.2 (11.6) | 78.1 (12.2) | 82.3 (9.1) | 0.8 | |
| Awakenings (#) | 32.0 (17.7) | 35.9 (13.8) | 54.0 (26.4) | 7.3† | 1, 2 <3 |
| Micro-arousal index (events/h) | 11.6 (4.0) | 13.2 (5.3) | 19.7 (8.2) | 10.2‡ | 1, 2 <3 |
| Stages transitions (#) | 210.3 (72.5) | 208.3 (46.6) | 292.0 (76.0) | 11.5‡ | 1, 2 <3 |
| Apnea-hypopnea index (events/h) | 2.3 (1.8) | 9.1 (1.6) | 33.9 (12.8) | 102.5‡ | 1 <2 <3 |
| Apnea index (events/h) | 1.0 (1.4) | 2.8 (2.4) | 23.3 (4.6) | 46.4‡ | 1, 2 <3 |
| Hypopnea index (events/h) | 1.3 (1.3) | 6.3 (2.2) | 10.6 (5.2) | 38.1‡ | 1 <2 <3 |
| Mean oxygen saturation (%) | 95.1 (0.8) | 94.7 (1.3) | 94.1 (0.9) | 5.0* | 1 >3 |
| Minimal oxygen saturation (%) | 89.6 (3.3) | 88.6 (2.8) | 83.2 (5.2) | 16.5‡ | 1, 2 >3 |
| Sleep time with oxygen saturation <90 % (min) | 0.4 (0.9) | 1.7 (5.6) | 11.1 (14.5) | 8.9‡ | 1, 2 <3 |
| Oxygen saturation drops >3 % index (events/h) | 0.8 (0.8) | 3.0 (2.2) | 17.2 (11.2) | 39.9‡ | 1, 2 <3 |

Results are presented with mean (standard deviation). ANOVAs were performed, except for proportion differences that were assessed with chi-square tests; OSA, obstructive sleep apnea; n/a, non applicable; *p<0.05; †p<0.01; ‡p<0.001

***Statistical analyses***

DTI analyses were performed within FSL. Voxel-wise one-tailed T-tests were performed using the command "randomise" between groups to assess white matter FA, MD, AD and RD at a p-threshold of $p<0.05$ family-wise error (FWE)-corrected for multiple comparisons.

For complementary neuroimaging analyses techniques, i.e., FW imaging, volumetry and WMH quantification, statistics were performed with SPSS 19 (IBM SPSS Statistics, New York, USA). Two-tailed ANCOVAs were performed between the three groups with a p-threshold set at $p<0.05$, and significant differences were further investigated with post-hoc tests.

Because body mass index (BMI) was higher in moderate-severe OSA individuals compared with both control and mild OSA groups (see Table 2), it was included in all statistical analyses as a covariate. Moreover, the moderate-severe OSA group had significantly more men than other groups. Additional analyses were performed replacing BMI by sex as a covariate in order to maximize statistical power.

**RESULTS**

Table 2 presents demographic, clinical and polysomnographic variables of control, mild OSA and moderate-severe OSA groups. Groups' mean for neuroimaging variables are presented in Table E1 of the online data supplement.

***Reduced diffusivity in mild and moderate-severe OSA***

Participants with mild OSA showed widespread reductions of MD compared to controls when adjusting for BMI in three white matter clusters, with the first cluster covering more than 16 000 voxels. These areas of reduced MD are shown in Table 3A, Fig. 1A and individual averages for these clusters are shown in Fig. 2A. When sex was included as a covariate instead of BMI, mild OSA individuals still showed the same widespread reductions in MD compared to controls (two clusters; 19777 and 40 voxels; same or adjacent coordinates).

Secondly, the mild OSA group had lower white matter RD compared to controls in four clusters when adjusting for BMI. These areas of reduced RD are shown in Table 3B, Fig. 1B and individual averages for these clusters are shown in Fig. 2B. When sex was included as a covariate instead of BMI, mild OSA individuals still showed reduced RD in the same white matter tracts compared to controls (three clusters; 8278, 3220 and 74 voxels; same coordinates).

Our third observation is that the mild OSA group had lower AD compared to controls when adjusting for BMI. These areas of reduced AD are shown in Table 3C, Fig. 1C and individual averages for this cluster are shown in Fig. 2C. When sex was included as a covariate instead of BMI, mild OSA individuals still showed the same widespread reductions in AD compared to controls (five clusters; 18349, 274, 263, 49 and 24 voxels; same or adjacent coordinates).

Regarding the moderate-severe OSA group, we found that they had intermediate levels of diffusivity between controls and mild OSA, which led to non significant group differences in most white matter tracts (Fig. 1 and 2). Nonetheless, the moderate-severe OSA group had significantly lower AD compared to controls when adjusting for BMI in the body of the corpus callosum, which is shown in Table 3D, Fig. 1D, and individual averages for this cluster are shown in Fig. 2D. When sex was included as a covariate instead of BMI, the reduced AD in the corpus callosum of moderate-severe OSA individuals was still observed compared to controls, although the cluster was smaller (one cluster; 83 voxels, same coordinates). No other group difference was found for the moderate-severe OSA group compared to either the mild OSA or control group.

In summary, reduced diffusivities in mild OSA individuals compared to controls were found in multiple projection and association fibers as well as within commissural fibers. Regarding the moderate-severe OSA group, the only group difference was found in the body of the corpus callosum where they showed reduced AD compared to controls. No between group difference was observed for FA. These group differences were independent of the BMI, and the same results were obtained when sex was used as a covariate.

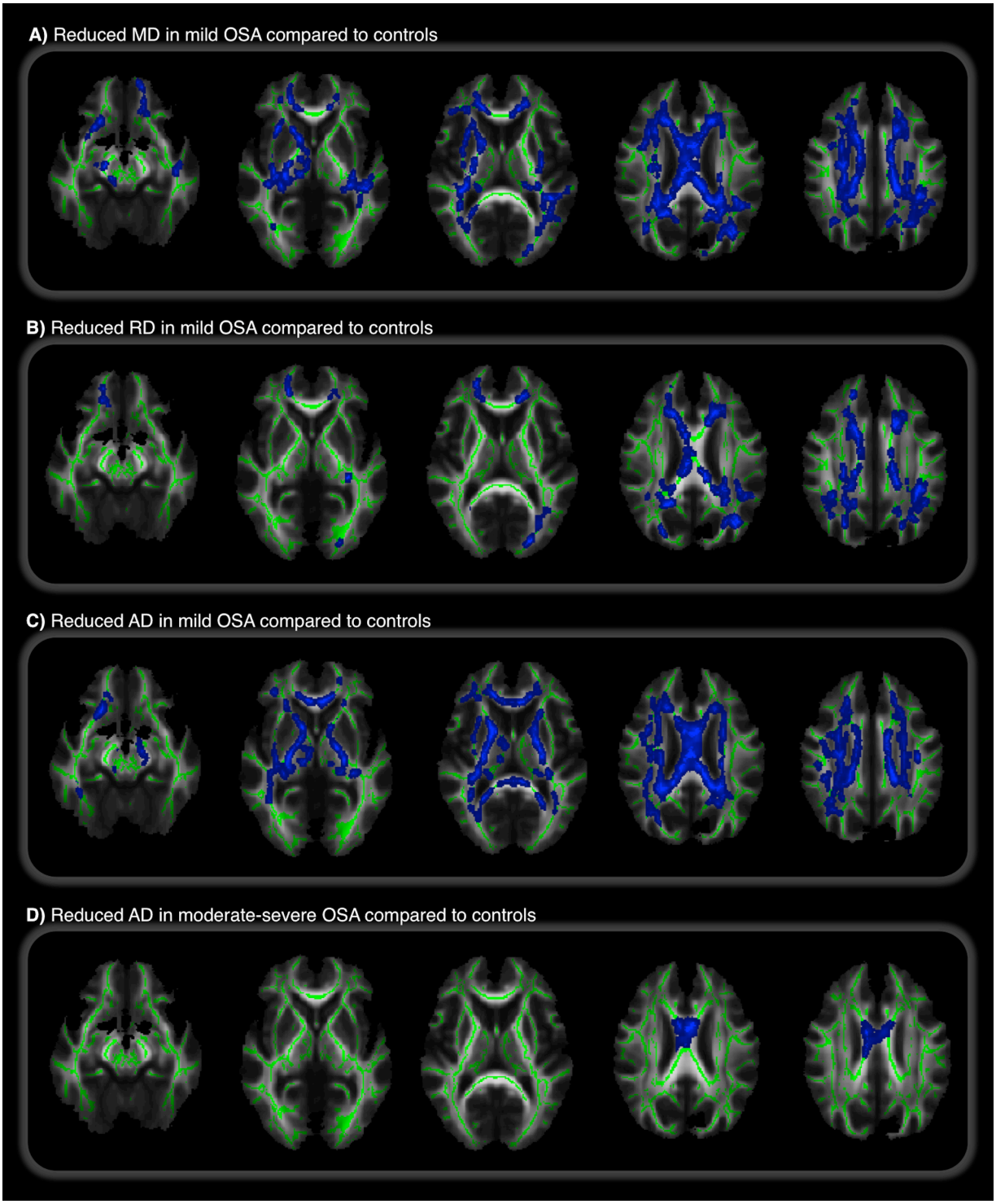


**Figure 1.** TBSS DTI analysis revealed reduced A) MD, B) RD, C) AD in mild OSA compared to controls in multiple white matter tracts as well as reduced C) AD in moderate-severe OSA compared to controls in the corpus callosum.

Group differences were considered significant at FWE-corrected $p<0.05$ and BMI was included as a covariate.

