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Review article

Structural and functional neural adaptations in obstructive sleep apnea: An activation likelihood estimation meta-analysis

Masoud Tahmasian[a,b,1], Ivana Rosenzweig[c,1], Simon B. Eickhoff[d,e], Amir A. Sepehry[f], Angela R. Laird[g], Peter T. Fox[h,i], Mary J. Morrell[c,j,k], Habibolah Khazaie[a,*], Claudia R. Eickhoff[e,l]

[a] Sleep Disorders Research Center, Kermanshah University of Medical Sciences (KUMS), Kermanshah, Iran
[b] National Brain Mapping Center, Shahid Beheshti University (General & Medical campus), Tehran, Iran
[c] Sleep and Brain Plasticity Centre, Department of Neuroimaging, IOPPN, King's College and Imperial College, London, UK
[d] Institute of Clinical Neuroscience & Medical Psychology, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
[e] Institute of Neuroscience and Medicine (INM-1), Research Center Jülich, Jülich, Germany
[f] Division of Neurology, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada
[g] Department of Physics, Florida International University, Miami, FL, USA
[h] Research Imaging Institute, University of Texas Health Science Center, San Antonio, TX, USA
[i] South Texas Veterans Health Care System,San Antonio, TX 78229, USA
[j] Academic Unit of Sleep and Breathing, National Heart and Lung Institute, Imperial College London, UK
[k] NIHR Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London, UK
[l] Department of Psychiatry, Psychotherapy, and Psychosomatics, RWTH Aachen University, Aachen, Germany

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ABSTRACT

Obstructive sleep apnea (OSA) is a common multisystem chronic disorder. Functional and structural neuroimaging has been widely applied in patients with OSA, but these studies have often yielded diverse results. The present quantitative meta-analysis aims to identify consistent patterns of abnormal activation and grey matter loss in OSA across studies. We used PubMed to retrieve task/resting-state functional magnetic resonance imaging and voxel-based morphometry studies. Stereotactic data were extracted from fifteen studies, and subsequently tested for convergence using activation likelihood estimation. We found convergent evidence for structural atrophy and functional disturbances in the right basolateral amygdala/hippocampus and the right central insula. Functional characterization of these regions using the BrainMap database suggested associated dysfunction of emotional, sensory, and limbic processes. Assessment of task-based co-activation patterns furthermore indicated that the two regions obtained from the meta-analysis are part of a joint network comprising the anterior insula, posterior-medial frontal cortex and thalamus. Taken together, our findings highlight the role of right amygdala, hippocampus and insula in the abnormal emotional and sensory processing in OSA.

Contents

* Corresponding author at: Sleep Disorders Research Center, Kermanshah University of Medical Sciences (KUMS), Kermanshah, PO Box: 6719851151, Iran.
E-mail addresses: Sepehryaa@alumni.ubc.ca (A.A. Sepehry), hakhazaie@gmail.com (H. Khazaie).
[1] These authors contributed equally to this work.

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1. Introduction

Obstructive sleep apnea (OSA) is a chronic disorder that arises from recurrent partial or complete pharyngeal obstruction during sleep (Hiestand et al., 2006; Jordan et al., 2014; Kapur, 2010; Netzer et al., 2003; Rosenzweig et al., 2015). In patients with OSA, this leads to nocturnal apneas and hypopneas, intermittent hypoxia, reoxygenation and hyper-/hypocapnia events, along with sleep fragmentation, and changes in cerebral blood flow (Baril et al., 2015; Shiota et al., 2014; Yadav et al., 2013). The prevalence of OSA is noticeable in general population and around 50% in patients with cardiovascular or metabolic disorders (Khazaie et al., 2013, 2011; Lévy et al., 2015; Lurie, 2011).

