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Sleep apnea: Altered brain connectivity underlying a working-memory challenge

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ABSTRACT

Obstructive sleep apnea (OSA) is characterized by the frequent presence of neuro-cognitive impairment. Recent studies associate cognitive dysfunction with altered resting-state brain connectivity between key nodes of the executive and default-mode networks, two anti-correlated functional networks whose strength of activation increases or decreases with cognitive activity, respectively. To date no study has investigated a relationship between cognitive impairment in OSA and brain connectivity during an *active* working-memory challenge. We thus investigated the effect of OSA on working-memory performance and underlying brain connectivity.

OSA patients and matched healthy controls underwent functional magnetic resonance imaging (*f*MRI) scanning while performing a 2-back working-memory task. Standard *f*MRI analyses highlighted the brain regions activated at increasing levels of working-memory load, which were used as seeds in connectivity analyses. The latter were based on a multiregional Psycho-Physiological-Interaction (PPI) approach, to unveil group differences in effective connectivity underlying working-memory performance.

Compared with controls, in OSA patients normal working-memory performance reflected in: a) reduced interhemispheric effective connectivity between the frontal "executive" nodes of the working-memory network, and b) increased right-hemispheric connectivity among regions mediating the "salience-based" switch from the default resting-state mode to the effortful cognitive activity associated with the executive network. The strength of such connections was correlated, at increasing task-demands, with executive (Stroop test) and memory (Digit Span test) performance in neuro-cognitive evaluations.

The analysis of effective connectivity changes during a working-memory challenge provides a complementary window, compared with resting-state studies, on the mechanisms supporting preserved performance despite functional and structural brain modifications in OSA.

1. Introduction

Obstructive Sleep Apnea (OSA) is a common clinical sleep disorder characterized by chronically fragmented sleep and intermittent hypoxemia, i.e. repeated episodes of oxygen desaturation alternating with episodes of reoxygenation (Peppard et al., 2013). OSA is associated with medical and psychological consequences (including obesity, hypertension, increased risk for vascular disease, depression, and excessive daytime sleepiness) (Rosenzweig et al., 2014; Stansbury and Strollo, 2015), and with neuro-cognitive impairments mainly involving executive functioning, attention and memory (Kylstra et al., 2013).

The increasing severity of cognitive impairments with aging (Sforza and Roche, 2012) may either reflect higher susceptibility of the aging brain to the neurological effects of OSA (Grigg-Damberger and Ralls, 2012), or reduced efficiency of compensatory mechanisms supporting cognitive performance in elderly (Ayalon et al., 2009). The latter hypothesis has been supported by neuroimaging studies addressing the neural correlates of cognitive impairment in OSA, typically with tasks tapping working-memory such as the n-back task. Different studies have reported increased or decreased brain activity, particularly in

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frontal (Thomas et al., 2005) and hippocampal (Castronovo et al., 2009) cortex, attributed either to compensatory mechanisms supporting performance (Castronovo et al., 2009) or to brain damage secondary to nocturnal hypoxemia (Ayalon et al., 2010; Gildeh et al., 2016). The former interpretation is supported by evidence on the effects of continuous positive airway pressure (cPAP) treatment. Increased hippocampal and left fronto-lateral activity, alongside reduced right fronto-lateral activity, has been reported in pre-treatment OSA (Castronovo et al., 2009). This over-recruitment reversed after treatment, possibly reflecting an increase in hippocampal and frontal grey matter volume correlating with the improvement in executive function, memory and attention (Canessa et al., 2011; Kim et al., 2016).

Recent interpretations of the neuro-cognitive impairment in OSA emphasize the role of *altered connectivity* among key structures for executive and memory processes, i.e. fronto-parietal regions, hippocampus, cerebellum and thalamus (Rosenzweig et al., 2014). This proposal found support in neuroimaging studies addressing *intrinsic* functional connectivity, i.e. the temporal correlation between activity in different brain networks at rest. These studies have highlighted, in OSA, abnormal activity in the right anterior insula, a crucial node of the salience network associated with high-level cognitive control and attentional processes (Menon and Uddin, 2010). Namely, intrinsic functional connectivity between the right anterior insula and the default mode network is reduced in patients, and the degree of such reduction is positively correlated with OSA severity (Zhang et al., 2015; see Khazaie et al., 2017).

To date, however, no study has investigated a relationship between cognitive impairment and *task-related brain connectivity* in OSA. While resting-state and active tasks involve largely overlapping connectivity patterns in normal subjects (Hampson et al., 2006; Canessa et al., 2017), also with the n-back task (Sala-Llonch et al., 2012), an active challenge may be more suitable to highlight subtle disease effects. Evidence on task-related abnormal connectivity in OSA may thus inform current models of neuro-cognitive impairment in this disease, and provide a baseline reference for assessing treatment effects.