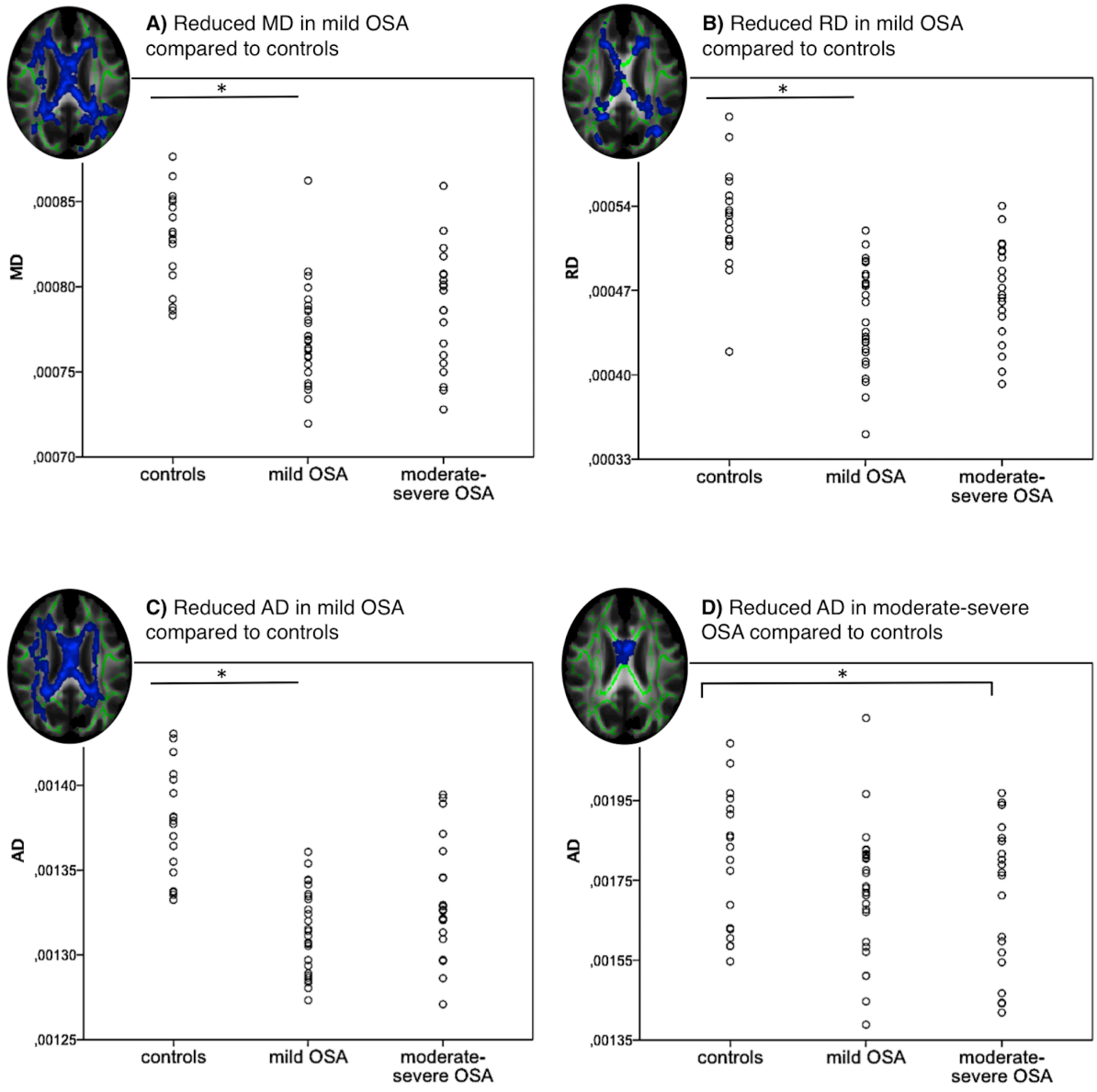


**Figure 2.** Average raw DTI metrics values in significant voxel-wise clusters for every subject.

While mild OSA showed significant and diffuse reductions in A) MD, B) RD, and C) AD compared to controls, moderate-severe OSA subjects had intermediate diffusivity values between controls and mild OSA leading to no significant difference in most white matter tracts. However, in the corpus callosum, the moderate-severe OSA group had significantly reduced D) AD compared to controls. Group differences were considered significant at FWE-corrected $p<0.05$ and BMI was included as a covariate.

**Table 3.** Reduced diffusivity in mild and moderate-severe OSA groups compared to controls

| Cluster size | T | Peak MNI coordinates | | | Fibre type and white matter tracts (lobes or regions) |
|---|---|---|---|---|---|
| **A) Reduced MD in mild OSA compared to controls** | | | | | |
| 16151 | 5.26 | 31 | -46 | 16 | Projections |
| 209 | 4.32 | -30 | -30 | 2 | — Bilateral corona radiata (cingulate, frontal, parietal, temporal) |
| 78 | 3.21 | -30 | -18 | 9 | — Internal capsule (Right anterior/posterior limb, bilateral retrolenticular) |
| | | | | | — Right cerebral peduncle |
| | | | | | — Bilateral posterior thalamic radiation |
| | | | | | Association |
| | | | | | — Bilateral external capsule |
| | | | | | — Bilateral fornix and stria terminalis |
| | | | | | — Left sagittal stratum |
| | | | | | — Right superior longitudinal fasciculus (frontal, temporal) |
| | | | | | — Left superior longitudinal fasciculus (frontal, parietal, temporal, occipital) |
| | | | | | — Left inferior longitudinal fasciculus (temporal) |
| | | | | | Commissural |
| | | | | | — Left tapetum |
| | | | | | — Corpus callosum (splenium, body and genu) |
| **B) Reduced RD in mild OSA compared to controls** | | | | | |
| 5795 | 4.91 | 18 | 50 | -4 | Projection |
| 2919 | 4.45 | -22 | -82 | 11 | — Bilateral corona radiata (cingulate, frontal, parietal, temporal) |
| 37 | 4.04 | -28 | -20 | -7 | — Internal capsule (Left retrolenticular) |
| 21 | 4.05 | -30 | -30 | 2 | — Bilateral posterior thalamic radiation |
| | | | | | Association |
| | | | | | — Left fornix |
| | | | | | — Stria terminalis |
| | | | | | — Right superior longitudinal fasciculus (parietal) |
| | | | | | — Left superior longitudinal fasciculus (parietal, temporal, occipital) |
| | | | | | Commissural |
| | | | | | — Left tapetum |
| | | | | | — Corpus callosum (splenium, body and genu) |

| | | | | | |
|---|---|---|---|---|---|
| **C) Reduced AD in mild OSA compared to controls** | | | | | |
| 17376 | 5.52 | -28 | -47 | 19 | Projection<br>— Bilateral corona radiata (anterior cingulate, frontal, parietal, temporal)<br>— Internal capsule (Bilateral anterior/posterior limb, bilateral retrolenticular)<br>— Bilateral cerebral peduncle<br>— Bilateral posterior thalamic radiation |
| | | | | | Association<br>— Bilateral external capsule<br>— Right sagittal stratum<br>— Right superior longitudinal fasciculus (frontal, parietal, temporal)<br>— Left superior longitudinal fasciculus (frontal, temporal) |
| | | | | | Commissural<br>— Bilateral tapetum<br>— Corpus callosum (splenium, body and genu) |
| **D) Reduced AD in moderate-severe OSA compared to controls** | | | | | |
| 2178 | 4.47 | -5 | 1 | 26 | Commissural<br>— Body of the corpus callosum |

T-Tests were adjusted for body mass index. Voxel-wise analysis performed within FSL considered significant at a threshold-free cluster enhancement FWE-corrected for multiple comparisons at $p<0.05$ with 10 000 conditional Monte Carlo permutations. MNI, Montreal Neurological Institute; OSA, obstructive sleep apnea; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity.

### *Reduced FW fraction in mild OSA individuals*

A significant ANCOVA was observed for the average FW fraction, adjusted for BMI and CSF volume. Post-hoc analyses revealed that the mild OSA group had lower averaged FW fraction compared to controls. The same result was observed when sex was entered as a covariate instead of BMI. No group difference was found for the moderate-severe OSA group.

A lower FW fraction correlated with a lower average AD in the large cluster observed between the mild OSA and controls, adjusted for CSF volume, age and BMI.

### *Increased regional cerebral volume in OSA groups*

Adjusted for BMI, significant ANCOVAs were observed for the volume of the following structures: brainstem, cerebellum white matter, corpus callosum, total subcortical

gray matter, left thalamus, left hippocampus, right hippocampus and left amygdala. Post-hoc analyses revealed that hypertrophy was observed for these regions in both mild and moderate-severe OSA groups compared to controls. When sex was entered as a covariate instead of BMI, post-hoc analyses revealed increased volumes of total subcortical gray matter, left thalamus, bilateral hippocampi and bilateral amygdala in mild and moderate-severe OSA groups compared to controls. Moreover, corpus callosum and cerebellum white matter volumes were increased in mild OSA individuals compared to controls.

No between-group difference was observed for cortical white matter, cortex, ventricles, intracranial, and CSF volumes. No area of decreased volume with increasing OSA severity was found.

***No increased WMH in OSA***

No group difference was observed for WMH volume with either BMI or sex as a covariate.

## DISCUSSION

In this study, we aim to better understand how different severity of OSA in late middle-aged and older adults affects brain health, and more specifically white matter diffusion characteristics. Our results showed that, rather than presenting the standard pattern of increased diffusivities and reduced FA observed with neurodegeneration (Sexton *et al.*, 2011; Sun *et al.*, 2014), individuals with mild OSA had widespread reductions of diffusivity metrics (MD, RD, AD) along white matter tracts compared to controls. This pattern was combined with a lower FW fraction and hypertrophic white matter and subcortical gray matter structures. Subjects with moderate-severe OSA did not show this pattern of widespread diffusivity reduction compared to controls: they only showed decreased AD limited to the corpus callosum combined with hypertrophic white matter and subcortical gray matter structures.

A similar pattern of reduced diffusivity was previously reported in middle-aged individuals with moderate-severe OSA individuals (see Table 1). While one group reported reduced MD, AD and RD (Kumar *et al.*, 2012; Kumar *et al.*, 2014b), another reported reduced MD (Castronovo *et al.*, 2014). Therefore, our mild OSA group of older adults showed a similar DTI diffusivity pattern than middle-aged individuals with moderate-severe OSA in

previous studies. The present study adds to the literature by showing that these altered white matter diffusion characteristics are also observed in mild OSA. The impacts of mild OSA are currently a source of debate in the literature (Brown, 2007; Littner, 2007; Chowdhuri *et al.*, 2016).

***Significance of reduced white matter water diffusivities in OSA***

A clear understanding of what DTI metrics measure is necessary to infer on underlying pathophysiological processes in OSA, and that insight comes mostly from animal or human studies with histopathology measurements. Diffusivity metrics correspond to the magnitude of water diffusion in specific directions, where AD is the diffusion magnitude along axons, RD is perpendicular to axons, and MD is the average diffusivity in all directions. MD decreases with cell proliferation, reactive gliosis and cytotoxic edema, but increases with cell death and vasogenic edema (Anderova *et al.*, 2011). AD mostly reflects axonal microstructure. Reduced AD is observed in the case of beaded or fragmented axons, and cytotoxic edema but then, increased AD is reported when microglial cells clear axonal debris that hindered water diffusion (Boretius *et al.*, 2012; Zhang *et al.*, 2012; Winklewski *et al.*, 2018). RD mostly represents myelin integrity. Pathological processes that lead to reduce RD include separation of myelin sheaths that restrict water movement and cytotoxic edema while increased RD is generally representative of demyelination (Shereen *et al.*, 2011; Boretius *et al.*, 2012; Zhang *et al.*, 2012; Winklewski *et al.*, 2018). In the present study, early cellular damage, reactive gliosis and cytotoxic edema may be the underlying processes leading to reduced AD in both mild and moderate-severe OSA groups, and reduced MD and RD in the mild OSA.

We did not find reduced FA in OSA contrary to what was reported by others (see Table 1). FA is a relative anisotropy index computed with all directions: water molecules that diffuse in an anisotropic fashion have a preferential direction, which is the case in cerebral white matter. A high FA is considered to be a marker of good white matter integrity, although this assumption should be made carefully as several confounding factors can interact. In fact, FA can be decreased by a low AD, a high RD or both concomitantly. In our participants with mild OSA especially, concomitant reductions in AD and RD may have resulted in unchanged FA.

***Possible cytotoxic edema and reactive gliosis in OSA***

Histopathological studies reported above suggest that the present pattern of reduced diffusivities in OSA, especially in mild OSA individuals, might reflect underlying processes including cellular damage, reactive gliosis and cytotoxic edema. In our study, reduced fractional FW in mild OSA suggests a lower proportion of extracellular water, and thus, supports the hypothesis that intracellular cytotoxic edema and/or reactive gliosis is occurring. Indeed, reduce extracellular water fraction would be explained by both the presence of more water inside cells (cytotoxic edema) or the presence of more cells (reactive gliosis). In animal models, the acute stage following cerebral hypoxia/ischemia is characterized by reduced water diffusivities (MD, RD, AD) as well as histologic evidence of cytotoxic edema, reduced extracellular water fraction, and reactive gliosis (Anderova *et al.*, 2011; Shereen *et al.*, 2011; Pitkonen *et al.*, 2012). Interestingly, cytotoxic edema, increased total water content, and reactive gliosis were also observed in animal models of OSA (Aviles-Reyes *et al.*, 2010; Baronio *et al.*, 2013). Increased gray matter and white matter volumes in the present study in both mild and moderate-severe OSA also point to edema. Cerebral swelling was reported in edema due to hypoxia in altitude (Kallenberg *et al.*, 2007; Sagoo *et al.*, 2017). Moreover, in a previous study by our group, we found that nocturnal hypoxemia values were associated with multiple regions of gray matter hypertrophy and thickening (Baril *et al.*, 2017c). It should be noted, however, that oxygen saturation was not significantly different between mild OSA and control groups (see Table 2). Physiological changes during sleep might thus be present in mild OSA but not represented by standard polysomnographic variables. In fact, although they are highly correlated, arterial and cerebral tissue oxygen saturation do not necessarily change in the same manner during apneas and hypopneas (Valipour *et al.*, 2002).

***Potential biphasic relationship between OSA severity and white matter diffusion characteristics***

Only reduced AD located in the corpus callosum was observed in moderate-severe OSA cases. A new finding of our study is that OSA is not linearly associated with white matter diffusion characteristics: altered white matter diffusion characteristics in moderate-severe OSA were considerably less extensive than what was observed in mild OSA (see Fig. 1C versus 1D).

Water diffusivity metrics, especially MD, are known as stage-specific measures (Ahlhelm *et al.*, 2002; Anderova *et al.*, 2011; Pitkonen *et al.*, 2012; Ryan *et al.*, 2013), which decrease first in acute stages and increase later on in chronic stages. Thus, reduced diffusivities (MD, RD, AD) in mild OSA cases may represent an acute response (cytotoxic edema, reactive gliosis) to the obstructions that occurred the night before or in the few preceding nights. The transition between acute and chronic stages can be characterized by a pseudo-normalization of DTI metrics, which is an apparently normal DTI pattern with competing mechanisms that increased and decreased water diffusivity concomitantly (Zhang *et al.*, 2012). Moderate to severe OSA may be associated with a more complex cascade of competing but potentially more severe mechanisms (cytotoxic and vasogenic edema, reactive gliosis, cellular loss) that results in a transient apparent normalization of DTI metrics, except for the reduced AD in the corpus callosum. Consistently, in ischemic conditions, normal diffusivity was observed with a large array of competing pathological mechanisms (Li *et al.*, 2002). We did not observe changes in FW in moderate-severe OSA cases, suggestive of a more balanced intracellular/extracellular water ratio. We observed however hypertrophic structures in both mild and moderate-severe OSA groups, probably reflecting the presence of edema regardless of its intracellular/extracellular distribution.

A biphasic white matter diffusion pattern could occur in response to OSA (Rosenzweig *et al.*, 2015). First, adaptive and compensatory mechanisms could be observed in mild OSA followed by cellular loss and potential neurodegeneration when the disease worsens. A longitudinal biphasic pattern in cerebral diffusion data was previously reported in familial Alzheimer's disease and ischemic stroke (Ahlhelm *et al.*, 2002; Anderova *et al.*, 2011; Pitkonen *et al.*, 2012; Ryan *et al.*, 2013) where reduced diffusivity later becomes increased diffusivity. A recent study observed that in cognitively normal individuals, early neurodegenerative stages were characterized by cortical thickening as well as reduced FW and MD (Montal *et al.*, 2018). This pattern was progressively reversed to an increased FW and MD associated with cortical atrophy in later asymptomatic stages and symptomatic dementia (Montal *et al.*, 2018). Although we did not find increased diffusivity in our sample, increased RD in subjects with severe OSA was reported (Chen *et al.*, 2015). This supports the hypothesis that more severe OSA may be associated with more severe impact on brain health

characterized by increased diffusivity. Our moderate-severe OSA group may not be severe enough to observe increased diffusivity (four with AHI>40/h).

We did not observe statistically significant difference between mild and moderate-severe OSA regarding DTI metrics, which could be caused by the failure of the continuous AHI to distinguish between different levels of OSA severity, or by overlapping underlying mechanisms resulting in an intermediate DTI metric levels in moderate-severe OSA individuals (See Fig. 2). Moreover, unchanged WMH levels were observed in OSA, which was reported in some previous studies (Schulz *et al.*, 2013; Castillo *et al.*, 2015; Lutsey *et al.*, 2016), while others reported more WMH in OSA (Kim *et al.*, 2013; Baik *et al.*, 2015; Del Brutto *et al.*, 2017; Song *et al.*, 2017). Increased diffusivity is associated with a higher WMH load (Svard *et al.*, 2017), which might explain why our sample characterized by reduced white matter water diffusivities did not present more WMH.

***Limitations***

Despite the fact that we included BMI and sex as covariates, our sample did not include many women or obese individuals. These factors may play a role into the potentially delicate balance dictating whether adaptive or maladaptive mechanisms are present. Increased diffusivity was reported in obese OSA subjects compared to non-obese OSA individuals (Kilicarslan *et al.*, 2014). Reduced FA was observed only in women with OSA but not in men in another study (Macey *et al.*, 2012).

DTI with TBSS is a sensitive technique but is less reliable in regions of crossing fibers. However, the fact that we found clusters of white matter diffusivity changes as big as 16000 voxels that crossing fibers is not the source of our findings in OSA. Second, especially in mild OSA, the presence of reduced FW and increased focal gray and white matter volumes support our hypothesis and are consistent with DTI findings.

***Conclusions***

In this study, we sought to evaluate how OSA affects cerebral white matter. We found that mild OSA showed widespread white matter diffusivity reductions compared to controls. In contrast, moderate-severe OSA was characterized by focal reduced axial diffusivity in the corpus callosum compared to controls. The novelty of our study is the investigation of both

mild and moderate-severe OSA in middle-aged and older adults, which led to a better understanding of how OSA affects the aging brain. Our results add to others that found that mild OSA leads to adverse outcomes (Jahn *et al.*, 2016; Luz *et al.*, 2016). One of the strengths of our study is the combined use of neuroimaging methods, including FW imaging, a novel technique with great potential that support our DTI results.

We hypothesized that OSA provoke adaptive and maladaptive mechanisms at different levels of severity. Mild OSA may be associated with an acute response characterized by cytotoxic edema combined with reactive gliosis, leading to water being more restricted by cells and thus, to reduce diffusivity in all directions. Mild OSA worsens to moderate-severe OSA in about half untreated individuals (Sahlman *et al.*, 2007). Thus, mild OSA may be a potential therapeutic window to prevent cerebral damage and cognitive decline. Interestingly, reduced diffusivity in OSA individuals was reported to be reversible after a one-year treatment (Castronovo *et al.*, 2014). Moderate-severe OSA might be characterized with competing adaptive and maladaptive mechanisms that lead to an apparent partial normalization of DTI metrics, including reactive gliosis and cytotoxic edema as well as cellular loss and vasogenic edema. Because our study was cross-sectional, longitudinal studies are needed to clarify whether more severe OSA of longer duration in the elderly feature increased diffusivity and cognitive decline. Since there are no current therapies to cure dementia, the identification of modifiable risk factors, such as OSA, remains the most promising intervention to prevent or slow neurodegeneration.

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## SUPPLEMENTARY DATA

## DETAILED METHODS

### *Sample and protocol*

We recruited 65 subjects aged between 55 and 85 years old from a sleep apnea clinic waiting list (N=9) and through newspaper ads (N=56) to have a sample with a wide range of obstructive sleep apnea (OSA) severity, from non-OSA controls to severe OSA. Exclusion criteria were: neurological or psychiatric diseases, cerebrovascular diseases, dementia, history of traumatic brain injury, pulmonary diseases, sleep disorders other than OSA, being treated for OSA, morbid obesity (body mass index [BMI]>40), the usage of medication that influence sleep, breathing or brain functioning (e.g., benzodiazepines, anticonvulsants, sedatives, antidepressants, antipsychotics), and drug and alcohol abuse.

### *Polysomnographic recording*

We have extensively described our full-night in-laboratory polysomnography protocol in previous studies by our group (Baril *et al.*, 2015; Gosselin *et al.*, 2016; Baril *et al.*, 2017c). This recording included the following measurements: thoraco-abdominal strain gages, oronasal cannula and thermal sensors, transcutaneous finger pulse oximeter, electroencephalogram, electrooculograms, chin and anterior tibialis electromyograms and electrocardiogram. An experienced medical electrophysiology technologist performed sleep and respiratory scoring based on the American Academy of Sleep Medicine guidelines (Iber *et al.*, 2007; Berry *et al.*, 2012). The apnea-hypopnea index (AHI) was computed as follows: apneas+hypopneas/sleep duration in hours. Participants were divided into three groups: a control group (AHI ≤5/h), a mild OSA group (AHI>5 to ≤15/h) and moderate-severe OSA (AHI >15/h). This classification was based on published standard recommendations (American Academy of Sleep Medicine Task Force, 1999). The apneas were defined as an airflow reduction of ≥90 % lasting >10 s. Hypopneas were defined as an airflow reduction of ≥30 % lasting >10 s accompanied by either an oxygen desaturation of ≥3 % or an arousal according to the current 2012 criteria (Berry *et al.*, 2012). It should be noted that criteria for the scoring of hypopneas were modified over time, which can affect the severity classification by affecting the AHI (Duce *et al.*, 2015). Therefore, comparisons between studies on mild OSA should be made carefully.

***Questionnaires***

All subjects completed the Index of Vascular Burden (Villeneuve *et al.*, 2009), which is the summation of self-reported cardiovascular conditions and risk factors, including hypertension, hyperlipidemia, diabetes, and coronary diseases. The Epworth Sleepiness Scale (Johns, 1991), the Beck Depression Inventory-II (Beck *et al.*, 1996) and the Beck Anxiety Inventory (Beck *et al.*, 1988) were used to characterize groups. The Montreal Cognitive Assessment was used to characterize global cognitive performance (Nasreddine *et al.*, 2005).

***Genotyping***

*BDNF* rs6265 Val66Met and *APOE4* alleles were genotype to ensure that carriers did not differ between groups, and thus, did not influence white matter analyses. Our group published the detailed genotyping protocol previously (Gosselin *et al.*, 2016).

***Magnetic resonance imaging acquisition***

All subjects were tested using a 3 Tesla magnetic resonance imaging (MRI) system (Magnetom Trio, Siemens Healthcare, USA) with a 32-channel head coil. First, a three-dimensional T1-weighted Turbo Flash multi-echo magnetization-prepared rapid gradient-echo was acquired with the following parameters: repetition time=2530 ms / root mean square of four echo times=1.64 ms, 3.50 ms, 5.36 ms, 7.22 ms; matrix size=256x256; field of view=256x256 mm; voxel size=1.0 mm isotropic; flip angle=7 º; and 176 sagittal orientations, pixel bandwidth=651 Hz/Px. In addition, a T2-weighted sequence (repetition time=6100 ms; echo time=98 ms; 35 slices; matrix size=448x358 mm; field of view=220 mm; voxel size=0.49x0.49x3.0 mm; flip angle=120º; pixel bandwidth= 223 Hz/Px) and a fluid-attenuated inversion recovery (FLAIR) sequence (repetition time=9000 ms; echo time=89 ms; 35 slices; matrix size=256x174 mm; field of view=220 mm; voxel size=0.43x0.43x3.0 mm; flip angle=130 º; pixel bandwidth= 283 Hz/Px) were acquired.

Afterward, a pulsed spin echo diffusion-weighted imaging sequence (echo-planar imaging) was acquired for all subjects. A reference image without diffusion was acquired (b=0 s/mm$^2$). Sixty-four uniformly distributed directions were acquired with a b-value=1000s/mm$^2$ with the following parameters: repetition time=9100 ms; echo time=89 ms; 72 slices; matrix

size= 120x120 mm; field of view= 240x240 mm; voxel size=2.0 mm isotropic; flip angle= 90 º; pixel bandwidth=1667 Hz/Px.

***Tract-Based Spatial Statistics and Diffusion tensor imaging processing***

Diffusion tensor imaging (DTI) scans were pre-processed with the Toolkit for Analysis in Diffusion MRI described online (www.unf-montreal.ca/toad/html/en/; Functional Neuroimaging Unit, *Institut Universitaire de Gériatrie de Montréal*, Montreal, Canada). This automated pipeline includes several steps: eddy-current and motion correction; upsampling to anatomical image resolution; registration of diffusion-weighted images to the anatomical image and atlas registration; MRtrix 3.0 tensor reconstruction with a iteratively reweighted linear least square estimator; and the extraction of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD).

After the pre-processing, all Tract-Based Spatial Statistics (TBSS) steps were performed with FSL as it is described online (www.fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/UserGuide; Analysis Group, FMRIB, Oxford, UK). FA images were registered, transformed non-linearly, and aligned to the FRMB58_FA standard-space image. Images also underwent an affine transformation to the Montreal Neurological Institute (MNI) 152 space. A mean FA skeleton of all subjects was then created and a threshold of 0.3 was chosen in order to maximize the elimination of voxel containing gray matter and cerebrospinal fluid (CSF). The thresholded mean FA skeleton determined which voxels were investigated. Individual FA data of all subjects was then projected onto the thresholded mean FA skeleton to perform statistical analyses. All these steps were also applied to MD, AD and RD images of all subjects, resulting in mean skeleton images and individual projected images for each metric.

