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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.

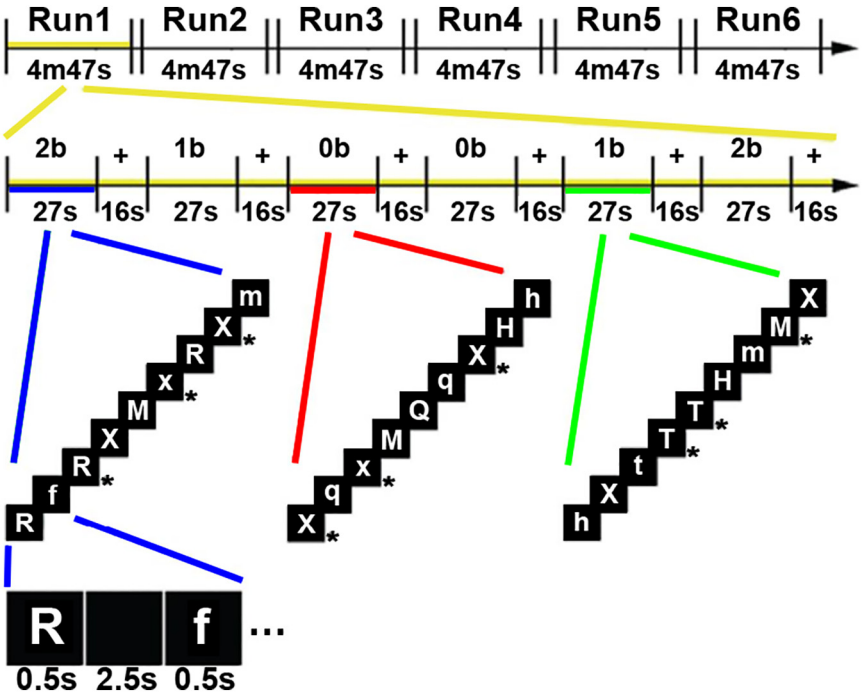

Fig. 1. Experimental design.
The study included 6 functional runs, each lasting 4 m 47 s (top). Every run included 2 blocked repetitions of each task (27 s) in a pseudo-random order, separated by a rest period (white-cross fixation; 16 s) (middle). Each task entailed a sequence of 9 letters, 3 of which (33%, indicated by asterisks) were "targets" (bottom). Subsequent letters, lasting 0.5 s, were separated by a black screen lasting 2.5 s. Reproduced from Castronovo et al. (2009; doi: 10.1164/rccm.201005-0693OC).

2.5. Experimental design and procedure

Participants underwent one MRI scanning session, composed by 6 functional runs lasting 4 min 47 s each (Fig. 1). We used an epoch design for the presentation of the stimuli, with every run including 2 blocked repetitions of each task (0-back, 1-back, 2-back) in a pseudo-random order. Each epoch, lasting 27 s, started with a screen displaying the instructions (2.4 s), followed by a sequence of 9 letters of which 3 (33%) were targets. Letters were successively presented in the center of the screen for 0.5 s, and were separated by a black screen interval lasting 2.5 s.

Both stimuli and instructions were depicted in white font on a black background. Participants responded to target letters by pressing one button on a keyboard with their right index finger. Successive blocks were separated by an implicit baseline (white fixation-cross) lasting 16 s. The order of the functional runs was individually randomized for every participant. Visual stimuli were viewed via a back-projection screen located in front of the scanner and a mirror placed on the head coil. The software Presentation 11.0 (http://www.neurobs.com) was used both for stimuli presentation and subjects' answers recording. All participants underwent a training session before scanning to ensure accurate task performance (> 80%). Due to technical problems with the response recording system, it was not possible to evaluate the behavioral performance of one control subject.

2.6. fMRI data acquisition

Anatomical T1-weighted and functional T2*-weighted MR images were acquired with a 3 Tesla Philips Achieva scanner (Philips Medical Systems, Best, NL), using an 8-channel Sense head coil (sense reduction factor = 2). Functional images were acquired using a T2*-weighted gradient-echo, echo-planar (EPI) pulse sequence (30 interleaved slices parallel to the bicommissural line, covering the whole brain, TR = 1700 ms, TE = 30 ms, flip angle = 85 degrees, FOV = 240 mm × 240 mm, no gap, slice thickness = 4 mm, in-plane resolution = 2 mm × 2 mm). Each scanning sequence comprised 167 sequential volumes. A high-resolution T1-weighted anatomical scan (150 slices, TR = 600 ms, TE = 20 ms, slice thickness = 1 mm, in-plane resolution 1 mm × 1 mm) was also acquired for each subject.

2.7. fMRI data preprocessing and statistical analyses

We performed image preprocessing and statistical analyses using SPM8 (http://www.fil.ion.ucl.ac.uk/spm), implemented in Matlab v7.4 (Mathworks, Inc., Sherborn, MA). For all participants, we discarded the first 5 volumes of every run to allow for T1 equilibration effects. The remaining 1002 volumes from each subject underwent a standard spatial pre-processing including spatial realignment to the first volume and unwarping, slice-timing correction with the middle slice in time as a reference, spatial normalization into the standard Montreal Neurological Institute (MNI) space (Friston et al., 1995; Worsley and Friston, 1995) and resampling in $2 \times 2 \times 2\,mm^3$ voxels, as well as spatial smoothing with a 8 mm full-width half-maximum (FWHM) isotropic Gaussian kernel.