We thus addressed the effect of OSA on brain connectivity underlying working-memory performance in the n-back task. We investigated whether our previous evidence of inter-hemispheric differences, in OSA patients vs. controls, reflects abnormal connectivity among the brain regions underlying task performance. On the basis of neuropsychological (Kylstra et al., 2013) and resting-state *f*MRI (Rosenzweig et al., 2014) evidence, we predicted that OSA patients would display abnormal connectivity between the networks triggering the salience-based switch from rest to executive control (Seeley et al., 2007).

2. Methods

2.1. Participants

The sample is the same of our previous *f*MRI study on brain activity associated with a working-memory challenge in OSA (Castronovo et al., 2009). Seventeen never-treated male OSA patients (mean age = 43.9 years, standard deviation [SD] = 7.5, mean education level = 12.2 years, SD = 2.9) and 15 male age- and education-matched healthy controls (mean age = 42.15 years, SD = 6.6, mean education level = 13.2 years, SD = 3.1) were recruited. All participants were right-handed (Oldfield, 1971) monolingual native speakers of Italian, and had normal or corrected-to-normal visual acuity. Participants had no evidence of stroke, uncontrolled hypertension (> 100/160), respiratory failure, and no current use of any psychoactive medications. Neuropsychiatric disorders or dementia were excluded based on the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). Inclusion criteria for OSA patients were: (a) diagnosis of severe OSA (apnea/hypopnea index [AHI > 30; see Section 2.2), and (b) age between 30 and 55 years. Healthy controls had an AHI < 5. In patients, Restless Legs Syndrome and Periodic Limb Movements were excluded based on a structured sleep interview performed by a sleep specialist, while insomnia was ruled out by 1-week sleep diary prior to inclusion in the study. Exclusion criteria were: (a) symptoms of cognitive deterioration (as indicated by a Mini-Mental score below 24), or (b) brain structural abnormalities, after evaluation of MR images by an experienced neuroradiologist. All participants, including healthy controls, reported regular sleep-wake schedules based on daily sleep diaries with an average total sleep time (TST) of 6.9 ± 1.1 h in the 4 days prior the study. All patients underwent a full nocturnal polysomnography (PSG), as well as an assessment of neuro-cognitive functioning (attention, memory and executive function), sleepiness (ESS), mood (BDI) and quality of life (SF-36). Three OSA patients were excluded from group-level analyses due to excessive head movements (> 3 mm) during scanning. Participants provided their written informed consent to the experimental procedure, which was previously approved by the local ethics committee.

2.2. Polysomnography

All OSA patients underwent PSG the night before functional scanning. Based on PSG, we defined apnea events as a ≥80% drop of respiratory amplitude, lasting at least 10s. Hypopneas were defined as a 50% drop of respiratory amplitude, lasting at least 10s, associated with repeated respiratory effort and arousals or oxygen saturation drops ≥3%. We defined the apnea/hypopnea index (AHI) as an index of the number of apnea and hypopnea events per hour of sleep. Time of oxygen saturation (SpO2) below 90% during total sleep, as well as the lowest nocturnal oxygen saturation value and the mean of the lowest peaks of SpO2 were also recorded. An arousal index (ArI) was calculated as the total number of arousals per hour of sleep (Iber et al., 2007), for subsequent correlation analyses with brain connectivity strength.

2.3. Neuropsychological evaluation

Both OSA patients and controls underwent a brief neuropsychological evaluation, lasting approximately 30 min, which included Rey word list recall (learning, recall, and recognition memory), Stroop color-word interference test (executive functions: inhibition, selective attention), Paced Auditory Serial Addition Test (PASAT; vigilance and executive functions). Participants were also administered the self-report Epworth Sleepiness Scale (ESS) to evaluate the subjective daytime somnolence, the Beck Depression Inventory (BDI) to evaluate mood, as well as the Quality of Life (SF-36) questionnaire. All tests were administered and scored according to standard procedures (Lezak et al., 2012).

2.4. Working-memory task during functional scanning

Participants performed a verbal version of the n-back task (Callicott et al., 1999; Nystrom et al., 2000; Owen et al., 2005), a classical test of working memory. In this task, the participant is required to monitor a series of stimuli and to respond whenever a stimulus (the “target” stimulus) is presented that is the same as the one presented *n* trials previously, where n is a pre-specified integer, usually 1, 2, or 3. Since the stimuli appear continuously, the task requires to temporarily store each of them in memory for evaluation (based on the contingent task), and to discard it before the appearance of the next one. Stimuli were pseudo-random sequences of letters, and three conditions were used that varied WM load (storage and manipulation demands) incrementally from zero to two items. In the 0-back condition, participants responded to a single pre-specified target letter (“X”). In the 1-back and 2-back conditions the target was any letter identical to the one presented 1 or 2 trials back, respectively.

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