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Resting state functional thalamic connectivity abnormalities in patients with post-stroke sleep apnoea: a pilot case-control study

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Abstract. – OBJECTIVE: Sleep apnoea is common after stroke, and has adverse effects on the clinical outcome of affected cases. Its pathophysiological mechanisms are only partially known. Increases in brain connectivity after stroke might influence networks involved in arousal modulation and breathing control. The aim of this study was to investigate the resting state functional MRI thalamic hyper connectivity of stroke patients affected by sleep apnoea (SA) with respect to cases not affected, and to healthy controls (HC).

PATIENTS AND METHODS: A series of stabilized strokes were submitted to 3T resting state functional MRI imaging and full polysomnography. The ventral-posterior-lateral thalamic nucleus was used as seed.

RESULTS: At the between groups comparison analysis, in SA cases versus HC, the regions significantly hyper-connected with the seed were those encoding noxious threats (frontal eye field, somatosensory association, secondary visual cortices). Comparisons between SA cases versus those without SA, revealed in the former group significantly increased connectivity with regions modulating the response to stimuli independently to their potentiality of threat (prefrontal, primary and somatosensory association, superolateral and medial-inferior temporal, associative and secondary occipital ones). Further significantly functionally hyper connections were documented with regions involved also in modulation of breathing during sleep (pons, midbrain, cerebellum, posterior cingulate cortices), and in the modulation of breathing response to chemical variations (anterior, posterior and para-hippocampal cingulate cortices).

CONCLUSIONS: Our preliminary data support the presence of functional hyper connectivity in thalamic circuits modulating sensorial stimuli, in patients with post-stroke sleep apnoea, possibly influencing both their arousal ability and breathing modulation during sleep.

Key Words
Resting state functional MRI, Sleep apnoea, Stroke, Polysomnography, Arousal.

Introduction

Sleep apnoea (SA) increases the risk of death, cardiovascular diseases, and stroke[1]. After a stroke, SA is highly prevalent[2], and stroke patients affected by SA have a worse clinical outcome than those not affected[3,4]. Involuntary control of breathing (i.e. changes in breathing mediated by hypoxic or hypercapnic stimuli) and arousal state are tightly connected one to the other: chemoreceptor stimulation produces arousal and, conversely, respiratory chemoreflex is arousal state dependent[5,6]. The neural mechanisms that underlie the reciprocal interactions between involuntary control of breathing and arousal are important because many sleep-related pathologies manifest as breathing disorders[7]. The ventral group of thalamic nuclei is involved in both wakefulness and chemosensation. Functional MRI (fcMRI) studies in awake healthy humans have shown that chemo-stimulation activates ventral-posterior-lateral thalamic nuclei (vpl-Th-n)[8,9]. Thalamic connections modulate arousability either by the direct action on the threshold of cortical areas to gate internal and external stimuli, or by the Ascending Reticular Activating System (ARAS)[10-12]. Resting state fcMRI (rs-fcMRI) allows to reliably study spontaneous brain activity under resting conditions, based on the blood oxygenation level–dependent (BOLD) signal, which arises from differences

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in local magnetic field in-homogeneities caused by changes in blood flow and deoxyhemoglobin content in the "active" tissue[13]. Rs-fcMRI, therefore, represents specific patterns of synchronous activity of anatomically separated brain regions[14], and is often used to study the functional organization of brain networks in healthy[15] and in stroke individuals[16-18]. Fluctuations in BOLD signal are correlated between regions of the motor network, both within and across hemispheres of the brain[19], and represent composite functional relationships of the anatomical paths that exist between brain regions[20]. Stroke induces widespread effects in functional connectivity between remote regions not directly lesioned[17,21]. Persistent increases in connectivity have been detected at rest in adult rat models of traumatic brain injury[22]. Following stroke enhanced functional activity has been reported, involving cortical and subcortical areas anatomically or functionally connected to the damaged ones[23-28]. Although the functional meaning of those "hyper connections" is still debated[17,29], it was postulated to represent compensatory neuronal plasticity phenomena[30], possibly affecting both arousal state and breathing during sleep[31]. We report here the preliminary results of a single center case-control study aimed at investigating the rs-fcMRI hyper connectivity of vpl-Th-n in stroke patients affected by SA, and to compare acquired data to those of cases not affected and to healthy controls (HC). The hypothesis is that SA and arousability may result from altered (more active) thalamic networks connectivity, consequent to their reorganization after stroke. This information may change the diagnostic and therapeutic approach to patients with SA after stroke.