Several recent studies highlighted that OSA contributes to emotional and cognitive decline, and it is increasingly considered as one of the rare modifiable risk factors for neurodegenerative dementia (Osorio et al., 2015; Rosenzweig et al., 2015; Yaffe et al., 2014, 2011). If untreated, OSA can result in varying degrees of cognitive deficits such as difficulties with attention, memory, executive functioning, and quality of life (Kryger et al., 2011; Rosenzweig et al., 2015). In addition, excessive daytime sleepiness, labile interpersonal relationships, and decreased work and school efficiency have all been documented in OSA patients (Kryger et al., 2011; Rosenzweig et al., 2015; Twigg et al., 2010). Moreover, it is recognized that OSA patients are two to thirteen times more likely to experience a driving-related traffic accident (Ellen et al., 2006; Karimi et al., 2015a, 2015b; Khazaie and Maroufi, 2014). Such accidents are more likely to occur in those who manifest greater daytime sleepiness, but are not necessarily related to sleepiness alone (Ellen et al., 2006; Weaver and George, 2011). In addition to cognitive and emotional deficits, increased prevalence of OSA in several psychiatric disorders has been reported, of which major depressive disorder (MDD), anxiety, and posttraumatic stress disorder (PTSD) appear best documented (Gupta and Simpson, 2015; Sharafkhaneh et al., 2005).

It has been suggested that adaptive and maladaptive processes both occur in patients with OSA in response to hypoxemia (Rosenzweig et al., 2015). The fine balance of these processes, and its eventual impact on neurocognitive and emotional performance, will depend on the stage of this dynamic process, effects on other organ systems, cognitive reserve, and idiosyncratic susceptibility (Lavie, 2015; Rosenzweig et al., 2016a,b, 2015; Sforza and Roche, 2012). Although these deficits are not always reversed with treatment (McDaid et al., 2009), a meta-analysis (Marshall et al., 2006) and a meta-review (Bucks et al., 2013) suggest beneficial effects of treatment (e.g. continuous positive airway pressure (CPAP)) on cognitive performance, sleepiness and neural injury in patients with OSA.

Over the last three decades, numerous structural and functional neuroimaging studies, including voxel-based morphometry (VBM), task functional magnetic resonance imaging (fMRI), and resting-state fMRI (rs-fMRI) have been conducted on patients with OSA. Structural and functional MRI imaging studies, however, often point to diverse results in OSA (Celle et al., 2015; Morrell and Glasser, 2011). The variability of the findings has been suggested to be due to relatively small sample sizes, with heterogeneous patient groups that differed in several key respects (e.g. diagnostic criteria, IQ, age, gender, and the imaging acquisition, preprocessing, and analysis methods); for more detailed discussion, please refer to (Gozal, 2013; Macey, 2012; Morrell and Glasser, 2011). To date, OSA structural studies have used a spatially unbiased analytical approach, such as commonly used mass-univariate approaches that rely on conservative statistical thresholds mandated by the large number of voxels compared between-groups (Ashburner and Friston, 2000). On the other hand, task fMRI studies used a variety of paradigms to study functional disturbances in particular disease. Recently, the activation likelihood estimation (ALE) method has been proposed as a useful methodology that, using coordinate-based meta-analyses (CBMA), provides a powerful tool to attain a synoptic view of distributed neuroimaging findings and different neuroimaging methods (e.g. structural and functional) in an objective and quantitative fashion (Eickhoff et al., 2009; Turkeltaub et al., 2002). More specifically, CBMA method searches for "where" in the brain the amount of convergence between reported foci is more than expected by chance, which yields to statistical inference on the integration of previous findings (Eickhoff and Bzdok, 2013; Eickhoff et al., 2012; Laird et al., 2009a; Turkeltaub et al., 2002).

Only structural OSA studies were hitherto analysed using the ALE method (Weng et al., 2014), and in order to fully address some of the previously raised concerns in the field about the diversity of these findings, we undertook the ALE meta-analysis of both functional and structural abnormalities recorded in patients with OSA. Our aim was to elucidate converging findings and to emphasize important brain nodes as highlighted via different neuroimaging modalities. We then functionally characterized the obtained regions that showed neurobiological aberrations in OSA patients by means of the BrainMap database, and also assessed their brain wide co-activation patterns to reveal networks that are (conjointly) connected to these obtained areas.

2. Methods

2.1. Search strategies and study selection

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher