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CLINICAL REVIEW

Desperately seeking grey matter volume changes in sleep apnea: A methodological review of magnetic resonance brain voxel-based morphometry studies

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SUMMARY

Cognitive impairment related to obstructive sleep apnea might be explained by subtle changes in brain anatomy. This has been mainly investigated using magnetic resonance brain scans coupled with a voxel-based morphometry analysis. However, this approach is prone to several methodological pitfalls that may explain the large discrepancy in the results reported in the literature. We critically reviewed twelve papers addressing grey matter volume modifications in association with obstructive sleep apnea. Finally, based on strict methodological criteria, only three studies reported robust, but conflicting, results. No clear evidence has emerged and exploring brain alteration due to obstructive sleep apnea should thus be considered as an open field. We provide recommendations for designing additional robust voxel-based morphometry studies, notably the use of larger cohorts, which is the only way to solve the under-powered issue and the underestimated role of confounders in neuroimaging studies.

Introduction

Obstructive sleep apnea/hypopnea (OSA) is characterized by the repetitive occurrence of partial or complete pharyngeal collapse during sleep ended by oxyhemoglobin desaturation and/or micro-arousals. It is a growing health concern, with a prevalence ranging from 4% in men in middle-aged patients [1] to 50% in the elderly population [2]. Many adverse consequences are claimed to be associated with sleep apnea, such as sleepiness and associated car accidents [3], cardiovascular disease [4], cognitive impairment [5], diabetes [6], or even Alzheimer's disease [7], though some of these links remain debated in the scientific community.

This paper will only focus on OSA. Central sleep apnea [8] mainly caused by a defect in respiratory control is frequently encountered in heart failure as well as in the elderly or after a stroke and represents a specific entity. Hence, the relationship between central sleep apnea and brain structure abnormalities will not be explored in this paper.

Cognitive impairment, as well as the potential link with Alzheimer's disease, suggests that brain structures are altered in OSA. Brain insult may result from sleep fragmentation due to micro-arousals and intermittent hypoxemia (i.e., the repetition of a desaturation-reoxygenation sequence), which are the hallmarks of sleep apnea. In rodent models exposed to intermittent hypoxia, this intermittent hypoxemia is associated with cell death in some brain structures, particularly in the hippocampus [9].

Several authors have explored potential modifications of brain anatomy in patients with OSA using structural magnetic resonance (MR) brain scans and the voxel-based morphometry (VBM) methodology. The published results vary significantly and recently, two review papers [10,11] and a meta-analysis [12] have attempted to draw conclusions from the synthesis of these data. Although some of the authors [10,11] indicated that the discrepancies in the

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Abbreviations

AHI	apnea/hypopnea index
BMI	body mass index
BRAVO	brain volume
CPAP	continuous positive airway pressure
DTI	diffusion tensor imaging
ESS	Epworth sleepiness score
FDR	false discovery rate
FWE	family wise error
FWHM	full width at half maximum
GLM	general linear model
GM	grey matter
MPRAGE	magnetization prepared rapid acquisition gradient echo
MR/MRI	magnetic resonance/magnetic resonance imaging
OSA	obstructive sleep apnea
SPGR	spoiled gradient recalled
SPM	statistical parametric mapping
SVC	small volume correction
TIV	total intracranial volume
VBM	voxel-based morphometry
WM	white matter

literature probably reflect differences in image processing and statistical methods, a systematic analysis of the methodology adopted to produce the published results has not yet been conducted.

As a result, the goal of our paper was to question the neuroimaging methodology, from magnetic resonance imaging (MRI) acquisition to statistics used in the MRI/OSA literature and, consequently, the interpretation of results. Therefore, we first defined the minimum set of methodological criteria to be respected for a statistically robust exploration of the grey matter (GM) modifications using VBM. We then reviewed all studies addressing this point in OSA patients. Based on our predefined criteria, we critically reviewed the relevant literature and selected the robust papers to conclude about the possible GM modification due to OSA. We finally proposed methodological guidelines for further studies.