We assessed the consistency of spatial normalization across subjects by computing the spatial correlation between the SPM EPI template and the smoothed normalized mean image of the realigned volumes. Such correlation was not significantly different across groups (mean controls = 0.9635; mean OSA = 0.9627; $t(54) = 0.4616$, $p = 0.6476$). Moreover, none of participants exceeded a cutoff of mean ± 3 SD, indicating a reliable and consistent spatial normalization. The Motion Fingerprint toolbox (http://www.medizin.uni-tuebingen.de/kinder/en/research/neuroimaging/software/) highlighted no significant group difference in scan-to-scan head motion (controls' mean: 0.078 mm ± 0.060; patients' mean: 0.109 mm ± 0.039; $t(54) = 1.60$, $p = 0.12$). The resulting time series across each voxel were high-pass filtered to 1/128 Hz, and serial autocorrelations were modeled as an Auto Regressive AR(1) process.

We performed two statistical analyses of *f*MRI data, via random-effect models implemented in a 2-level procedure (Friston et al., 1999).

The main categorical analysis was aimed at providing the psychological regressor (2-back vs. 1-back) for subsequent Psycho-PhysiologicaI-Interaction (PPI) analyses of task-related brain connectivity (Friston et al., 1997; Friston, 2011). At the first level we modeled blocks lasting 27 s, corresponding to the onset of 0-back, 1-back and 2-back tasks. We additionally modeled nuisance predictors coding for session effects and, despite the lack of significant group differences, scan-to-scan head motion. These regressors were convolved with a canonical hemodynamic response function (HRF), and the

Table 1
Demographic, clinical and neuro-cognitive variables.

	Controls (n = 14)	OSA (n = 14)	p-Value
Demographic and clinical variables			
Age (y)	42.15 ± 6.64	43.93 ± 7.78	n.s.
Education (y)	13.23 ± 3.09	12.57 ± 2.71	n.s.
BMI (kg/m^2)	26.10 ± 2.50	30.29 ± 4.76	0.01
AHI	–	50.14 ± 24.84	–
Mean spO2	–	89.09 ± 5.62	–
Time spO2 below 90% (min.)	–	26.19 ± 23.16	–
PAP use (min/night)	–	349.36 ± 34.15	–
Neuro-cognitive variables			
Rey's List (learning)	58.00 ± 7.01	48.70 ± 9.67	0.005
Rey's List (recall)	13.00 ± 1.96	10.59 ± 2.48	0.003
PASAT (number of errors)	5.13 ± 3.58	21.53 ± 10.07	< 0.0001
Stroop test (response time)	23.07 ± 8.14	39.12 ± 21.88	0.008
Stroop test (number of errors)	0.73 ± 1.03	5.31 ± 3.57	< 0.0001
ESS – sleepiness	3.00 ± 1.25	11.94 ± 5.47	< 0.0001
BDI – mood	1.46 ± 2.16	3.76 ± 3.94	0.013
SF-36 (quality of life)	80.89 ± 9.38	68.9 ± 19.72	0.027

BMI: body-mass index; AHI: apnea/hypopnea index; spO2: oxygen saturation; PAP: positive airway pressure; PASAT: Paced Auditory Serial Addition Test; ESS: Epworth sleepiness scale; BDI: Beck depression inventory; n.s.: statistically non significant.

corresponding parameter estimates were obtained at each voxel by maximum-likelihood estimation. We then used the resulting parameter estimates to produce, for every subject, "contrast images" corresponding to the effects of interest, i.e. 0-back, 1-back, 2-back, with respect to the implicit baseline level. At the second level we entered such images in an ANOVA to test the effect of different difficulty levels on task-related brain activity.

A second analysis, based on a parametric modeling of task difficulty, was aimed at assessing the consistency between the present and our previous *f*MRI results (Castronovo et al., 2009) despite a different preprocessing of *f*MRI data (see further details in Supplementary materials).

We used a threshold of $p < 0.05$ family-wise-error (FWE) corrected for multiple comparisons at the voxel level. We used the SPM Anatomy toolbox 2.2c (Eickhoff et al., 2005) to localize brain activations on cytoarchitectonic probabilistic maps of the human brain.

2.8. The effect of OSA on task-related effective connectivity

We then used Psycho-PhysiologicaI-Interaction (PPI) modeling (Friston et al., 1997) to investigate group differences in functional neural interactions underlying working-memory performance. The classical PPI approach highlights a significant increase/decrease of effective connectivity between a seed region and all other brain voxels in association with a given context, by regressing the activity at any point in the brain on the activity of the seed region. PPI represents an advancement with respect to functional connectivity analyses based on pairwise temporal correlation, which cannot disambiguate context-specific connectivity from resting-state connectivity or connectivity associated with a common neuromodulatory input. To discount correlations due to shared task inputs, indeed, the PPI model also includes as nuisance covariates the activity of the seed region and an experimental context, i.e. the physiological and psychological factors, respectively. The resulting regression coefficient thus represents, at every voxel, the degree of *effective* connectivity, i.e., change in activity per unit change in the seed region, or in simpler words a measure of the influence one neural system has on another, due to a psychological variable here represented by the task being 2-back vs. 1-back. This also entails that, unlike functional connectivity analyses based on temporal correlation, the effective connectivity between two given voxels may be asymmetric, thus informing about the direction of modulatory effects of one region over another.

Table 2
N-back performance during *f*MRI scanning.

Behavioral measure	Control (n = 14)	OSA (n = 14)	p-Value
0-Back			
Number of errors (/36)	0.27 ± 0.46	0.64 ± 0.93	n.s.
Missed responses (/36)	0.20 ± 0.56	0.57 ± 1.09	n.s.
Response time (s)	0.55 ± 0.17	0.51 ± 0.12	n.s.
1-Back			
Number of errors (/36)	0.40 ± 0.63	0.57 ± 1.40	n.s.
Missed responses (/36)	0.67 ± 1.23	1.29 ± 1.73	n.s.
Response time (s)	0.57 ± 0.18	0.54 ± 0.13	n.s.
2-Back			
Number of errors (/36)	1.73 ± 1.49	2.50 ± 2.07	n.s.
Missed responses (/36)	2.60 ± 3.30	3.57 ± 3.58	n.s.
Response time (s)	0.58 ± 0.17	0.60 ± 0.18	n.s.

n.s. non statistically significant.

Here we employed multiregional PPI (Cocchi et al., 2014), a generalization of the classical PPI approach assessing the connectivity between any *pairs of regions* among a pre-specified set of seeds rather than the connectivity between a seed and any brain voxel. This approach has already proven useful in the analysis of functional and effective connectivity of large-scale brain networks (Cocchi et al., 2012, 2014).

We first used the CONN toolbox (https://sites.google.com/view/conn/) to implement different denoising steps aiming to remove from voxel time-series non-neural noise related to subject-specific head motion parameters and physiological noise related to cardiac and respiratory sources, by means of the "anatomical component-based noise correction" (aCompCorr) method (Behzadi et al., 2007; Layden et al., 2017) (see Supplementary materials). This approach estimates noise from subject-specific masks of white matter (WM) and cerebro-spinal fluid (CSF) resulting from the segmentation of T1-weighted images. An indirect effect of this approach is thus to discount the potential contribution of subject-specific anatomical differences (including those associated with voxel-wise grey-matter volume) on brain activity and connectivity.

We selected 17 seeds corresponding to 6 mm-radius spheres centered on the coordinates of the maxima of the clusters highlighted by the contrast "2-back vs. 1-back" in the categorical analysis of *f*MRI data previously described. For each seed and participant we extracted the first eigenvariate of the whole timeseries, representing a summary of the responses within the region, from which we deconvolved the hemodynamic response function (HRF). We then multiplied such measure of the seed activity with the psychological factor (the "2-back minus 1-back" contrast) to determine the PPI signal, which was finally convolved with the HRF. As previously mentioned, we additionally modeled the "2-back minus 1-back" regressor and the activity of the seed region (i.e. the psychological and physiological factors, respectively) to discount correlations due to shared task inputs. We used multiple general linear models to investigate task-dependent influences of any given region upon another, with the dependent and explanatory variables being, respectively, the activity of the target region and the PPI term associated with the seed region. For all pairs of regions resulting from our 17 seeds we additionally assessed whether, in patients, the differential strength of connectivity in 2-back minus 1-back was positively or negatively related with: a) an arousal index resulting from polysomnographic recordings (see Section 2.2), or b) executive performance in the Stroop and Digit span (forward and backward) tasks, as assessed during the neuropsychological evaluation (see Section 2.3). This corresponds to testing an interaction between n-back difficulty and the relationship between brain connectivity and offline cognitive performance. Despite the lack of a significant group difference, we additionally modeled scan-to-scan head motion to remove its potential influence on brain connectivity.

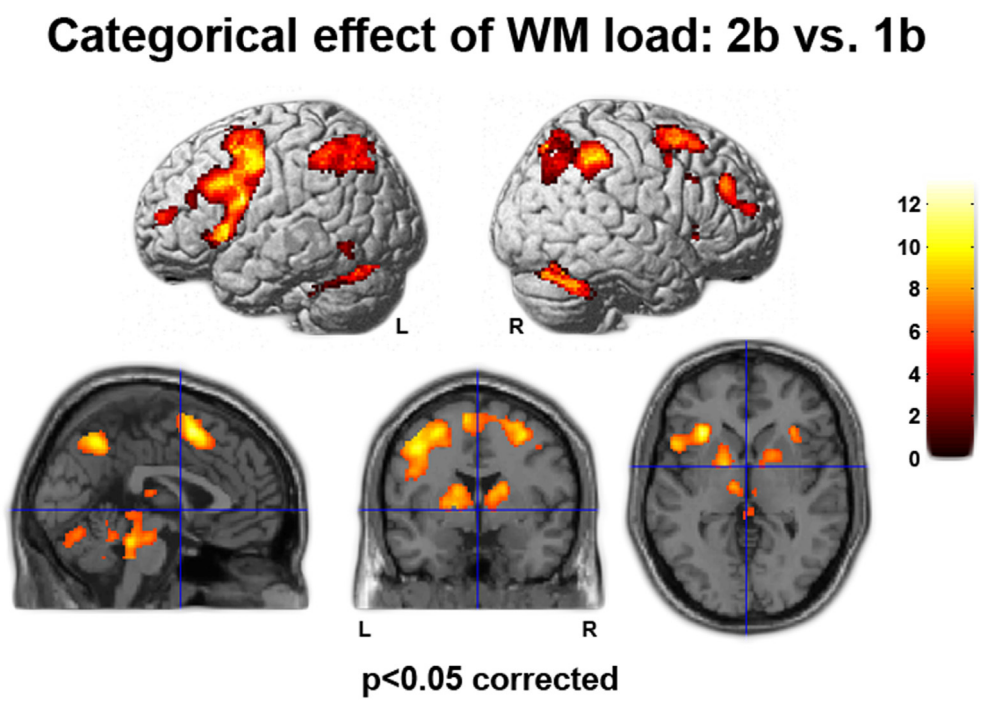

Fig. 2. Neural correlates of n-back performance.
The brain regions highlighted by a categorical modeling of 2-back vs. 1-back conditions in the whole sample of patients and controls. The statistical maps were thresholded at $p < 0.05$ family-wise error (FWE) corrected for multiple comparisons.

We reported as statistically significant only the results surviving a $p < 0.05$ threshold corrected for multiple comparisons with False Discovery Rate (FDR; Genovese et al., 2002).

2.9. The relationship between functional and morphometric levels of analysis

We additionally pursued a Voxel-Based-Morphometry (VBM) approach to address a possible relationship between the functional and structural neural bases of cognitive impairment in OSA. Namely, we assessed whether the strength of the connections which also displayed a significant group difference in the relationship with cognitive performance reflects the morphometric properties of their seed regions.

The VBM pre-processing, performed with SPM, entailed 4 steps on T1-weighted anatomical images (Ashburner and Friston, 2000): a) bias correction of intensity non-uniformities; b) spatial normalization to the standard MNI space; c) extraction of GM from the normalized images; (d) smoothing (8 mm FWHM) of the normalized images. We then used the same masks specified as seeds in CONN (see Section 2.8) to extract, from VBM images, average GM density values for off-line statistical analyses. We used a two-sample *t*-test to compare GM density in patients vs. controls, and a Pearson's correlation to assess a relationship between GM density and the strength of the effective connections which also displayed a significant group difference in the relationship with cognitive performance.

We applied a statistical threshold of $p < 0.05$ FDR corrected for multiple comparisons.

3. Results

3.1. Neuropsychological evaluation

Group comparisons highlighted no significant group difference in demographic variables (Table 1). Instead, compared with controls OSA patients displayed reduced performance in all cognitive measures alongside higher BMI and sleepiness.

3.2. Behavioral performance during scanning

We assessed participants' performance on the n-back task via two-sample *t*-tests, with the number of wrong responses, the number of missed responses or response time as dependent variables. As previously reported (Castronovo et al., 2009), no significant difference between OSA patients and controls was observed in any of these analyses and n-back conditions (all p-values > 0.05; Table 2).

3.3. Group differences in task-related brain activity

The categorical *f*MRI analysis resulted in neural activations consistent with the fronto-parietal and fronto-medial activity associated with performing the n-back (Owen et al., 2005) (Fig. 2; Table 3). Modeling task-difficulty in a parametric analysis confirmed this evidence (see Supplementary materials).

The “2-back vs. 1-back” comparison represented the psychological factor underlying PPI analyses of effective connectivity. In the whole sample of subjects this comparison resulted in the bilateral activation of a wide frontolateral-frontomedial-parietal network encompassing the superior and inferior parietal lobules bilaterally, the supplementary motor area (SMA) in the medial wall, as well as the precentral gyrus, fronto-insular cortex (pars triangularis of the inferior frontal gyrus and anterior insula), cerebellum and thalamus (Fig. 2).

VBM results showed no significant group difference in GM density in any of the clusters highlighted by *f*MRI data.

3.4. Group differences in task-related effective connectivity

We assessed the effect of OSA on brain connectivity underlying working-memory performance among the brain regions associated with the 2-back vs. 1-back comparison in the whole sample.

Compared with controls, OSA patients displayed *reduced* effective connectivity from the right frontopolar cortex (FPC) and middle frontal gyrus to the left FPC (Fig. 3). In addition, they displayed significantly *increased* effective connectivity from a) the right FPC to the thalamus, b)

Table 3
Neural correlates of n-back performance: 2-back vs. 1-back.

K	H	Anatomical region	Labeling	x	y	z	t-score
5479	L	Insula Lobe		−30	24	4	11.94
	L	Posterior-Medial Frontal		−2	10	56	11.62
	L	Precentral Gyrus		−42	0	44	10.62
	L	Middle Frontal Gyrus		−28	0	56	9.87
	R	Middle Frontal Gyrus		28	4	56	9.48
	L	IFG (pars Opercularis)	Area 44	−48	14	4	9.25
	L	IFG (pars Triangularis)	Area 44	−50	16	2	9.22
115	L	Middle Frontal Gyrus		−34	52	10	8.05
333	R	Middle Frontal Gyrus		38	38	30	8.65
	R	Middle Frontal Gyrus		36	52	16	7.46
34	R	Precentral Gyrus		44	2	46	6.93
8	R	IFG (pars Opercularis)	Area 45	52	20	32	6.01
90	R	Insula Lobe		34	24	−2	7.86
5310	L	Inferior Parietal Lobule	Area hIP3 (IPS)	−30	−56	44	13.22
	L	Precuneus	Area 7A (SPL)	−8	−66	48	12.03
	L	Inferior Parietal Lobule	Area hIP1 (IPS)	−36	−48	44	11.75
	R	Inferior Parietal Lobule	Area hIP2 (IPS)	46	−40	48	10.85
	R	Superior Parietal Lobule	Area 7P (SPL)	16	−72	52	10.24
	R	Precuneus		12	−60	50	8.65
37	L	Inferior Temporal Gyrus		−54	−58	−8	6.84
1306	L	Putamen		−18	4	6	11.64
		Thalamus	Thal: Prefrontal	−16	−14	18	9.84
3256	R	Cerebelum (VI)	Lobule VI	28	−64	−28	11.47
	R	Cerebellum (Crus 1)	Lobule VIIa crus 1	34	−54	−34	10.5
	L	Cerebellum (Crus 1)	Lobule VIIa crus 1	−42	−64	−28	9.27
	L	Cerebellum (VI)	Lobule VI	−30	−62	−24	9

The brain regions which were more strongly activated by performing the 2-back vs. 1-back task ($p < 0.05$ family-wise-error (FWE) corrected for multiple comparisons). Anatomical labeling was performed based on the overlap between each cluster and available cytoarchitectonic probability maps on the Anatomy Toolbox for SPM (v.2.2c; Eickhoff et al., 2005).
K: cluster extent in number of voxels ($2 \times 2 \times 2\,mm^3$); H: hemisphere; L: left; R: right; IFG: inferior frontal gyrus; IPS: intraparietal sulcus; SPL: superior parietal lobule.

the right insula to the right inferior parietal cortex, and c) the thalamus to the right FPC and right inferior parietal cortex.

We also examined a relationship between the differential strength of task-related connectivity in 2-back vs. 1-back and cognitive performance in tests assessing short-term memory (Digit span forward), working-memory (Digit span backward) and executive functioning (Stroop test) in OSA patients. Higher response-times on the Stroop were associated with reduced connectivity in the 2-back (vs. 1-back) from the left FPC to the right FPC, and from the right inferior parietal cortex to the right insula (Fig. 4 and Table 4).

Decreased performance at the Stroop reflected reduced connectivity from the dorsal anterior cingulate cortex to the right FPC. In contrast, higher performance on both the forward and backward digit span tasks reflected in increased connectivity from the right inferior parietal cortex to the medial precuneus.

For none of these connections the strength of connectivity was significantly related with a) grey matter density in the seed regions; b) an “arousal index” resulting from polysomnography recordings.

4. Discussion

We addressed the neural correlates of cognitive impairment in OSA in terms of effective connectivity between the brain regions underlying executive performance. While previous studies have addressed this issue by exploring intrinsic brain connectivity at rest, here we compared never-treated OSA patients with age- and education-matched healthy controls to assess task-related connectivity underlying a working-memory challenge in the n-back (Fig. 1).

A preliminary analysis of the brain activation pattern associated with increasing task-difficulty confirmed the well-known involvement of fronto-medial, fronto-lateral and parietal regions in working-memory (Owen et al., 2005) (Fig. 2). Moreover, a priori analyses based on our previous findings (Castronovo et al., 2009) confirmed that, in OSA patients compared with controls, normal working-memory performance is associated with increased left fronto-lateral activity and reduced right fronto-lateral activity.

Analyses of effective connectivity based on multiregional Psycho-Physiological-Interaction (PPI; Friston et al., 1997; Cocchi et al., 2014) provided novel cues into the neural bases of such abnormal organization of the working-memory network in OSA. In particular, the present data highlight *altered inter- and intra-hemispheric connectivity* among the lateral prefrontal, parietal and insular cortex as a biomarker of neurocognitive impairment in OSA (Figs. 3–4).

First, we observed *reduced* effective connectivity from the right FPC and dorsolateral prefrontal cortex to the left FPC in OSA patients vs. controls. All these regions are crucial components of a network, including also the inferior parietal cortex, supporting working-memory performance in the n-back task (Callicott et al., 1999; Owen et al., 2005).

Within this network, specific subprocesses have been linked to individual regions. The lateral prefrontal cortex has been suggested to contribute to the *strategic* control of working-memory processing, by selecting appropriate high-level organizational chunks to reduce the overall cognitive load and facilitate memory (Owen et al., 2005). In contrast, the role of parietal cortex in the n-back task has been interpreted in terms of storage and rehearsal of stimuli throughout task-performance (Smith and Jonides, 1998). In particular, the right-hemispheric region showing abnormal connectivity in OSA patients involves the dorsal sector of the inferior parietal cortex. The latter has been typically associated with domain-independent executive processes supporting tasks which require high attentional effort, such as those involving high working-memory load (Ravizza et al., 2004). The outputs of these regions are likely to converge on the FPC, which plays a key role in the coordination of information processing and integration of results between multiple separate cognitive operations required to accomplish supramodal higher-order goals (Owen et al., 2005; Koechlin et al., 1999).

In addition, the left vs. right frontopolar nodes of this network have been suggested to play different roles in working-memory performance. The left FPC is crucially involved in integrating and coordinating information from multiple brain regions (Koechlin et al., 1999), such as in the case when information on a primary task has to be integrated into an ongoing secondary task (De Pisapia et al., 2007). Its right-hemispheric counterpart has been associated either with sub-goal coordination (Braver and Bongiolatti, 2002) or with resuming an ongoing task following interruption by a subgoal (De Pisapia et al., 2007). Overall, the available evidence highlights the left FPC as the main hub of the working-memory network, integrating and coordinating signals from upstream brain regions.