***Free-water imaging***

We used the free-water (FW) imaging model described by Pasternak et al., which has been extensively described (Pasternak *et al.*, 2009). To summarize the model, it uses diffusion-weighted MRI data to estimate both the tissue and isotropic FW compartments in each voxel, as implemented in AMICO (Daducci *et al.*, 2015). This results in a FW fraction map for every subject with every voxel ranging from 0 to 1. Value approaching 1 corresponds

to voxel in the CSF, which are composed of water that diffuses almost completely freely with no brain tissue. Values approaching 0 correspond to brain tissue with minimal FW diffusion in the extracellular space. The average FW fraction brain value was extracted for each subject and adjusted in statistical models for the volume of CSF (see volumetric extraction). By adding CSF as a covariate to investigate the FW fraction that is not CSF.

***Volumetric extraction***

MRI T1-weighted images were processed using FreeSurfer image analysis suite version 5.3.0, which has been extensively described online (www.surfer.nmr.mgh.harvard.edu/; Laboratory for Computational Neuroimaging, Center for Biomedical Imaging, Charlestown, MA, USA). The complete processing pipeline named "recon-all" was run, which includes: automated affine registration to the MNI305 atlas, removal of non-brain tissues, volumetric segmentation and labeling of brain structures based on voxel intensities and a registered probabilistic atlas (Fischl *et al.*, 2002). Volumes were extracted from subjects' aseg.stats file, including white matter volumes (brainstem, cortical white matter, cerebellum white matter, corpus callosum) and gray matter volumes (cortex, total subcortical, bilateral thalamus, caudate, putamen, pallidum, hippocampus, amygdala). Moreover, ventricles volume, intracranial volume and CSF volume were also extracted.

***White matter hyperintensities quantification***

The volume of white matter hyperintensities (WMH) was segmented with the lesion growth algorithm into the Lesion Segmentation Toolbox version 2.0.15 (www.statistical-modelling.de/lst.html; Morphometry Group and Department of Statistics, Munich, Germany; Structural Brain Mapping Group, Jena, Germany) implemented in SPM12 (www.fil.ion.ucl.ac.uk/spm/software/spm12/; Wellcome Trust Centre for Neuroimaging, London, UK) and MATLAB 9.1 (www.mathworks.com/; MathWorks, Natick, MA, USA). The toolbox co-register TI-weighted and FLAIR MRI images. A binary lesion map is constructed for hyperintense areas on FLAIR images using a pre-chosen threshold of 0.1 (but 0.2 for 9 subjects). As suggested in the guidelines of the lesion segmentation toolbox, these thresholds were chosen visually by assessing the efficiency of several thresholds between 0.05 and 1.0 to correctly identified WMH for every subject. The visual inspection was confirmed

with the previous identification of WMH by a neuroradiologist. WMH volume is then obtained for each subject in ml.

***Statistical analyses***

Statistics were performed with SPSS 19 (IBM SPSS Statistics, New York, USA), except for DTI analyses that were performed within FSL. To assess if groups differed for demographic and sleep data, one-way ANOVAs or chi-square tests were performed between control, mild OSA and moderate-severe groups. To assess group differences of white matter FA, MD, AD and RD within FSL, voxel-wise one-tailed T-tests were performed using the command "randomise". Threshold-free cluster enhancement family-wise error (FWE)-corrected for multiple comparisons at $p<0.05$ was used to identify significant group effects with 10 000 conditional Monte Carlo permutations. These statistical tests were therefore performed on every voxel of the white matter skeleton.

For all other neuroimaging analyses (FW, volumetry, WMH), individual values were extracted for each subject. These results had either one value per subject (FW fraction, WMH) or a few values (volumetry) as opposed to hundreds for voxel-wise DTI analyses. Therefore, these analyses did not warrant inter-subject MRI spatial normalization or multiple comparisons' correction. Two-tailed ANCOVAs were performed between the three groups, and significant differences were further investigated with post-hoc tests. The p-threshold was set at $p<0.05$. For FW imaging, volume of CSF was added as a covariate to investigate group differences of FW fraction.

Because BMI was higher in moderate-severe OSA individuals compared with both control and mild OSA groups (see Table 2), it was included in all statistical analyses as a covariate. Moreover, the moderate-severe OSA group had significantly more men than other groups (see Table 2). Additional analyses were performed replacing BMI by sex as a covariate. Covariates (BMI and sex) were included in different statistical models instead of concomitantly in order to maximize statistical power since our control and moderate-severe groups had 18 and 20 subjects respectively. Although age has known effects on cerebral structure, we did not include it as a covariate in statistical models since no group difference was observed.

**Table E1.** Mean neuroimaging values in control, mild and moderate-severe OSA groups

| Variables | Control [1] | Mild OSA [2] | Moderate-Severe OSA [3] | *p* | Post-hoc tests |
|---|---|---|---|---|---|
| ***White matter DTI metrics*** | | | | | |
| MD (clusters) | 0.00083 (0.00003) | 0.00077 (0.00003) | 0.00079 (0.00004) | *†‡ | 1>2 |
| RD (clusters) | 0.00053 (0.00004) | 0.00045 (0.00004) | 0.00047 (0.00001) | *†‡ | 1>2 |
| AD (cluster) | 0.00138 (0.00003) | 0.00131 (0.00003) | 0.00133 (0.00004) | *†‡ | 1>2 |
| AD (corpus callosum) | 0.00180 (0.00017) | 0.00172 (0.00016) | 0.00171 (0.00018) | *†‡ | 1>3 |
| ***FW fraction*** | 0.044 (0.005) | 0.041 (0.004) | 0.044 (0.005) | †‡ | 1>2 |
| ***WMH (ml)*** | 3.0 (2.7) | 1.9 (1.9) | 2.2 (1.5) | ns | |
| ***Volumetry ($mm^3$)*** | | | | | |
| Intracranial volume | 1 498 747 (100 167) | 1 527 744 (141 252) | 1 576 641 (141 102) | ns | |
| Cerebrospinal volume | 1149 (218) | 1135 (228) | 1150 (216) | ns | |
| Cortical white matter | 419 138 (42 977) | 447 721 (56 361) | 448 485 (575 41) | ns | |
| Cerebellum white matter | 24 751 (2982) | 28 068 (4310) | 26 613 (4408) | †‡ | †1<2, 3, ‡1<2 |
| Brainstem | 20 056 (2003) | 22 146 (2171) | 22 236 (2474) | † | 1<2, 3 |
| Corpus callosum | 2567 (399) | 2960 (489) | 2868 (407) | †‡ | †1<2, 3, ‡1<2 |
| Cortex | 426 198 (31 987) | 436 660 (36 817) | 451 647 (44 728) | ns | |
| Total subcortical gray matter | 49 937 (3464) | 53 445 (4199) | 55 102 (5033) | †‡ | 1<2, 3 |
| Left thalamus | 6404 (575) | 7243 (856) | 7489 (987) | †‡ | 1<2, 3 |
| Right thalamus | 6275 (534) | 6671 (706) | 6811 (967) | ns | |
| Left caudate | 3398 (385) | 3463 (398) | 3636 (392) | ns | |
| Right caudate | 3516 (327) | 3592 (405) | 3773 (424) | ns | |
| Left putamen | 4732 (499) | 4936 (546) | 5087 (688) | ns | |
| Right putamen | 4453 (476) | 612 (574) | 4801 (579) | ns | |
| Left pallidum | 1331 (227) | 1428 (225) | 1480 (247) | ns | |
| Right pallidum | 1269 (143) | 1370 (165) | 1377 (174) | ns | |
| Left hippocampus | 2246 (496) | 3833 (455) | 3893 (386) | †‡ | 1<2, 3 |
| Right hippocampus | 3611 (440) | 3994 (426) | 4025 (412) | †‡ | 1<2, 3 |
| Left amygdala | 1306 (239) | 1489 (250) | 1512 (186) | †‡ | 1<2, 3 |
| Right amygdala | 1303 (152) | 1424 (184) | 1478 (175) | ‡ | 1<2, 3 |

Results are presented in the format mean (standard deviation). OSA, obstructive sleep apnea; DTI, diffusion tensor imaging; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity; FWE, Family-wise error;

FW, free-water imaging; WMH, white matter hyperintensities; ns, non-significant. *Voxel-wise analysis performed within FSL considered significant at a threshold-free cluster enhancement FWE-corrected for multiple comparisons at $p<0.05$ with 10 000 conditional Monte Carlo permutations. †Significant a $p<0.05$ when adjusted for body mass index. ‡Significant at $p<0.05$ when adjusted for sex.

# Chapitre 6. Discussion

## 6.1. Résumé des résultats obtenus

Avec les récentes avancées établissant un lien entre l'AOS et l'incidence de la démence, il est impératif de mieux comprendre comment l'AOS affecte la santé cérébrale. Dans les revues de littérature (Chapitre 2, Revues de la littérature 1 & 2), nous synthétisons les récentes découvertes liant l'AOS et la démence. Dans la Revue de la littérature 1, nous rapportons que l'AOS chez les personnes âgées est associée de façon indépendante au déclin cognitif, au trouble cognitif léger et à la démence. Nous soulevons également le rôle potentiel des perturbations du sommeil et de l'hypoxie dans l'altération de la plasticité synaptique et dans la production de processus pathophysiologiques propres à la démence de type Alzheimer. Dans la Revue de la littérature 2, nous établissons une liste de biomarqueurs de démence qui pourraient être évalués pour clarifier la relation entre l'AOS à la neurodégénérescence. Dans cette revue, nous montrons que plusieurs biomarqueurs associés à l'incidence de la démence ont aussi été retrouvés à des niveaux anormaux dans l'AOS. Ceci met en lumière plusieurs mécanismes potentiels communs entre l'AOS et la démence. L'AOS, par le biais de plusieurs mécanismes pathologiques, pourrait ainsi affecter la fonction et la structure du cerveau et donc, le rendre plus vulnérable aux processus neurodégénératifs. La neuroimagerie s'est avérée utile dans le contexte du vieillissement pathologique pour prédire le déclin cognitif et clarifier comment le cerveau vieillissant est affecté.

Ainsi, l'objectif de cette thèse était d'évaluer la relation entre l'AOS et le fonctionnement et la structure cérébrale chez des personnes âgées de plus de 55 ans. Le résumé des résultats obtenus est présenté dans le Tableau 1. Dans l'Article 1, nous avons évalué le fonctionnement cérébral au repos par le biais du flot sanguin cérébral régional en TEMP en relation avec plusieurs variables représentant la sévérité de l'AOS. Bien que seulement les personnes avec une AOS sévère présentaient de l'hypoperfusion, plusieurs corrélations ont été retrouvées. De l'hypoperfusion du cortex latéral et de l'hyperperfusion des structures sous-corticales médianes ont été observées en association avec plusieurs variables liées à la sévérité de l'AOS. Nous avons émis l'hypothèse que les hypoperfusions pouvaient représenter des dommages neuronaux et des processus neurodégénératifs tandis que les hyperperfusions localisées pouvaient être la représentation de processus compensatoires.

**Tableau 1.** Résumé des changements cérébraux observés dans l'AOS dans cette thèse

| | AOS LÉGÈRE | AOS MODÉRÉE | AOS SÉVÈRE |
|---|---|---|---|
| **Flot sanguin cérébral régional**<br>TEMP<br>Articles 1 et 2 | Aucune différence de groupe | Aucune différence de groupe | ↓ dans le cortex pariétal |
| | ↓ dans le cortex fronto-insulaire avec l'AOS en sommeil paradoxal | ↓ dans le cortex frontal, pariétal et temporal avec les évènements respiratoires, le ronflement, la somnolence et l'obésité<br>↑ dans les structures sous-corticales avec les évènements respiratoires, la fragmentation du sommeil et l'obésité<br>↓ dans le cortex fronto-insulaire avec l'AOS en sommeil paradoxal et dans le cortex pariéto-temporal avec l'AOS en sommeil lent | |
| **Matière grise mesurée par la volumétrie et l'épaisseur corticale**<br>IRM – Article 3 | ↑ dans le cortex frontal, pariétal et le thalamus avec l'hypoxémie et les perturbations respiratoires | ↑ dans le cortex frontal, cingulaire, pariétal et dans l'amygdale avec l'hypoxémie, les perturbations respiratoires et la fragmentation du sommeil | |
| **Matière blanche mesurée par les métriques de diffusion**<br>IRM – Article 4 | ↓ de la diffusivité axiale, radiale et moyenne dans les fibres d'association, de projection et commissurales | ↓ de la diffusivité axiale dans le corps calleux | |
| **Diffusion d'eau libre**<br>IRM – Article 4 | ↓ | Aucune différence de groupe | |
| **Matière blanche mesurée par la volumétrie**<br>IRM – Article 4 | ↑ dans le cervelet, le tronc cérébral et le corps calleux | ↑ dans le cervelet, le tronc cérébral et le corps calleux | |

Les éléments présentés en gris sont des différences de groupe comparativement au groupe témoin; les éléments présentés en bleu sont des corrélations. AOS, apnée obstructive du sommeil; TEMP, tomographie par émission monophotonique; IRM, imagerie par résonance magnétique.

Dans l'Article 2, nous avons évalué le fonctionnement cérébral au repos éveillé mesuré en TEMP, en relation avec l'AOS observée sommeil paradoxal et en sommeil lent séparément. Les évènements respiratoires en sommeil paradoxal étaient corrélés avec des régions hypoperfusées différentes de celles retrouvées en sommeil lent. De plus, chez les participants avec une AOS de faible sévérité, les évènements respiratoires en sommeil paradoxal étaient également associés à des hypoperfusions localisées, tandis que ceux en sommeil lent ne montraient pas cette association. Le type de sommeil qui est perturbé par les évènements respiratoires qui caractérisent l'AOS semble donc influencer le fonctionnement cérébral à l'éveil. De plus, les évènements respiratoires en sommeil paradoxal seraient plus dommageables pour le fonctionnement cérébral chez les individus avec une plus faible sévérité d'AOS.

Dans l'Article 3, notre objectif était de clarifier les changements de structure de matière grise en association avec des marqueurs de sévérité de l'AOS. Pour ce faire, nous avons évalué la matière grise avec la méthode de morphométrie basée sur le voxel, la volumétrie et l'épaisseur corticale mesurée en IRM. Une analyse en composantes principales nous a permis d'évaluer la contribution indépendante de l'hypoxémie, de la fragmentation du sommeil et des perturbations respiratoires. Bien que nous n'ayons pas observé de changements avec la méthode de morphométrie basée sur le voxel, nous avons observé plusieurs augmentations d'épaisseur corticale et de volume de matière grise en relation avec l'hypoxémie majoritairement, mais également avec la fragmentation du sommeil et les perturbations respiratoires. Ces résultats étaient aussi présents quand les participants avec de l'AOS sévère n'étaient pas inclus dans l'analyse. Nous avons émis l'hypothèse que ces augmentations dans notre échantillon composé principalement de participants asymptomatiques représentent potentiellement des mécanismes adaptatifs et réactifs.

Dans l'Article 4, nous voulions évaluer comment la sévérité de l'AOS affecte la matière blanche cérébrale. Nous avons mesuré l'intégrité de celle-ci par le biais de plusieurs méthodes : l'imagerie par tenseur de diffusion, l'imagerie de l'eau libre, la volumétrie et les hyperintensités. L'AOS légère était associée à une plus faible diffusivité moyenne, axiale, radiale étendue dans plusieurs faisceaux de la matière blanche et à une plus petite fraction d'eau libre. Dans l'AOS modérée à sévère, une réduction de la diffusivité axiale était localisée

dans le corps calleux seulement, suggérant une normalisation apparente des métriques de diffusion. Ainsi, l'AOS légère semble affecter la matière blanche et les différents niveaux de sévérité de l'AOS pourraient être caractérisés par des mécanismes pathologiques différents.

En résumé, nous avons observé que l'AOS chez les personnes âgées de plus de 55 ans est associée à des dysfonctions cérébrales caractérisées principalement par des hypoperfusions et quelques hyperperfusions localisées, des changements de structure de la matière grise caractérisés par de l'hypertrophie et des changements d'intégrité de la matière blanche caractérisés par une réduction de la diffusivité et de la fraction d'eau libre. Nous avons aussi observé que plusieurs facteurs influencent la santé cérébrale dans l'AOS, y compris la sévérité de l'AOS, les variables associées à l'AOS (hypoxie, fragmentation du sommeil, perturbations respiratoires), le phénotype (AOS en sommeil paradoxal) et la symptomatologie diurne (somnolence, cognition et humeur).

## 6.2. Modèle intégratif des changements cérébraux dans l'AOS

### *6.2.1. Trajectoire biphasique des changements cérébraux dans l'AOS*

Dans les conditions caractérisées par des dommages cérébraux importants, comme la démence et la maladie d'Alzheimer ou encore les AVC, le profil de neuroimagerie généralement observé correspond à de l'hypoperfusion (Osawa *et al.*, 2004; Shim *et al.*, 2006), de l'atrophie de la matière grise (Stebbins *et al.*, 2008; Pini *et al.*, 2016) ainsi qu'à une anisotropie réduite et une diffusivité augmentée dans la matière blanche (Alexander *et al.*, 2007; Sexton *et al.*, 2011). Ce profil est donc observé dans le contexte de dommages et de pertes cellulaires. Dans cette thèse, les résultats obtenus en neuroimagerie dans l'AOS ne sont que partiellement similaires à ce profil de dommage cérébral. En effet, bien que l'AOS soit associée à une hypoperfusion comme il était attendu dans un contexte de pertes cellulaires, des augmentations locales de la perfusion ainsi que les changements en IRM dans l'AOS ne correspondent pas à ce profil. Dans la littérature, l'AOS a été associée à des augmentations et des réductions pour chacune des modalités de neuroimagerie (voir Chapitre 1). Ceci suggère que l'AOS pourrait être associée à une trajectoire biphasique des changements cérébraux.

Dans cette thèse, des similarités entre le profil observé avec l'AOS chez les personnes âgées de plus de 55 ans et les stades précurseurs ou aigus de dommages cérébraux peuvent être relevées. Par exemple, dans les premiers stades de neurodégénérescence, des hyperperfusions régionales compensatoires, de l'hypertrophie de la matière grise, des réductions de la diffusivité dans la matière blanche et une réduction de la fraction de l'eau libre ont été rapportées (Chen *et al.*, 2011b; Codispoti *et al.*, 2012; Beason-Held *et al.*, 2013; Ryan *et al.*, 2013; Mak *et al.*, 2017; Montal *et al.*, 2018). Un profil similaire a également été rapporté dans les stades aigus après un AVC (Ahlhelm *et al.*, 2002; Nguyen *et al.*, 2005; Butcher *et al.*, 2007). Ainsi, comme d'autres auteurs avant nous (Rosenzweig *et al.*, 2015), nous émettons l'hypothèse que l'AOS pourrait avoir un impact biphasique sur le cerveau, qui d'une part serait associée à des processus aigus, réactifs, adaptatifs, compensatoires et potentiellement réversibles et, d'autre part, à des processus plus chroniques, pathologiques, neurodégénératifs, mésadaptés et irréversibles. Il est à noter que des processus « aigus » pourraient être en réaction à l'AOS de la nuit ou des quelques nuits précédentes. Quant à eux, les changements plus chroniques pourraient être des dommages tissulaires accumulés au cours des mois et des années en réponse à une AOS non traitée. La nature des processus causés par l'AOS dicterait donc les changements cérébraux mesurés en neuroimagerie.

Les effets biphasiques de l'hypoxie sont bien connus. Puisque l'oxygène est le substrat de l'énergie, l'hypoxie peut évidemment endommager le cerveau et créer des dommages cellulaires importants. Par contre, le concept de préconditionnement ischémique accorde un rôle neuroprotecteur à l'hypoxie. Des expositions courtes à de l'hypoxie intermittente légère ont été associées à une neuroprotection relative face à des dommages ischémiques subséquents (Almendros *et al.*, 2014). Une analogie pour expliquer le principe de préconditionnement ischémique est le vaccin : on présente un élément potentiellement toxique dans des conditions et des quantités adéquates pour permettre au système de se préparer à se défendre et se protéger face aux prochaines expositions. Il a été suggéré qu'un des substrats du préconditionnement ischémique pouvait être une meilleure réponse vasculaire qui limiterait l'impact d'une hypoxie subséquente. Dans un modèle animal, des niveaux différents d'hypoxie intermittente avant une lésion cérébrale ischémique étaient soit partiellement neuroprotecteurs ou provoquaient des dommages tissulaires plus importants (Jackman *et al.*,

2014). Dans l'AOS, une étude intéressante montre que, pour une sévérité similaire, les personnes avec une AOS et un haut niveau d'hypoxémie montraient de meilleures performances cognitives que les personnes avec une AOS ayant des niveaux d'hypoxémie plus légers (Hoth *et al.*, 2013). Bien que l'aspect biphasique de la fragmentation du sommeil soit moins bien documenté que pour l'hypoxie, certaines études suggèrent l'existence de ce type de relation sur le cerveau. Les perturbations du sommeil sont connues pour affecter négativement le fonctionnement cérébral (Medic *et al.*, 2017), mais autant une courte qu'une longue durée de sommeil ont été associées à un risque augmenté de désordre cognitif (Wu *et al.*, 2017).

### *6.2.2. Mécanismes potentiels et résultats de neuroimagerie*

Les mécanismes potentiels sous-tendant les changements cérébraux dans l'AOS ont été discutés dans chacun des articles séparément. Brièvement, les mécanismes candidats incluent l'œdème, l'inflammation, la gliose réactive, des modifications de la morphologie cellulaire et des mécanismes neurodégénératifs. Ces mécanismes ont tous été rapportés en relation avec l'AOS chez l'humain ou dans des modèles animaux imitant l'AOS (Aviles-Reyes *et al.*, 2010; Baronio *et al.*, 2013; Unnikrishnan *et al.*, 2015; Yun *et al.*, 2017).

À une extrémité de cette trajectoire biphasique se trouvent les processus aigus et réactifs. Une augmentation de la taille des cellules (œdème intracellulaire, gliose réactive, embranchement neuronal) et de leur quantité (gliose réactive, recrutement de cellules inflammatoires) augmenterait le volume et l'épaisseur corticale et diminuerait la diffusivité des molécules qui seraient restreintes par les cellules (Morocz *et al.*, 2001; Anderova *et al.*, 2011; Zhang *et al.*, 2012; Caverzasi *et al.*, 2014; Dall'Acqua *et al.*, 2017). La perfusion cérébrale régionale pourrait être augmentée par le biais de processus inflammatoires ou par des augmentations de perfusion compensatoires (Binks *et al.*, 2008; Sen *et al.*, 2016; Sagoo *et al.*, 2017). Par contre, il est possible que les cellules élargies par de l'œdème fonctionnent de façon moins efficace et provoquent une réduction de la perfusion régionale par une réduction de leur activité (Murr *et al.*, 1993). Les résultats observés en neuroimagerie dans cette thèse pourraient donc correspondre majoritairement à un stade aigu et réactif dans l'AOS. À l'autre extrémité de cette trajectoire biphasique se trouvent les processus pathologiques et chroniques. Une perte cellulaire (mort neuronale et gliale, neurodégénérescence, réduction de la taille des

cellules) réduirait l'épaisseur et le volume de la matière grise, augmenterait la diffusivité des molécules d'eau dans la matière blanche puisque celles-ci seraient moins limitées par les cellules et réduirait la perfusion des régions atteintes (Osawa *et al.*, 2004; Anderova *et al.*, 2011; Zhang *et al.*, 2012; Montal *et al.*, 2018; Phillips *et al.*, 2018). L'apparition d'hyperintensités de la matière blanche cérébrale serait quant à elle observée lorsqu'il y a des pertes cellulaires localisées (Wardlaw *et al.*, 2015). Dans la Figure 2, la trajectoire de chacune des modalités de neuroimagerie est représentée selon ce modèle biphasique des changements cérébraux dans l'AOS pour les résultats observés dans cette thèse (lignes continues) et les changements observés dans d'autres articles de la littérature ou dans un contexte de neurodégénérescence (lignes pointillées).