Patients and Methods

Patients and Diagnostic Work-up

A continues series of stroke patients admitted to the Emergency Department Stroke Unit of our University Hospital were screened over a six months' period. Were eligible all acute ischemic strokes, confirmed by CT or MRI images, without time limits from stroke onset. Causes for exclusion were: general contraindications to MRI, any other known disease possibly influencing sleep or breathing during sleep (i.e. obstructive SA syndrome, sleep disorders, or polyneuropathy). At stroke onset, immediately before discharge and then at 3 months after stroke onset, participants were submitted to a complete clinical and diagnostic work-up. The study was conducted with the understanding and written consent of each participant according to the Declaration of Helsinki, and ethical approval was provided by the Institutional Review Board of our University Hospital.

Stroke Workup

Stroke workup included estimation of stroke severity by means of National Institutes of Health Stroke Scale (NIHSS), and assessment of both risk factors and causes of stroke, according to TOAST criteria[32-34].

Sleep Work-up

Sleep work-up included daytime sleepiness estimation with the Epworth Sleepiness Scale (ESS) questionnaire[35], screening for obstructive SA related symptoms other than daytime sleepiness[36], and an overnight home based full polysomnography (PSG)[37]. PSG was performed by the hand-held 34 channel Morpheus Ambulatory recorder by Micromed®S.r.l. Ambulatory 34 Channels. Home based PSG was preferred to standard laboratory recording in order to allow the patients to sleep in their home setting, without the need for adaptation. The following parameters were recorded: body position; rib-gage and abdominal respiratory efforts (Dual thoracic-abdominal respiratory inductance Plethysmography belts by Micromed®S.r.l. Accessories EPM915x A); oro-nasal airflow (thermistor transducer by Micromed®S.r.l. Accessories EPMs 1450-S); O2 saturation (finger pulse oximeter sensor); 8 EEG channels (2 frontal, 2 central, 2 temporal, 2 occipital); right and left electro-oculography, sub mental electromyography from surface electrodes, and ECG. Morpheus was retrieved the morning after the day on which the sensors were attached. Data were downloaded to the SystemPlusEvolution software, and subsequently analyzed by a sleep expert by the Rembrandt Sleep View software. Only PSGs with a total recording time > 4 hours and a total sleep time (TST) > 2 hours during which both NREM and REM sleep episodes were present were considered adequate. Sleep-stage scoring was done visually according to standard criteria[37].

Definitions

Sleep apnoea was defined as the cessation of airflow for at least 10 seconds. The SA was scored as obstructive (OSA) for absent nasal pres-

sure fluctuations with continued thoracic and/or abdominal efforts; it was scored as central (CSA) in the absence of thoracic and/or abdominal efforts. Central periodic breathing (CPB) was defined so as recommended[38]. A hypopnea was scored for a reduction for at least 10 seconds of 50% or more in nasal pressure. The nasal pressure signal was considered unreliable during periods of breathing through the mouth, as detected from the oral thermistor signal. During these periods, hypopneas were scored for a lower than 50% decrease in both thoracic and abdominal movement signals, lasting for 10 seconds or more, that were associated with an O_2 desaturation of more than 3%, or an arousal[37]. The number of apnoeas and apnoeas plus hypopneas/hour of sleep was expressed as apnoea-hypopnea index (AHI). SA was diagnosed for AHI > 5[35]. Arousals were defined as an abrupt change from a deeper stage of NREM sleep to a lighter stage, or from REM sleep toward wakefulness, with the possibility of awakening as the final outcome[39]. Arrhythmias were defined as any disturbance of the normal rhythmic beating of the heart according to Guilleminault et al[40].