Our evidence of decreased effective connectivity from the main right-hemispheric components of the working-memory brain network to its left frontopolar hub may thus represent a neural marker of *impaired interhemispheric coordination* in OSA patients. An analogous interpretation, in terms of impaired functional coordination of homotopic brain regions, has been proposed for other neuro-psychiatric disorders such as schizophrenia (Hoptman et al., 2012), major depressive disorder (Wang et al., 2013) and Alzheimer's dementia (Wang et al., 2015). In support to its clinical significance, in all these studies the

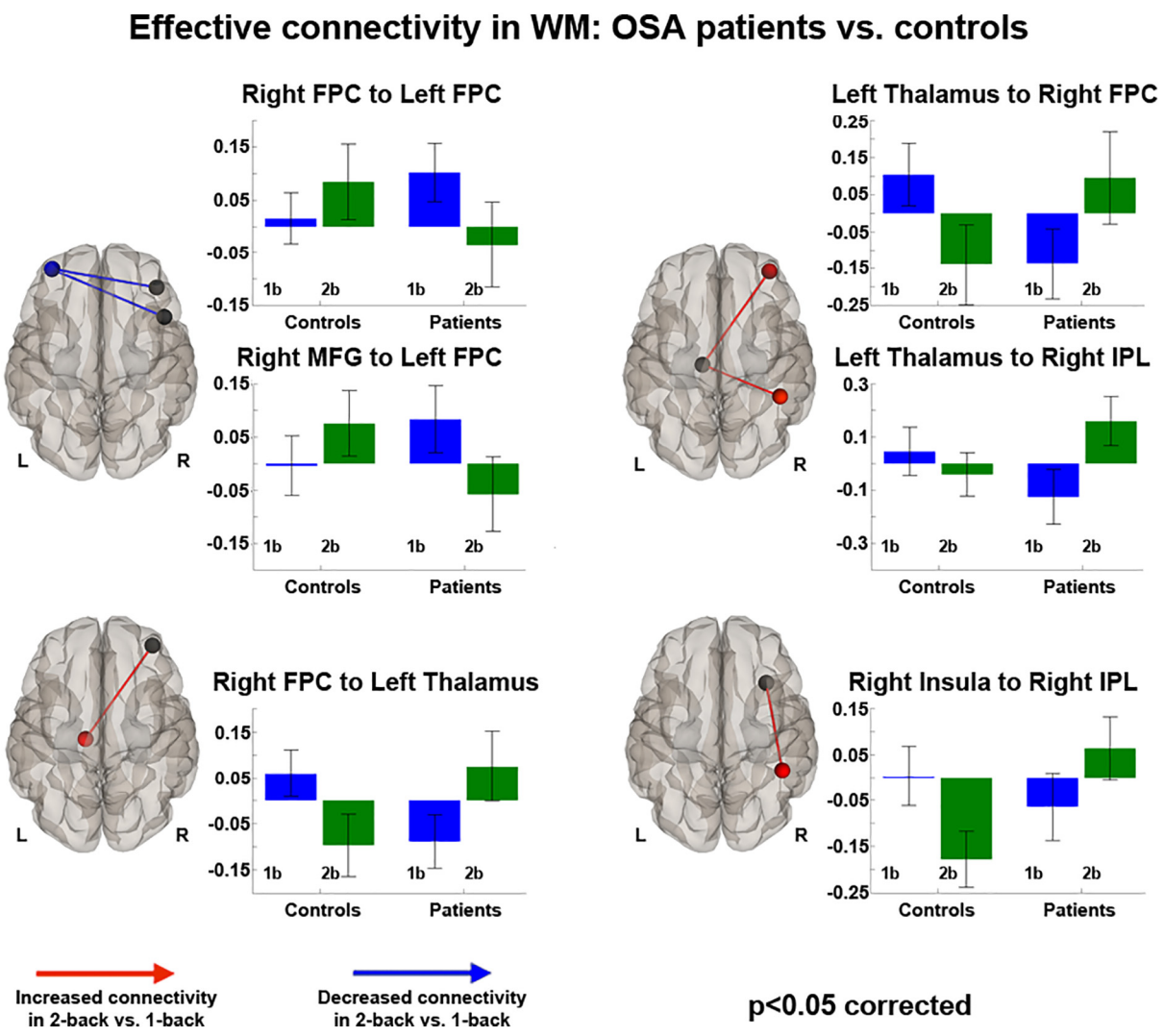

Fig. 3. Altered brain connectivity underlying working-memory in OSA.
The figure depicts a significant interaction between group (OSA vs. controls) and task (2-back vs. 1-back) on effective connectivity underlying working-memory performance. Blue and red lines represent, respectively, a decrease or increase in effective connectivity in OSA patients (vs. controls), among the brain regions underlying 2-back (vs. 1-back) performance. Such lines represent effective connections, i.e. the causal influence that the "source" region (black circle) exerts on the "target" region (colored circle), as highlighted by Psycho-Physiological-Interaction (PPI) analyses (Friston et al., 1997). For each panel, histograms depict the strength (mean ± standard deviation) of effective connectivity associated with the 1-back (blue columns) and 2-back (green columns), in OSA patients (right-sided columns) and controls (left-sided columns). The statistical maps were thresholded at $p < 0.05$ corrected for multiple comparisons with False Discovery Rate.

degree of reduction in interhemispheric connectivity, particularly in prefrontal regions, correlates with the severity of clinical symptoms or cognitive impairments. In line with these results, we also found a relationship between the extent of reduction of interhemispheric connectivity and decreased cognitive performance in tasks performed outside the MR scanner (Fig. 4). In particular, decreased effective connectivity to the right FPC from the left FPC and dorsal anterior cingulate cortex reflected, respectively, in slower and worse performance at the Stroop-task.