Il y a possiblement un recoupement entre les éléments de cette trajectoire biphasique. En effet, des processus aigus/chroniques ou réactifs/pathologiques pourraient être présents de façon concomitante chez un même individu. Dans le cas d'une balance égale entre les deux extrémités de cette trajectoire, une pseudo-normalisation pourrait empêcher l'observation de changements en neuroimagerie. Par exemple, une pseudo-normalisation des métriques de diffusion apparait de façon transitoire après un AVC (Ahlhelm *et al.*, 2002). Ceci est dû à la présence de processus qui réduisent et augmentent la diffusivité de façon concomitante. Ce pourrait être le cas chez les personnes avec AOS modérée à sévère chez qui nous observons des changements de diffusivité dans la matière blanche plus restreints. Il est également possible que certaines régions cérébrales soient plus vulnérables et présentent des processus de nature différente que ceux observés dans d'autres régions. Ce modèle de processus biphasiques pourrait donc expliquer les différences retrouvées dans la littérature par rapport aux changements de neuroimagerie dans l'AOS (voir Chapitre 1).

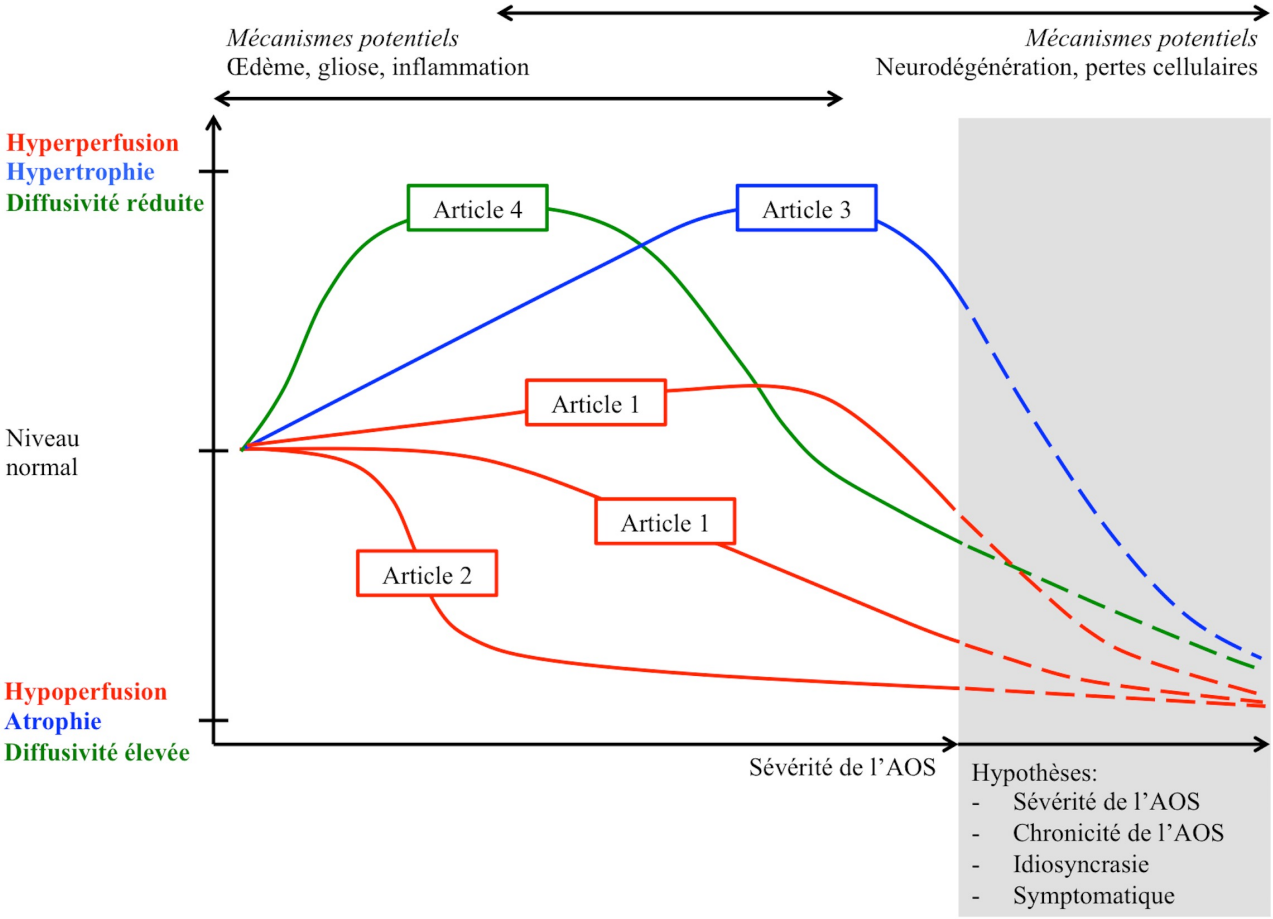


**Figure 2.** Intégration des résultats et hypothèses mécanistiques des changements cérébraux dans l'AOS.

**Dans l'Article 1**, des hypoperfusions localisées ont été observées chez les personnes avec de l'AOS sévère et en association à plusieurs variables représentant la sévérité de l'AOS, bien que des hyperperfusions localisées ont aussi été observées avec certaines variables. **Dans l'Article 2**, l'AOS en sommeil paradoxal était associée à des hypoperfusions localisées qui étaient également observées chez les personnes avec une AOS globalement plus légère. **Dans l'Article 3**, des hypertrophies locales de la matière grise ont été observées en association à l'hypoxémie principalement, ce qui était également observé lorsque les personnes avec une AOS sévère n'étaient pas considérées. **Dans l'Article 4**, l'AOS légère était associée à une réduction étendue de diffusivité moyenne, axiale et radiale dans la matière blanche accompagnée par une réduction de la fraction d'eau libre extracellulaire. Dans l'AOS modérée à sévère, seulement une réduction de la diffusivité axiale a été observée. **Le panneau gris** représente la trajectoire plus chronique et pathologique que les changements cérébraux mesurés en neuroimagerie pourraient emprunter dans l'AOS. Ces changements (hypoperfusion, atrophie, diffusivité élevée) ont tous été rapportés dans l'AOS, dans la neurodégénérescence et dans le contexte de dommages tissulaires.

### *6.2.3. Sévérité, phénotype et chronicité de l'AOS*

Dans cette thèse, nous avons évalué la sévérité de l'AOS par le biais de l'IAH de façon continue ou par groupe, mais nous avons également évalué le phénotype de l'AOS par le biais d'autres marqueurs (voir Tableau 1). En effet, bien que l'IAH est un marqueur grossier de l'AOS, sa représentativité comme marqueur de sévérité de l'AOS est contestée dans la littérature (Farre *et al.*, 2015; Punjabi, 2016; Rapoport, 2016). En effet, les limites de l'IAH comme mesure incluent les variations de critères définissant les hypopnées à travers les années, les coupures arbitraires qui définissent les groupes de sévérité et le fait que le niveau d'hypoxémie ou de fragmentation du sommeil associé aux évènements respiratoires n'est pas nécessairement représenté par cet index (Farre *et al.*, 2015; Punjabi, 2016). Par contre, aucune autre mesure individuelle ne semble être un meilleur candidat pour définir correctement la sévérité de l'AOS (Rapoport, 2016). Bien que ce ne soit pas nécessairement possible pour l'instant en contexte clinique, l'utilisation combinée de plusieurs marqueurs différents représente probablement mieux la pathologie de l'AOS. Nos résultats suggèrent que plusieurs facteurs dans l'AOS influencent la santé cérébrale et les changements mesurés en neuroimagerie. En plus de la sévérité globale mesurée par l'IAH, nos résultats de neuroimagerie suggèrent que l'hypoxémie joue un rôle important dans les hypoperfusions régionales (Article 1) et dans les hypertrophies de la matière grise (Article 3).

Selon le modèle biphasique présenté dans cette thèse, deux individus avec de l'AOS pourraient présenter des changements cérébraux différents : ces personnes seraient donc à des points différents de la trajectoire biphasique. Comme présenté dans la Figure 2 et le Tableau 1, nos résultats suggèrent que différents niveaux de sévérité de l'AOS pourraient être associés à un profil distinctif de changements cérébraux. Chez les personnes avec de l'AOS plus légère, seulement des réductions de la diffusivité dans la matière blanche seraient observées. Ceci suggèrerait que la matière blanche serait affectée par un niveau de sévérité relativement bas d'AOS (Article 4). Dans certains phénotypes spécifiques comme chez les personnes avec AOS en sommeil paradoxal ou chez les personnes avec des niveaux plus élevés d'hypoxémie, l'AOS avec une sévérité globale plus légère serait aussi associée à une hypoperfusion localisée et à de l'hypertrophie de la matière grise respectivement (Article 2 et 3). De plus, d'autres phénotypes spécifiques présenteraient une hyperperfusion localisée, comme les apnéiques

avec de l'obésité ou avec plus de fragmentation du sommeil (Article 1). Dans l'AOS plus sévère, on observerait une hypoperfusion, une hypertrophie de la matière grise et une normalisation apparente des métriques de diffusivité dans la matière blanche. Par contre, il faut noter que notre échantillon de participants comprenait peu de personnes avec de l'AOS très sévères, ce qui pourrait expliquer pourquoi l'extrémité chronique et pathologique de la trajectoire biphasique n'est pas bien représentée dans nos études (panneau gris, Figure 2). En effet, dans notre échantillon total avec tous les participants inclus dans les études, 24 % présentaient de l'AOS sévère avec une moyenne d'IAH de 45 évènements respiratoires par heure de sommeil. Par contre, certaines études précédentes évaluant les changements cérébraux dans l'AOS démontraient une moyenne de sévérité globale beaucoup plus élevée, allant jusqu'à un IAH de 72 (voir (Shi *et al.*, 2017b) pour une méta-analyse). En résumé, la sévérité globale ainsi que certains phénotypes de l'AOS pourraient dicter les changements cérébraux observés et donc, donner de l'information sur les processus cérébraux sous-jacents.

Un même individu pourrait montrer un profil différent de neuroimagerie dans le temps. Bien que nos résultats aient été obtenus à l'aide d'études transversales, il est possible de croire qu'un même individu pourrait montrer des différences au niveau des marqueurs de neuroimagerie dans le temps. Bien que ce ne soit pas le cas pour l'AOS modérée à sévère (Sforza *et al.*, 2017), l'AOS de sévérité légère tend à devenir modérée à sévère dans environ la moitié des cas après quelques années (Sahlman *et al.*, 2007). Avec une augmentation de la sévérité de l'AOS dans le temps, une personne pourrait développer des processus cérébraux de plus en plus pathologiques. De plus, un facteur important, mais malheureusement impossible à mesurer est la chronicité de l'AOS. L'AOS est souvent asymptomatique, spécialement chez les personnes âgées (Morrell *et al.*, 2012). Plusieurs personnes avec AOS ne sont pas au courant de leur condition, ce qui rend très difficile d'estimer la durée de l'AOS. De plus, même quand le patient reconnait la présence de symptômes, il se passe généralement plusieurs années avant le diagnostic et le traitement (Rahaghi and Basner, 1999). L'exposition répétée aux arrêts respiratoires sur plusieurs années dans l'AOS non traitée pourrait causer des dommages tissulaires plus importants et faire pencher la balance biphasique du côté pathologique et chronique. Dans notre échantillon, il est impossible de savoir combien de temps nos participants apnéiques présentaient la condition. Nous pouvons émettre l'hypothèse

que plusieurs d'entre eux pouvaient avoir développé la condition récemment puisque l'incidence de l'AOS augmente avec l'âge (Tufik *et al.*, 2010) et qu'ils étaient tous nouvellement diagnostiqués. Très peu d'études ont évalué les changements de neuroimagerie dans l'AOS non traitée. Dans une des seules études effectuées chez les personnes âgées, les personnes avec AOS non traitée montraient un amincissement du cortex après trois mois contrairement aux personnes traitées, et ce, malgré un niveau de base similaire chez les deux sous-groupes (qui pourrait être une normalisation apparente) (Dalmases *et al.*, 2015a). Ceci suggère que la chronicité de l'AOS non traitée pourrait causer plus de dommages tissulaires et donc, changer le profil observé en neuroimagerie.

### *6.2.4. Impact de l'AOS sur la santé cérébrale dans le vieillissement*

Un des facteurs ayant le potentiel de moduler la balance des processus réactifs/pathologiques ou aigus/chroniques est l'âge. Nos études sont parmi les seules à avoir évalué spécifiquement les changements cérébraux en relation avec l'AOS chez les personnes âgées de plus de 55 ans. Bien que des résultats similaires au profil de neuroimagerie que nous observons aient été rapportés chez des personnes plus jeunes (voir Chapitre 1), la majorité a rapporté un profil de dommages cérébraux potentiellement plus chronique et pathologique. Ceci suggère que le cerveau des personnes âgées est peut-être mieux outillé pour réagir de façon adaptative à l'AOS. Dans un modèle animal d'AOS, une réduction de la production de stress oxydatif en réponse aux apnées a été observée chez les animaux plus âgés comparativement aux plus jeunes (Dalmases *et al.*, 2014; Veasey, 2014). Chez l'humain, des fluctuations hémodynamiques moins importantes en réponse aux éveils et une fonction vasculaire moins affectée par l'AOS ont été rapportées chez les personnes plus âgées (Goff *et al.*, 2008; Yim-Yeh *et al.*, 2010). Il a été proposé que le préconditionnement ischémique de l'AOS pourrait faciliter la présence de mécanismes adaptatifs dans la population âgée (Lavie and Lavie, 2006).

Par contre, c'est bien sûr la population âgée qui est la plus à risque de présenter des processus neurodégénératifs. Dans un modèle animal d'AOS, une mort neuronale plus importante a été observée suite à de l'hypoxémie intermittente chez les animaux plus âgés comparativement aux plus jeunes (Gozal *et al.*, 2003). Ainsi, le vieillissement pourrait être

associé à plus de mécanismes compensatoires que chez les individus plus jeunes pour contrer les effets de l'AOS. Cependant, lorsque ces mécanismes compensatoires échouent, les conséquences pathologiques sont potentiellement plus grandes chez les individus plus âgés que chez ceux qui sont plus jeunes. En effet, bien que l'AOS soit associée à une multitude de mécanismes suggérant un vieillissement accéléré, il a été proposé que des changements épigénétiques pouvaient expliquer les différentes présentations et conséquences de l'AOS (Gaspar *et al.*, 2017).

Des facteurs idiosyncrasiques spécifiques à un individu pourraient également affecter la balance des processus biphasiques (Rosenzweig *et al.*, 2015). Parmi ces facteurs, le profil génétique et épigénétique, le style de vie, l'alimentation et la balance d'oxydoréduction (stress oxydatif et antioxydant) pourraient tous être des déterminants de la présence de processus réactifs ou pathologiques et donc affecter le profil en neuroimagerie observé dans l'AOS. De plus, il semble y avoir une grande variabilité interindividuelle au niveau de la réponse à la privation de sommeil et de la fréquence cyclique de l'hypoxémie, deux facteurs qui pourraient affecter les dommages cérébraux suivant l'AOS (Van Dongen and Dinges, 2005; Rosenzweig *et al.*, 2015).

### *6.2.5. Combinaison des modalités de neuroimagerie*

Dans le contexte de la maladie d'Alzheimer, l'utilisation de plusieurs modalités de neuroimagerie a permis de clarifier le décours temporel des processus neurodégénératifs (Jack *et al.*, 2013; Iturria-Medina *et al.*, 2016). Les modèles les plus récents montrent que les changements de perfusion cérébrale sont parmi les premiers à être mesurés dans les stades précurseurs de la neurodégénérescence et seraient suivis par les changements de structure cérébrale et les déficits cognitifs (Iturria-Medina *et al.*, 2016). Dans cette thèse, puisque nous avons évalué la sévérité de l'AOS plutôt que les changements cérébraux dans le temps, il est possible d'interpréter nos résultats selon un modèle « dose-réponse » (voir Figure 2). Dans ce contexte, les changements de diffusivité de la matière blanche semblent être affectés les premiers, suivis des changements de perfusion cérébrale et de structure de la matière grise. La matière blanche pourrait être plus vulnérable à l'AOS et les dommages de la matière blanche pourraient par la suite contribuer aux changements de fonction et de structure de la matière

grise. Il est aussi possible que la méthode d'imagerie par tenseur de diffusion soit plus sensible que les autres méthodes de neuroimagerie aux changements cérébraux dans l'AOS. La combinaison des méthodes d'imagerie pourrait nous aider à identifier à quel point de la trajectoire biphasique se trouve un individu. En effet, une personne avec AOS présentant une hypoperfusion localisée, de l'hypertrophie de la matière grise et très peu de changements de diffusivité dans la matière blanche (suggérant une normalisation apparente) pourrait présenter des mécanismes sous-jacents plus pathologiques qu'un autre individu qui présente seulement une réduction de la diffusivité dans la matière blanche et de l'hypertrophie de la matière grise. Dans cet exemple, la structure de la matière grise ne nous permettrait pas d'identifier le point dans la trajectoire biphasique, mais l'utilisation multimodale des marqueurs de neuroimagerie nous donne plus d'informations sur les mécanismes potentiels sous-jacents.

### *6.2.6. Hypothèses alternatives*

Outre l'hypothèse de la trajectoire biphasique, d'autres hypothèses pourraient expliquer les changements en neuroimagerie que nous observons dans cette thèse. Depuis maintenant plusieurs années, il existe un débat dans la littérature sur les changements cérébraux dans l'AOS : est-ce l'œuf ou la poule ? Est-ce que les changements cérébraux sont la cause ou la conséquence de l'AOS ? D'une part, l'AOS pourrait être causée par des changements dans les régions cérébrales impliquées dans le contrôle moteur des voies respiratoires supérieures et du sommeil (Gozal, 2002). Dans cette thèse, nous abordons l'hypothèse inverse que les changements cérébraux seraient une conséquence de l'AOS (Morrell and Glasser, 2011). L'argument le plus important en faveur de cette dernière hypothèse est que plusieurs études ont montré que les changements cérébraux sont réversibles par un traitement de l'AOS (Canessa *et al.*, 2011; Castronovo *et al.*, 2014; Shiota *et al.*, 2014; Kim *et al.*, 2016; Lin *et al.*, 2016; Kim *et al.*, 2017).

Une autre hypothèse qui diffère de celle que nous proposons dans cette thèse est que l'AOS serait une condition neuroprotectrice. Ainsi, selon cette hypothèse, les changements que nous avons interprétés comme réactifs, aigus et adaptatifs seraient en réalité une meilleure intégrité cérébrale caractérisée par plus de neurones et de cellules gliales sans processus pathologique. Cette hypothèse vient principalement du concept de préconditionnement

ischémique. Elle provient également des études montrant de l'hypertrophie de l'hippocampe dans l'AOS, une région où des processus de neurogenèse sont possibles (Rosenzweig *et al.*, 2013). Par contre, les changements cérébraux observés dans cette thèse sont beaucoup plus étendus que l'hippocampe uniquement. De plus, un profil de changements cérébraux en neuroimagerie similaire à ce qui est obtenu dans cette thèse est observé dans les conditions aiguës ou précurseurs de la démence et des AVC (Ahlhelm *et al.*, 2002; Nguyen *et al.*, 2005; Butcher *et al.*, 2007; Chen *et al.*, 2011b; Codispoti *et al.*, 2012; Beason-Held *et al.*, 2013; Ryan *et al.*, 2013; Mak *et al.*, 2017; Montal *et al.*, 2018), deux conditions pathologiques qui ont été associées à l'AOS à de multiples reprises (King and Cuellar, 2016; Leng *et al.*, 2017). Pour ces raisons, nous interprétons les augmentations de volume de matière grise, de perfusion cérébrale et les réductions de diffusivité de la matière blanche comme des processus réactifs et potentiellement même adaptatifs/compensatoires, mais pas comme neuroprotecteurs.

## 6.3. Impact clinique des changements cérébraux dans l'AOS

### *6.3.1. Régions cérébrales impliquées*

Comme les travaux précédents de neuroimagerie dans l'AOS l'ont démontré, les régions démontrant des changements de perfusion cérébrale et de structure de la matière grise dans nos études couvrent plusieurs régions cérébrales du cortex frontal, pariétal et temporal ainsi que des structures sous-corticales. Il est à noter que le cortex occipital ne semble pas affecté par l'AOS dans les études présentées dans cette thèse. Au niveau de la matière blanche, les fibres d'association, de projection et la matière blanche commissurale étaient affectées par l'AOS. Comme pour le cortex, la matière blanche du lobe occipital était très peu affectée par l'AOS. Certaines régions ont été retrouvées comme affectées par l'AOS dans plusieurs de nos études (voir Tableau 1). Parmi ces régions, on retrouve la région frontale supérieure médiane, le gyrus frontal moyen, le gyrus frontal inférieur, le cortex pariétal et temporal latéral, et plusieurs régions sous-corticales et corticales médiales, incluant l'hippocampe et le gyrus parahippocampique, l'amygdale, et les ganglions de la base. Puisque ces régions cérébrales affectées par l'AOS sont étendues, les conséquences cognitives qui pourraient découler de ces atteintes sont très variées.

Bien qu'il ne soit pas clair pourquoi ces régions seraient préférentiellement affectées par l'AOS, nous pouvons formuler l'hypothèse que le réseau du mode par défaut, dont ces régions font partie, serait particulièrement sensible à l'AOS. Ce réseau se désactive lors de l'exécution de tâches attentionnelles, mais montre un haut niveau d'activité au repos éveillé, semblant ainsi impliqué dans l'activité mentale spontanée et celle liée à la réflexion sur soi (Raichle, 2015). Dû à son fonctionnement quasi constant et ses grandes demandes métaboliques, ce réseau pourrait être particulièrement vulnérable aux perturbations métaboliques (Simic *et al.*, 2014) comme l'hypoxie. En effet, l'activité et la connectivité de ce réseau sont altérées dans l'AOS (Sweet *et al.*, 2010; Zhang *et al.*, 2013).

### *6.3.2. Symptomatologie de l'AOS*

Dans cette thèse, les groupes de participants avec AOS ne présentaient pas de différence avec les participants témoins au niveau des scores de somnolence diurne (mesurés avec l'*Epworth Sleepiness Scale*), des symptômes de dépression et d'anxiété (mesurés avec le *Beck Depression Inventory II* et *Beck Anxiety Inventory*) et la performance cognitive globale (mesurée avec le *Montreal Cognitive Assessment*) et ce, dans toutes les études (voir les tableaux des études individuelles). Cette absence de différence entre les participants avec l'AOS et les sujets témoins était observée pour tous les niveaux de sévérité d'AOS. Ceci suggère que nos participants étaient relativement asymptomatiques.

Puisqu'il est connu que l'AOS affecte la somnolence, l'humeur et la cognition (Saunamaki and Jehkonen, 2007; Sforza *et al.*, 2015; Stranks and Crowe, 2016), il est possible que le profil de neuroimagerie suggérant des processus aigus et réactifs dans cette thèse soit celui d'individus asymptomatiques. Par exemple, l'hypertrophie de la matière grise est un marqueur de neuroimagerie retrouvé chez les individus asymptomatiques dans les premiers stades de la neurodégénérescence (Ryan *et al.*, 2013; Mak *et al.*, 2017; Montal *et al.*, 2018). En effet, il est possible que ce soit le profil de neuroimagerie plus pathologique et chronique de la trajectoire biphasique proposée qui soit associé avec une symptomatologie marquée (Figure 2, panneau gris). De façon consistante, les seules associations retrouvées avec la symptomatologie dans nos études étaient chez des individus présentant des hypoperfusions, un marqueur de neuroimagerie se trouvant potentiellement plus du côté pathologique de la

trajectoire biphasique. Dans l'Article 1, nous avons observé une hypoperfusion du cortex frontal médian en relation avec les niveaux de somnolence. Dans l'Article 2, l'AOS en sommeil paradoxal était associée à des hypoperfusions frontales et insulaires ainsi qu'à une performance cognitive moins bonne et plus de symptômes dépressifs (tendances statistiques). Dans notre échantillon majoritairement asymptomatique, les personnes avec certaines hypoperfusions localisées pourraient donc présenter des symptômes.

## 6.4. Forces des études

### *6.4.1. Inclusion de multiples sévérités et variables liées à l'AOS*

Une des forces importantes de cette thèse est l'inclusion de toutes les sévérités de l'AOS. En effet, plusieurs études dans le domaine, spécialement en neuroimagerie, ont considéré l'AOS comme une condition dichotomique entre des individus sans AOS et des personnes avec AOS modérée à sévère. Les personnes avec AOS légère sont particulièrement négligées dans la recherche, mais également dans le contexte clinique. La déclaration de l'*American Thoracic Society* publiée en 2016 souligne que l'AOS légère est largement sous-étudiée, ce qui rend les conclusions sur son impact neurocognitif très limitées (Chowdhuri *et al.*, 2016). Dans cette thèse, des niveaux de sévérité d'AOS légers et modérés étaient associés à des changements cérébraux, y compris une hypoperfusion régionale cérébrale (Article 2, AOS en sommeil paradoxal), une hypertrophie de la matière grise (Article 3, hypoxémie chez les personnes sans AOS sévère) et des changements étendus au niveau de la diffusivité dans la matière blanche cérébrale (Article 4, AOS légère). Cette thèse appuie donc l'hypothèse que l'AOS plus légère a le potentiel d'affecter négativement la santé cérébrale. Nos résultats suggèrent aussi que l'IAH est un marqueur incomplet de la sévérité de l'AOS, étant donné les multiples changements cérébraux observés avec d'autres variables comme l'AOS en sommeil paradoxal, l'hypoxémie, la fragmentation du sommeil et même le ronflement.

### *6.4.2. Techniques de neuroimagerie variées dans un groupe d'âge critique*

Comme mentionné en introduction, les études évaluant les changements cérébraux en neuroimagerie dans l'AOS sont très limitées dans la population vieillissante. Ceci est étonnant étant donné l'association épidémiologique entre l'AOS et le développement de la démence

(Leng *et al.*, 2017). Comment mentionné précédemment, l'utilisation de plusieurs modalités de neuroimagerie a permis de clarifier le décours temporel des processus neurodégénératifs (Jack *et al.*, 2013; Iturria-Medina *et al.*, 2016). Dans cette thèse, l'utilisation de plusieurs méthodes de neuroimagerie nous a permis de dresser un portrait plus complet de la façon dont l'AOS est associée à diverses caractéristiques cérébrales. Plusieurs des résultats obtenus dans cette thèse supportent les mêmes mécanismes sous-jacents. Par exemple, l'hypertrophie de la matière grise combinée à la réduction de la diffusivité de la matière blanche ainsi que la réduction de l'eau libre pointent toutes vers des processus réactifs et aigus, comme l'œdème et la gliose. Bien que la neuroimagerie soit une méthode indirecte pour mesurer des processus cellulaires *in vivo*, la combinaison de méthodes nous permet d'avancer des hypothèses sur ce qui se passe dans le cerveau des personnes avec AOS. Puisque l'AOS est un facteur de risque modifiable, une meilleure compréhension des ses impacts sur le cerveau a le potentiel à long terme de pouvoir ralentir ou même prévenir les processus neurodégénératifs. Bien qu'ils doivent être répliqués dans cette population, les résultats présentés dans cette thèse nous permettent de mieux comprendre comment l'AOS affecte la santé cérébrale.

## 6.5. Limites des études

### *6.5.1. Évolution temporelle des changements cérébraux dans l'AOS*

Dans nos études, nous montrons des associations entre la sévérité de l'AOS et les changements cérébraux. Il est possible que ces changements évoluent dans le temps, ce que n'a pas évalué cette thèse. Dans le contexte de l'AOS comme facteur de risque de neurodégénérescence, il est important de comprendre si les changements cérébraux sont stables ou si ceux-ci progressent. Nous proposons que la chronicité de l'AOS non traitée puisse être un facteur qui fait pencher la trajectoire biphasique vers des processus pathologiques et des changements cérébraux plus importants. Par contre, ce modèle doit être validé dans des études longitudinales.

### *6.5.2. Représentativité de la population étudiée*

Une des limites importantes de notre échantillon, mais également de la littérature dans l'AOS, est la faible proportion de femmes incluses. Puisque moins de femmes présentent de

l'AOS, plusieurs études ont inclus des hommes uniquement. Ceci entraine une lacune dans la littérature par rapport aux impacts de l'AOS sur la santé cérébrale des femmes. Une étude en imagerie par tenseur de diffusion a montré que la matière blanche des femmes était particulièrement vulnérable à l'AOS (Macey *et al.*, 2012), suggérant un effet différentiel de l'AOS sur les changements cérébraux selon le sexe. Dans cette thèse, plusieurs des analyses statistiques étaient ajustées pour le sexe, ce qui nous a permis d'évaluer l'effet de l'AOS indépendamment du sexe. Par contre, ceci ne nous permet pas de comprendre comment le sexe module l'effet de l'AOS sur le cerveau. Dans notre échantillon, le nombre de femmes incluses ne nous permettait pas de faire des analyses par sexe pour évaluer cette question.

Une autre limite de notre population est que nous n'avions pas de mesure de pathologie de la maladie d'Alzheimer qui aurait indiqué les stades de neurodégénérescence sous-jacents. Aucun participant inclus dans notre étude ne présentait de démence et environ 20 % présentaient des déficits cognitifs (sans différence entre les apnéiques et les personnes témoins sans AOS). Des mesures de bêta-amyloïde ou de la protéine tau nous auraient permis de comparer l'interaction entre les processus neurodégénératifs et la présence d'AOS sur les changements cérébraux.

## 6.6. Perspectives futures

### *6.6.1. Incidence de démence*

Nos résultats soulèvent la question suivante : est-ce que les changements cérébraux observés dans l'AOS sont prédictifs du déclin cognitif ? Des études de cohortes longitudinales pourraient identifier les marqueurs de neuroimagerie qui prédisent l'incidence d'un déclin cognitif et la démence. L'identification de tels marqueurs permettrait de clarifier et valider les mécanismes liant l'AOS au déclin cognitif. L'évaluation de l'effet d'un traitement par PPC sur la vitesse de progression du déclin cognitif permettrait de vérifier si l'AOS est véritablement un facteur de risque modifiable dont le traitement aurait le potentiel de prévenir la neurodégénérescence. Certains de ces changements cérébraux observés dans cette thèse seraient aigus et réversibles, comme le montrent des études précédentes utilisant la PPC (Castronovo *et al.*, 2014; Shiota *et al.*, 2014; Lin *et al.*, 2016; Kim *et al.*, 2017).

### *6.6.2. Identification des individus vulnérables aux changements cérébraux*

Lorsque les impacts des différents marqueurs de sévérité et des phénotypes d'AOS sur la santé cérébrale seront mieux connus, une approche intéressante serait le développement d'un outil permettant un calcul de risque de déclin cognitif. Par exemple, en génétique, les scores polygéniques combinent plusieurs gènes identifiés comme facteurs de risque d'une pathologie comme la maladie d'Alzheimer, ce qui permet une meilleure prédiction du développement de la neurodégénérescence (Desikan *et al.*, 2017). Le *Framingham Risk Score* combine plusieurs facteurs de risque cardiovasculaires pour estimer le risque de développer une maladie coronarienne (Wilson *et al.*, 1998). Dans l'AOS, un score pourrait être dérivé de certaines mesures de sévérité et d'autres facteurs de risque (comorbidités, profil génétique, etc.) pour établir le risque de développer des processus neurodégénératifs. Selon les résultats de neuroimagerie présentés dans cette thèse, une personne avec AOS en sommeil paradoxal ou présentant plus d'hypoxémie aurait probablement un score prédicteur d'un risque plus élevé.

## 6.7. Conclusion générale

En raison de sa très grande prévalence ainsi que son association avec de multiples conditions médicales, l'AOS non diagnostiquée et non traitée représente un cout énorme pour la société et pour les individus. Ceci lui a valu récemment le nom de « crise cachée de la santé publique » (Watson, 2016). Les récentes découvertes épidémiologiques et mécanistiques identifiant l'AOS comme un facteur de risque de neurodégénérescence ajoutent une motivation supplémentaire afin de bien comprendre les impacts de l'AOS (Leng *et al.*, 2017; Polsek *et al.*, 2018). En effet, la démence étant incurable, l'intervention sur ses facteurs de risque est de la plus grande importance. Dans ce contexte, il est étonnant que la majorité des études ayant évalué la santé cérébrale par le biais de la neuroimagerie dans l'AOS aient été faites chez des personnes d'âge moyen.

Cette thèse nous a permis de montrer que chez les personnes âgées de plus de 55 ans qui sont majoritairement asymptomatiques, l'AOS est associée à des changements cérébraux mesurés en neuroimagerie. Nous avons observé des dysfonctions cérébrales caractérisées par des fluctuations de la perfusion cérébrale régionale dans plusieurs régions du cerveau des personnes apnéiques. De plus, nous avons observé des changements dans la structure

anatomique de la matière blanche et de la matière grise dans l'AOS. Finalement, nous avons également observé que plusieurs facteurs affectent la nature des changements cérébraux dans l'AOS, incluant sa sévérité, mais aussi des facteurs connexes comme l'intensité de l'hypoxémie et le stade de sommeil pendant lequel l'AOS se présente. Le profil de changements cérébraux observés en neuroimagerie dans cette thèse suggère la présence de mécanismes sous-jacents qui sont aigus, réactifs et potentiellement réversibles.

Malgré l'existence d'un traitement efficace pour l'AOS, elle est sous-diagnostiquée et sous-traitée. Les conclusions de cette thèse montrent que l'AOS affecte la santé cérébrale, et ce même chez les personnes avec de l'AOS légère. En revanche, puisque les résultats de neuroimagerie retrouvés dans nos études sont similaires aux stades précurseurs et non aux stades avancés de dommages tissulaires, il pourrait exister une fenêtre thérapeutique importante dans l'AOS. En effet, un traitement efficace par PPC pourrait ralentir, ou même prévenir les processus neurodégénératifs. Ces résultats pourraient être un incitatif important au traitement par PPC pour non seulement les personnes avec de l'AOS, mais également les cliniciens et les décideurs de la santé publique. En plus du traitement par PPC, certains facteurs de risque modifiables de l'AOS sont également des facteurs de risque de démence. Le risque d'AOS et de démence est augmenté par l'obésité et la cigarette, tandis qu'il est diminué par l'activité physique et la modération de la consommation d'alcool (Berg, 2008; Baumgart *et al.*, 2015). Comme pour le traitement par PPC, mieux comprendre comment l'AOS affecte le cerveau pourrait être une motivation importante sur la modification du style de vie des personnes à risque. Ceci soulève l'importance d'identifier les individus à risque de présenter des processus neurodégénératifs dans la population apnéique.

Pour conclure, l'AOS est un trouble du sommeil fréquent qui est de plus en plus reconnu comme ayant des conséquences graves sur la santé cérébrale. L'AOS est une condition complexe avec une multitude de facteurs qui sont associés avec des changements cérébraux dans le vieillissement. Par contre, il existe un côté positif puisque ces changements cérébraux pourraient être réversibles et donc, un traitement efficace de l'AOS pourrait contribuer à réduire l'incidence de la neurodégénérescence.

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