Statistical Analysis

Statistical analysis was performed with SPSS (Statistical Package for Social Sciences – SPSS Inc., Chicago, IL, USA) version 23.0 for Windows. Patients with post-stroke SA were compared to those without apnoea in terms of age, gender, days from stroke to PSG evaluation, NIHSS at entry and at discharge from the Stroke Unit, body mass index (BMI), ESS, TST, total sleep period (TSP), sleep efficiency index (SEI), arousals/h sleep, sleep phases, arrhythmias/h of sleep, O_2 desaturation index (ODI), and causes of stroke. Categorical comparisons were analyzed using the two-tailed χ^2-test, and contingency analysis of 2×2 tables was performed via Fischer's exact test. Continuous data were analyzed using one-way Analysis of Variance (ANOVA). Correlation analyses were done using non-parametric tests (Spearman's rho). Statistical significance was set at $p<0.05$.

fMRI Acquisition and Analysis Methods

Stroke patients underwent conventional MRI and rs-fcMRI acquisitions on a single session (3 Tesla Siemens-Verio scanner equipped with a 12-channel head-coil), after 3 months from the acute event. Rs-fcMRI data of cases with SA were compared, separately, to rs-fcMRI data from 11 gender-matched HC and to those from patients without SA. During rs-fcMRI, subjects were instructed to keep their eyes closed, to remain motionless and to not think of anything. To minimize motion artifacts, subjects lay supine with pillows under the head, foam wedges at the sides and a retaining strap. Images were obtained using a interleaved Double-echo Turbo Spin Echo (TSE) sequence with proton density (PD), T2-weighted images (repetition time, TR: 3320 ms, echo time, TE: 10/103 ms, matrix: 384×384, field of view, FOV: 220 mm, slice thickness: 4 mm, gap: 1.2 mm, 50 axial slices), and a 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MP-RAGE) (TR: 2300 ms, TE: 2.98 ms, inversion time: 900 ms, flip angle: 9°, FOV: 256 mm, 208 slices in the sagittal plane, 1 mm isometric voxel). The rs-fcMRI study was performed with single-shot Echo-planar images (EPI) images (TR: 3000 ms, TE: 30 ms, flip angle: 90°, FOV: 240 mm, 46 axial slices, thickness: 3 mm, 140 volumes). A seed analysis approach was performed to identify those voxels showing functional signal time-courses correlated with the vpl-Th-n (Talairach Daemon Labels distributed with FSL-FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/) (peak Montreal Neurological Institute Coordinate System (MNI) coordinates: -18, -20, 4, with 3 mm radius). This region was selected because of its involvement in modulating the ventilatory response to chemical stimuli and in maintaining wakefulness[8,12]. Only the left vpl-Th-n was used as seed since one patient presented a lesion in the right thalamus, and because no differences should be expected in thalamus-cortical connectivity between the left and the right side. Functional data were processed using FSL as described previously[41], including motion correction, spatial smoothing with the 5 mm full width half maximal Gaussian kernel, and a temporal high-pass filter. MELODIC Independent Component Analysis (ICA) was performed in order to identify and remove noisy components due to scanner-related and physiological artifacts from the 4D fMRI data. Nonlinear registration using FMRIB's Nonlinear Image Registration Tool (FNIRT) was applied between the subject's structural and the standard space (the Montreal Neurological Institute 2 mm brain)[42]. Average time courses were extracted from seeds using FSL's feat query function. The pre-processed time series were then fitted with a linear model, consisting of a regressor representing the extract-

ed time courses. The spatially normalized effect size and standard error volumes served as input to a mixed effects group analysis in FSL FEAT. The modelled group and standard error were then divided to produce a volume whose voxels were T scores, subsequently transformed to Z scores. For both within- and between-group analyses, images were thresholded using clusters determined by $Z > 2.3$ and a corrected cluster significance threshold of $p < 0.05$, including at least 20 contiguous voxels.

Results

Twenty-eight patients entered the study. After the exclusion of cases that did not consent (n=3), of those with contraindication to MRI examination (n=6), or affected by diseases influencing possibly sleep and/or breathing during sleep (Parkinson disease n=1; known obstructive sleep apnoea n= 2; polyneuropathy n=4), 12 consecutive stroke patients were enrolled. Patients' mean age was 58.8±18 years. The mean BMI was 23.7±3 kg/m^2. The NIH-SS at discharge was 2±1.8 (range 0-6; median value 2). None of our cases presented language dysfunction. PSG was performed meanly 134.2±53 days after stroke (range: 87-282; median 124.5 days). In six cases (50%) a SA was registered. None of our patients was affected by CPB. No significant differences were found between patients with SA and non-apnoea-affected stroke cases in terms of demographics, clinical characteristics, risk factors or causes of stroke, risk factors for OSA, and PSG data (Table I). A significantly higher number of arrhythmias/h sleep was recorded in the group of cases without SA. Location of brain lesions at MRI after four months of stroke is reported in Table II.

Table I. Demographics, clinical characteristics, risk factors, polysomnographic data, and comparisons between stroke cases affected and not affected by sleep apnea.

	Cases affected by sleep apnea	Cases not affected by sleep apnea	*p* value*
Demographics			
Age (mean ± SD)	55 ± 22	63 ± 15	0.08
Gender (male) n (%)	5 (83)	2 (33)	0.08
Clinical characteristics (mean ± SD)			
Body Mass Index	25 ± 3	22 ± 4	0.37
Apnea-Hypopnea Index	12 ± 6	1 ± 1	**0.00**
Risk factors n (%)			
Hypertension	5 (83)	3 (50)	0.22
Smoke	1 (17)	1 (17)	0.89
Atrial fibrillation	0 (0)	0 (0)	/
Internal carotid artery stenosis	2 (33)	2 (33)	/
Diabetes mellitus	1 (17)	0 (0)	0.30
Ischemic heart diseases	1 (17)	0 (0)	0.30
Overweight	0 (0)	1 (17)	0.30
TOAST classification n (%)			0.75
Large vessels	1 (17)	1 (17)	
Embolic	0 (0)	0 (0)	
Lacunar	2 (33)	2 (33)	
Other/unknown	3 (50)	3 (50)	
PSG data (mean ± SD)			
Total sleep time (minutes)	324 ± 107	410 ± 85	0.42
Total sleep period (minutes)	372 ± 110	490 ± 73	0.21
Sleep efficiency index	78 ± 11	77 ± 13	0.35
Time spent in NREM (minutes)	80 ± 7.1	80 ± 7.3	0.74
Time spent in REM (minutes)	20 ± 7.1	19.3 ± 7.5	0.66
Arousals/h sleep	34 ± 21	18 ± 21	0.61
Arrhythmias/h sleep	1 ± 1	16 ± 35	**0.04**
Oxygen desaturation index	9 ± 7	4 ± 5	0.53

*χ^2 for categorical and T test for continuous variables.

Table II. Location of the brain lesions at conventional MRI performed after 3 months of stroke.

Patient N.	Patients not affected by sleep apnea	Patients affected by sleep apnea
1	Insula(r)	
2	Pons paramedial	
3	Frontal-temporal-parietal (r); Basal ganglia (r)	
4	Cerebellar cortex (bilatelally);Vermis (r)	
5	Frontal-precentral (l)	
6	Parietal cortex (l)	
7		Basal ganglia (l); Insula (l); Temporal-occipital(l)
8		Frontal-precentral (l)
9		Frontal-precentral (r)
10		Basal ganglia (r); Insula (r); Internal capsule (r)
11		Frontal-temporal (l); Caudate and lenticular nuclei
12		Thalamus (l)

r = right side; l = left side.

Whole Brain rs-fcMRI Connectivity

Within group comparisons

Brain areas that showed high intrinsic correlation ($p<0.05$, corrected) with the time-series of vpl-Th-n spontaneous activation patterns (i.e. significant high functional connectivity) in the 3 groups under investigation are shown in Figure 1 (A, B, C), and in Tables III-V. In HC, the structures of the midline functionally hyper connected with the seed included the contralateral thalamus, ipsilateral ventral portion of the pons, midbrain, and contralateral insular cortex. Hemispheric regions with significant higher functional connectivity with the seed were the prefrontal, the ipsilateral somatosensory association cortex, the contralateral angular gyrus, the medial-infe-

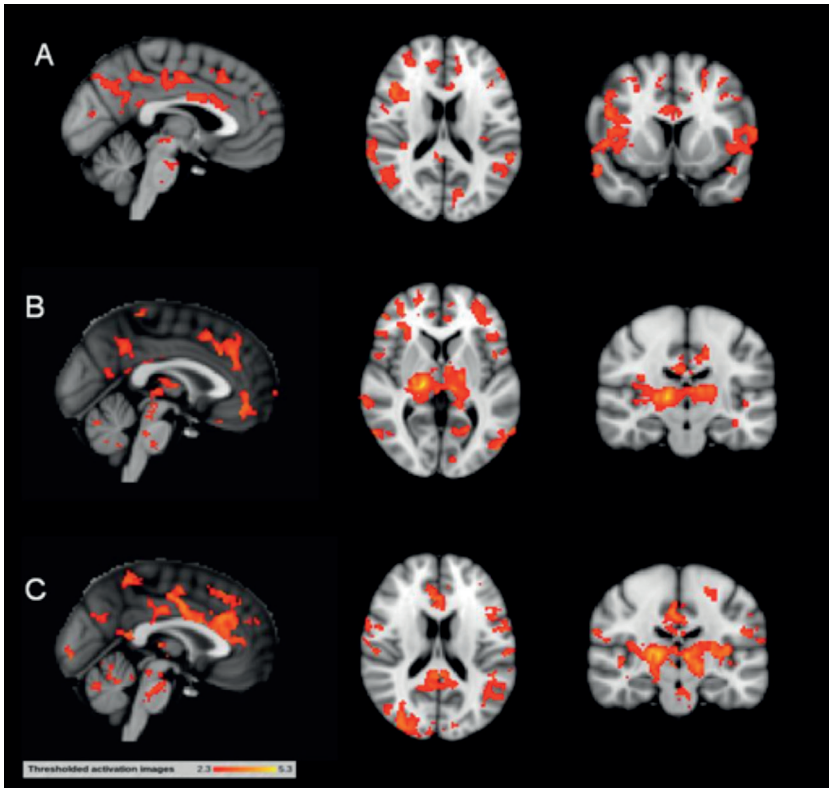

Figure 1. ***A,*** Healthy controls. ***B,*** Stroke cases not affected by sleep apnea. ***C,*** Stroke cases affected by sleep apnea.

Table III. Whole brain rs-fMRI connectivity of left ventral-posterior-lateral thalamic nucleus in healthy controls.

Brain lobe and region			Side	BA	Talairach coordinates in MNI space			Zmax
					x	y	z	
		Thalamus	r		18	-22	6	5,33
		Pons (ventral)	l		-8	-22	-40	3,62
		Midbrain	l		-2	-12	-14	2,36
		Insular cortex	r		4	20	-2	2,1
Frontal								
	Prefrontal	Dorso-lateral prefrontal cortex (MFG)	r	9	46	32	40	2,33
		Orbito-frontal area Broca's area (IFG)	r	11	12	48	-26	2,29
		Orbito-frontal area Broca's area (IFG)	l	11	-22	56	-26	2,28
		Pars opercularis (IFG)	r	44	62	16	28	2,19
		Dorso-lateral prefrontal cortex (MFG)	r	46	52	46	24	2,15
		Premotor and Supplementary Motor Cortices (SFG)	r	6	60	8	22	2,10
		Anterior prefrontal cortex (MFG)	l	10	-20	74	16	2,07
		Premotor and Supplementary Motor Cortices (SFG)	r	6	62	4	20	2,02
		Anterior prefrontal cortex (MFG)	r	10	0	50	-12	2,01
Parietal								
	Superolateral	Angulargyrus (IPL)	r	39	64	-62	24	2,38
		Somatosensory association cortex	l	7	-24	-54	68	2,11
Temporal								
	Medial/inferior	Inferior temporal gyrus (ITG)	l	20	-48	-24	-32	2,59
	Superolateral	Temporo-polar area (STG)	r	38	34	-20	-40	2,57
	Medial/inferior	Inferior temporal gyrus (ITG)	r	20	50	-22	-30	2,50
	Superolateral	Temporo-polar area (STG)	l	38	-62	12	-16	2,38
	Superolateral	Middle temporal gyrus	r	21	70	-8	-10	2,20
Occipital								
	Superolateral	Secondary visual cortex	r	18	24	-98	20	2,40
		Associative visual cortex	r	19	10	-84	46	2,38
		Associative visual cortex	l	19	-34	-92	30	2,28
		Secondary visual cortex	l	18	-12	-100	28	2,05
Limbic								
	Cingulate cortex (ventral posterior)		r	23	20	-42	24	2,01

Legend: Peak locations and significance of brain areas with increased connectivity with the left VPL-TN during resting state fMRI in 11 healthy controls. Data are reported according to the brain lobes and regions, and then ordered by significance; Zmax= maximum Z scores. MFG = middle frontal gyrus; IFG = inferior frontal gyrus; SFG = superior frontal gyrus; MFG = middle frontal gyrus; STG = superior temporal gyrus; IPL = inferior parietal gyrus; ITG = inferior temporal gyrus.

rior temporal gyrus, the supero-lateral temporal regions, the secondary and associative visual cortices bilaterally, and the contralateral ventral posterior cingulate cortex (Figure 1A; Table III). In the group of cases not affected by SA, a significantly hyper functional connectivity with the seed was found in the contralateral thalamus, in the cerebellum bilaterally, and in the ipsilateral hypothalamus. Regions with significant higher connectivity with the seed were also located in the prefrontal cortex, in the superolateral parietal regions, in the superior-lateral and medial inferior temporal regions, and in ipsilateral secondary and contralateral associative visual cortices (Figure 1B; Table IV). The group of cases with SA showed significantly hyper functional connectivity between left vpl-Th-n and the contralateral thalamus, the ventral portion of the ipsilateral pons, and the contralateral hypothalamus. The hemispheric regions significantly hyper connected to the seed were located in the prefrontal cortex, in the contralateral parietal lobe, in the supero-lateral and medial inferior temporal regions, and in the associative and secondary visual cortices bilaterally (Figure 1C; Table V).

Between groups comparisons

At rs-fcMRI connectivity comparisons analysis, patients with SA distinguished from HC for a significantly higher functional connectivity between the left vpl-Th-n and the pons-midbrain, contralateral cerebellum and thalamus, and the

Table IV. Whole brain rs-fMRI connectivity of left ventral-posterior-lateral thalamic nucleus in patients not affected by sleep apnea.

Brain lobe and region			Side	BA	Talairach coordinates in MNI space x	y	z	Zmax
		Thalamus	r		16	-20	4	5,31
		Cerebellum	l		-42	-44	-44	3,03
		Cerebellum	r		12	-88	-24	2,58
		Hypothalamus	l		-4	0	-12	2,56
Frontal								
	Prefrontal	Pars orbitalis Broca's area (IFG)	r	47	22	20	-32	2,95
		Pars orbitalis Broca's area (IFG)	l	47	-58	26	-14	2,79
		Anterior prefrontal cortex (MFG)	r	10	38	54	-18	2,72
		Orbito-frontal Broca's area (IFG)	r	11	24	32	-26	2,68
		Premotor and Supplementary Motor Cortices (SFG)	r	6	8	-14	66	2,66
Parietal								
	Superolateral	Angular gyrus (IPL)	l	39	-56	-74	36	3,06
		Somato sensory association cortex	r	7	34	-78	44	2,89
		Supramarginal gyrus (IPL)	l	40	-60	-28	42	2,80
		Primary somatosensory cortex	r	1	38	-44	66	2,73
		Somatosensory association cortex	l	7	-30	-70	60	2,60
		Supramarginal gyrus (IPL)	r	40	62	-24	42	2,60
		Supramarginal gyrus (IPL)	l	40	-52	-32	62	2,33
Temporal								
	Superolateral	Temporo-polar area (STG)	r	38	34	26	-38	3,32
	Medial/inferior	Inferior temporal gyrus (ITG)	l	20	-60	-26	-24	2,89
	Medial/inferior	Inferior temporal gyrus (ITG)	r	20	64	-34	-22	2,87
	Medial/inferior	Fusiform gyrus	l	37	-50	-46	-22	2,82
	Superolateral	Temporo-polar area (STG)	l	38	-24	22	-34	2,47
	Superolateral	Superior temporal gyrus (STG)	r	22	66	-42	14	2,44
Occipital								
	Superolateral	Secondary visual cortex	l	18	-18	-96	14	2,70
		Associative visual cortex	r	19	32	-94	26	2,49