Previous studies have shown that normal performance reflects in the recruitment of additional resources, i.e. heightened neural activity, in OSA patients (Castronovo et al., 2009; Cabeza et al., 2002). In line with this view, we additionally observed an increase in the strength of connectivity within the right hemispheric nodes of the working-memory network, i.e. from the right FPC to the thalamus, from the right insula to the right inferior parietal cortex, and from the thalamus to the right FPC and right inferior parietal cortex. These changes need to be considered alongside the over-recruitment of hippocampal and left fronto-lateral cortex, which we have previously shown to be reversed by CPAP treatment (Castronovo et al., 2009).

The present data are thus compatible with two altered functional mechanisms in OSA, both revolving around the reduced effective connectivity between right and left FPC.

On one hand, the reduced contribution from the right-hemispheric nodes of the executive network might elicit the recruitment of additional computational resources, reflecting in increased left prefrontal activity. On the other hand, besides the frontopolar and inferior parietal regions previously discussed, increased connectivity in OSA involves also the right anterior insula and thalamus. The former structure is a crucial hub of the "salience" network, including also the thalamus, striatum and amygdala, which plays a key role in detecting behaviorally relevant stimuli and coordinating neural resources to guide appropriate goal-directed responses (Uddin, 2015). In broader terms, the right anterior insula mediates the switch between the default-mode and frontal executive networks (Sridharan et al., 2008), i.e. between rest and effortful cognitive activity, depending on the salience of external stimuli with respect to behavioral goals. In this process, the insula is considered to link perceptual, cognitive and autonomic information, by