Methods

VBM standard pipeline and key methodological issues

VBM is a methodology developed to explore local brain volume changes [13] in which voxels are used as outcome measures to study the effects of explanatory variables. In the early days of VBM, Bookstein's controversy addressed some concerns regarding VBM methodology [14]. Fifteen years later, its statements remain true. The VBM pipeline, i.e., the image processing chain used to assess the possible tissue changes in MR brain scans due to some conditions, is composed of four steps: 1) image preprocessing, 2) modulation 3) model definition and 4) statistical analysis. The quality of each step clearly has a determinant influence on the quality of the final results and then on the interpretation. We defined a set of criteria to assess the quality of each step. Note that image acquisition is also an important step. In practice, image acquisition conditions may differ between studies, including different magnetic fields (from 1T to 3T), different voxel sizes (from 2*2*2 mm^3 to 1*1*1 mm^3) or the use of different MRI sequences (spoiled gradient recalled (SPGR), magnetization prepared rapid acquisition gradient echo (MPRAGE) and brain volume (BRAVO)). However, no clear quality criteria can be defined on these parameters.

Image preprocessing

VBM requires three basic steps: registration, segmentation and the subsequent spatial smoothing of the set of MR structural images for exploration. Since each individual brain image is different, each image must first be registered to a common reference. This step is crucial because imperfection in the registration of images among individuals may introduce bias to the statistics [14]. This reference can be either specific to the population under study and provided by a specific realignment algorithm, such as DARTEL [15], or a template based on the mean of several subjects, such as MNI305, which is based on the accurate realignment of MR brain scans of 305 healthy subjects. This latter reference allows for comparisons of the coordinates of the detected structural differences between studies using the same template. Segmentation provides a probability for each voxel to belong to a specific tissue. For instance, a probability equal to 0.8 for GM and 0.2 for white matter (WM) indicates that the corresponding voxel is likely to consist of GM. Spatial smoothing with a Gaussian kernel is then applied to respect the conditions of validity of the Gaussian random field theory, which is mainly used for statistical analysis, and also attenuates possible remaining differences between individual brains after registration.

For each study, the quality of the registration and segmentation steps crucially depends on the version of the corresponding algorithm available at that time. This dependence may explain why a reanalysis of a set of data with an upgraded version of the software could lead to different conclusions.

Statistical parametric mapping (SPM) is largely used in neuroimaging. The software was provided during the last 15 years in successive versions from SPM99 to SPM12 [16]. Clearly, each version provided improvements to some key steps compared to the previous one. SPM99 was released in January 2000 with a fully 3D nonlinear registration and used the MNI305 registration template as the default. Compared to SPM99, SPM2 contained few methodological improvements concerning registration and segmentation. In 2001, Good et al. [17] proposed a major modification to the protocol used up to the present called “optimized VBM”. This protocol aimed to correct the misclassification of some non-brain tissue by creating specific GM and WM templates, computing the transformation parameters to realign the segmented individual images to these specific templates, applying such parameters to the original images and finally segmenting the realigned images. SPM5 was a major improvement: it introduced the unified segmentation method [18] to realign and segment images in a combined and iterative manner. VBM5 was a VBM dedicated toolbox for the SPM5 version. SPM8 provided a new registration algorithm called DARTEL [15] which used an elastic deformation with a high number of degrees of freedom, and iteratively built a template specific to the studied population to considerably improve the quality of the fitting between each image and the computed template. The transformation of the template to a common reference, such as MNI305, was provided. Finally, unified segmentation was improved in modeling six head components, such as the fat signal from the scalp or signals from large veins, as opposed to only three brain tissues, a method often referred to as “New Segment”. This improvement permitted the removal of potential contamination from non-brain tissues that could lead to false positives.

Criterion 1: we considered that the more recent the software is, the more robust the result is; in particular, the use of elastic registration tools was of high importance.

Modulation

Modulation is an important aspect that we should consider. After realignment to a reference, the tissue volumes present in the realigned image may be modified due to the application of the