Legend: Peak locations and significance of brain areas with increased connectivity with the left ventral-posterior-lateral thalamic nucleus during resting state fMRI in 6 stroke patients not affected by sleep apnea. Data are reported according to the brain lobes and regions, and then ordered by significance. Zmax= maximum Z scores.

following cortical regions: the ipsilateral frontal eye field, the somatosensory association cortex, the contralateral secondary visual cortex, and the ipsilateral cingulate cortex (Figure 2A; Table VI). Relative to cases not affected by SA, patients with SA showed significantly higher connectivity between the left vpl-Th-n and the cerebellar cortex bilaterally, the ipsilateral pons, and the contralateral thalamus and insula. Several cortical regions showed significantly higher connection with the seed i.e. anterior prefrontal cortex bilaterally, the ipsilateral orbito-frontal area, the premotor and supplementary motor cortices bilaterally, the contralateral subgenual area of anterior cingulate cortex, the frontal eye field bilaterally, the pars triangularis of inferior frontal lobe, and the dorso-lateral prefrontal cortex bilaterally, the ipsilateral somatosensory association cortex, the primary somatosensory contralateral cortex, and ipsilateral supramarginal and angular gyri, the medial inferior temporal regions, the ipsilateral secondary and contralateral associative visual cortices and, finally, the anterior and posterior cingulate cortices (Figure 2B; Table VII).

Discussion

To test the hypothesis of a hyper activation of thalamus-cortical and subcortical connections modulating arousal state in stroke patients affected by SA, the brain networks functionally

Table V. Whole brain rs-fMRI connectivity of left ventral-posterior-lateral thalamic nucleus in patients with sleep apnea.

Brain lobe and region			Side	BA	Talairach coordinates in MNI space			Zmax
					x	y	z	
		Thalamus	r		18	-20	8	5,05
		Pons (ventral)	l		-8	-2	-30	2,62
		Hypothalamus	r		6	-4	-14	2,16
Frontal lobe								
	Prefrontal	Orbito-frontal area (IFG)	r	11	12	20	-28	2,80
		IFG Pars orbitalis	l	47	-50	44	-18	2,65
		Dorso-lateral prefrontal cortex (MFG)	r	46	58	52	-6	2,44
		Primary Motor Cortex (SFG)	l	4	-54	-10	54	2,33
		IFG pars triangularis	l	45	-58	34	18	2,28
		Anterior prefrontal cortex (MFG)	l	10	-18	72	4	2,24
		Premotor and Supplementary Motor Cortices (SFG)	r	6	38	-16	62	2,20
		IFG pars triangularis	r	45	54	42	-10	2,15
		Dorso-lateral prefrontal cortex (MFG)	l	46	-56	36	14	2,13
		Subgenual area (ACC)	r	25	4	18	-14	2,02
		Primary Motor Cortex (SFG)	r	4	48	-16	60	2,05
Parietal lobe								
	Inferior	Angulargyrus (IPL)	r	39	44	-88	36	2,25
		Supramarginal gyrus (IPL)	r	40	60	-46	44	2,12
Temporal lobe								
	Superolateral	Temporo-polar area (STG)	l	38	-36	18	-42	2,64
		Temporo-polar area (STG)	r	38	46	28	-34	2,48
		Middle temporal gyrus (MTG)	l	21	-68	-36	2	2,16
	Medial/inferior	Ectorhinal area (MTL)	l	36	-20	2	-30	2,41
		Inferior temporal gyrus (ITG)	l	20	-54	-4	-42	2,23
		Inferior temporal gyrus (ITG)	r	20	46	-16	-26	2,19
		Ectorhinal area (MTL)	r	36	58	-48	-26	2,10
Occipital lobe								
	Superolateral	Associative visual cortex	r	19	0	-90	36	2,17
		Secondary visual cortex	r	18	28	-98	-16	2,13
		Secondary visual cortex	l	18	-8	-98	16	2,09
		Associative visual cortex	l	19	-36	-70	-14	2,07