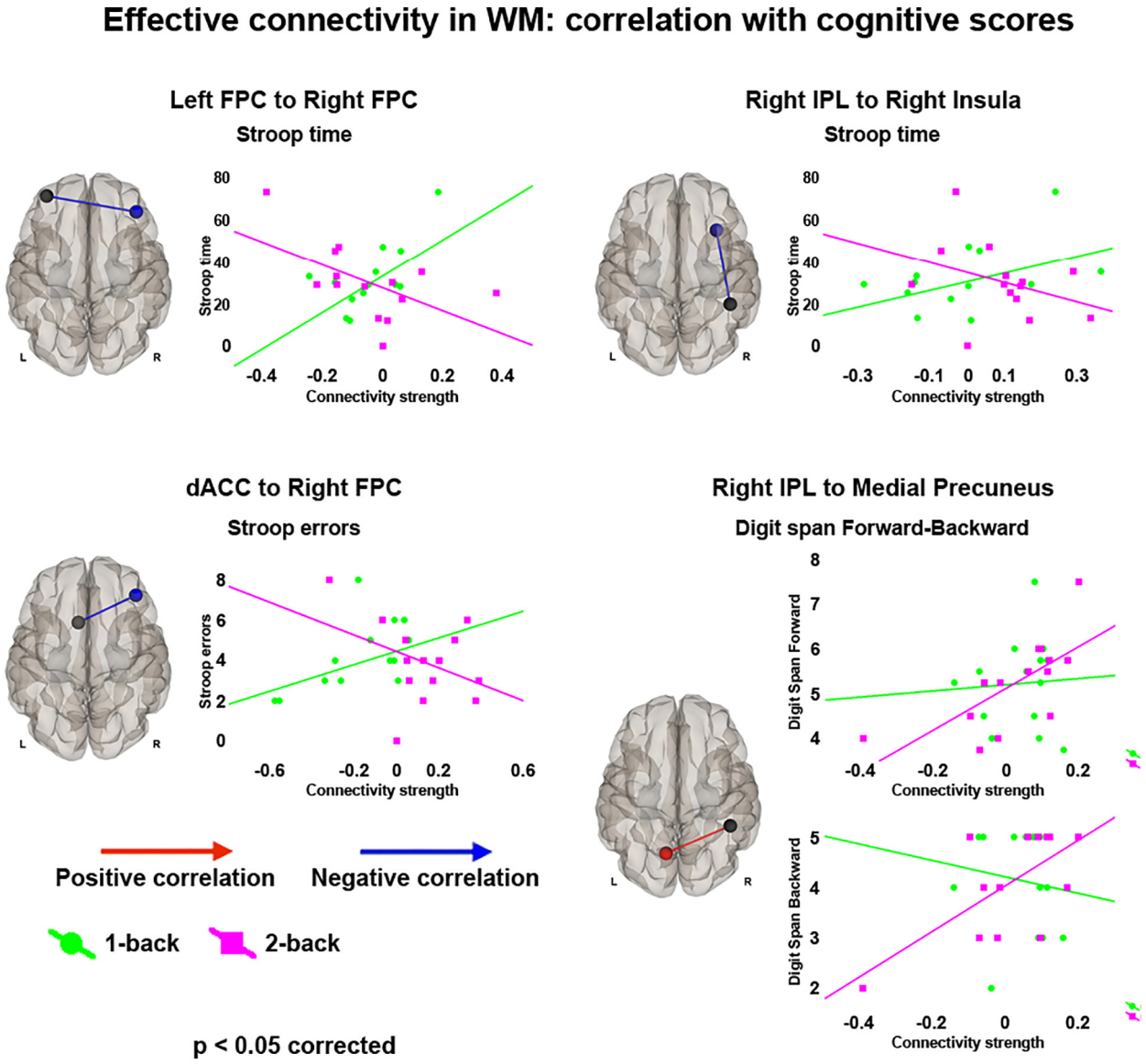

Fig. 4. Cognitive performance and brain connectivity in 2-back vs. 1-back in OSA.
The figure depicts a significant interaction between cognitive performance and effective connectivity in 2-back vs. 1-back tasks, i.e. the connections for which the strength of this correlation is significantly different across 2-back (magenta squares) and 1-back (green circles). As shown by categorized scatterplots, red and blue connections depict, respectively, a significantly stronger or weaker positive correlation with the 2-back than 1-back tasks.

Table 4
The relationship between task-related connectivity and neuro-cognitive functioning.

Connection & cognitive test	1-back		2-back		Interaction		
	Correlation	p-Value	Correlation	p-Value	F	DF	p-Value
left FPC-right FPC & Stroop Time	0.5296	0.0515	−0.5618	0.0366	13.29	1	0.001
right IPL-right Insula & Stroop Time	0.3984	0.1583	−0.3483	0.2224	6.87	1	0.016
dACC-right FPC & Stroop Errors	0.3494	0.2207	−0.3841	0.1751	11.95	1	0.002
right IPL-Precuneus & Digit Forward	0.0591	0.8409	0.6986	0.0054	6.32	1	0.019
right IPL-Precuneus & Digit Backward	−0.1373	0.6397	0.6652	0.0094	7.55	1	0.011

The columns on the left report the value and statistical significance of the correlation between cognitive performance and effective connectivity during the 1-back or 2-back tasks. The columns on the right indicate a significantly different relationship between cognitive performance and effective connectivity underlying the 2-back vs. 1-back conditions.

relaying salience signals related to the conditions of the body, generated by viscero-autonomics sensors and transmitted by thalamic nuclei (Uddin, 2015).

These findings are consistent with recent meta-analytic evidence of abnormal intrinsic brain activity in the right insula (Tahmasian et al., 2016) and GM atrophy in hippocampal and superior frontal cortex (Weng et al., 2014). Despite the lack of evidence on the hippocampus, which was not associated with n-back performance, our results indeed

highlight abnormal connectivity between the insular and prefrontal nodes of the salience network as a neural marker of impaired executive functioning in OSA.

Namely, the increased right-hemispheric connectivity from the thalamus and anterior insula (detecting behaviorally-relevant stimuli) to the frontopolar and inferior parietal cortex (underpinning working-memory performance) may underlie a salience-based mechanism attempting to restore normal connectivity in the whole network. This mechanism may represent the neurophysiological correlate of the higher threshold required, for the salience network, to switch from the "default" resting-state mode to the effortful cognitive activity associated with the fronto-parietal executive network at higher levels of daytime sleepiness. This functional mechanism may be subject to individual differences in disease severity, as suggested by the positive correlation between offline memory performance on both the forward and backward digit-span and connectivity from the right inferior parietal cortex to the medial precuneus.

The latter region, associated with visual memory retrieval (Callicott et al., 1999), may represent a visual buffer in working-memory tasks such as the n-back and backward digit-span, keeping track of previously encoded stimuli while discriminating between target and non-target current ones. A stronger connectivity from the right inferior parietal cortex associated with rehearsal processes (Owen et al., 2005) to the medial precuneus may thus reflect the stronger loading on processes supporting working-memory performance. This interpretation fits with resting-state *f*MRI evidence of abnormal activity in this region, associated with the posterior sector of the default-mode network, in OSA patients (Khazaie et al., 2017). In agreement with our interpretation of the observed findings, the reduced intrinsic connectivity between this region and the fronto-parietal executive networks has been suggested to underlie the defective salience-based switch from rest to effortful cognitive activity, possibly explaining OSA patients' deficits in sustained and divided attention (Rosenzweig et al., 2015, 2017).

5. Conclusions

Also in OSAs, like for healthy aging (Geerligs et al., 2015) or mild cognitive impairment (Catricalà et al., 2015), the analysis of abnormal task-related effective connectivity provides a complementary window, with respect to resting state studies, on the functional mechanisms supporting preserved cognitive performance despite functional and structural brain impairment. These results highlight the need of further studies addressing the potential usefulness of these changes as biomarkers of very early (prodromal) neurodegeneration (Pievani et al., 2014) and as a measure of treatment effects in multiple neuro-psychiatric conditions (Salvador et al., 2010).

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Author contributions

Nicola Canessa: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript.

Cinzia Castronovo: study concept and design, interpretation of data, study supervision.

Stefano F. Cappa: study concept and design, interpretation of data, critical revision of the manuscript for intellectual content, study supervision.

Sara Marelli: study concept and design, acquisition of data.

Antonella Iadanza: acquisition of data.

Andrea Falini: study concept and design, interpretation of data, study supervision.

Luigi Ferini-Strambi: study concept and design, interpretation of data, critical revision of the manuscript for intellectual content, study supervision

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2018.03.036.

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