Legend: Peak locations and significance of brain areas with increased connectivity with the left ventral-posterior-lateral thalamic nucleus during resting state fMRI in 6 stroke patients affected also by sleep apnea. Data are reported according to the brain lobes and regions, and then ordered by significance; Zmax= maximum Z scores.
Abbreviations: IFG=inferior frontal gyrus; MFG= middle frontal gyrus; SFG=superior frontal gyrus; ACC=anterior cingulate cortex; IPL=inferior parietal gyrus; STG=superior temporal gyrus; MTG=middle temporal gyrus; MTL= medial temporal lobe; ITG=inferior temporal gyrus.

hyper connected with vl-Th-n in a continuous series of stabilized stroke patients and in an equal number of gender-matched HC were investigated. Differently from both HC and cases not affected by SA, in the group of patients with full PSG documented SA, a hyper connectivity with the primary motor cortex, the subgenual portion of the anterior cingulated cortex (ACC), and the inferior parietal regions has been found. The thalamic-pontine functional connectivity was increased, involving the pons from its dorsal inferior portion to the ventral-rostral one. To reveal areas significantly more hyper connected with the seed among the groups, rs-fcMRI data acquired from cases affected by SA were subtracted from those not affected and from HC. This between groups comparison analysis has shown that, as respect to HC, in SA cases the regions significantly hyper connected to the seed were those involved in attentive processes and in encoding of noxious threats or aversive events (i.e. frontal eye field, somatosensory association and secondary visual cortices)[43-45]. Comparisons of rs-fcMRI thalamic connectivity of cases with SA relative to those without SA, revealed in the former group significantly increased functional connectivity with cortical regions modulating the response to external stimuli independently to

Table VI. rs-fMRI connectivity of left l ventral-posterior-lateral thalamic nucleus in stroke patients affected by sleep apnea as respect to healthy controls.

Brain lobe and region			Side	BA	Talairach coordinates in MNI space			Zmax
					x	y	z	
		Pons-Midbrain			-8	-30	-20	3,23
		Pons			14	-34	-24	3,07
		Cerebellum	r		18	-62	26	2,42
		Thalamus	r		10	-2	16	2,80
Frontal								
	Prefrontal	Frontal eye field	l	8	-10	62	32	2,44
Parietal								
	Medial/inferior	Somatosensory association cortex (SPL-PreCu)	l	7	-8	64	64	2,36
Occipital								
	Superolateral	Secondary visual cortex	r	18	22	-92	14	2,40
Limbic								
		Cingulate cortex (retrosplenial)	l	29	-2	-44	12	3,20
		Cingulate cortex (dorsal anterior)	l	32	-12	32	26	2,60

Legend: Peak locations and significance of brain areas with increased connectivity with the left ventral-posterior-lateral thalamic nucleus during resting state fMRI in 6 patients affected also by sleep apnea compared to 11 gender matched healthy controls. Data are reported according to the brain lobes and regions, and then ordered by significance; Zmax= maximum Z scores.

their potentiality of threat (i.e. prefrontal, primary and somatosensory association, superolateral and medial-inferior temporal, and associative and secondary occipital ones)[45]. Notably, with respect to both HC and cases not affected by SA, in patients with SA further significantly functionally hyper connections were documented with regions involved also in autonomic functions, including the modulation of breathing during sleep (i.e. pons, midbrain, cerebellum and posterior cingulate cortices)[7-9,46-65], and in those involved in the modulation of breathing response to chemical variations (i.e. anterior, posterior and para-hippocampal cingulate cortices)[8,9,48,61,62]. Honey et al[23] have

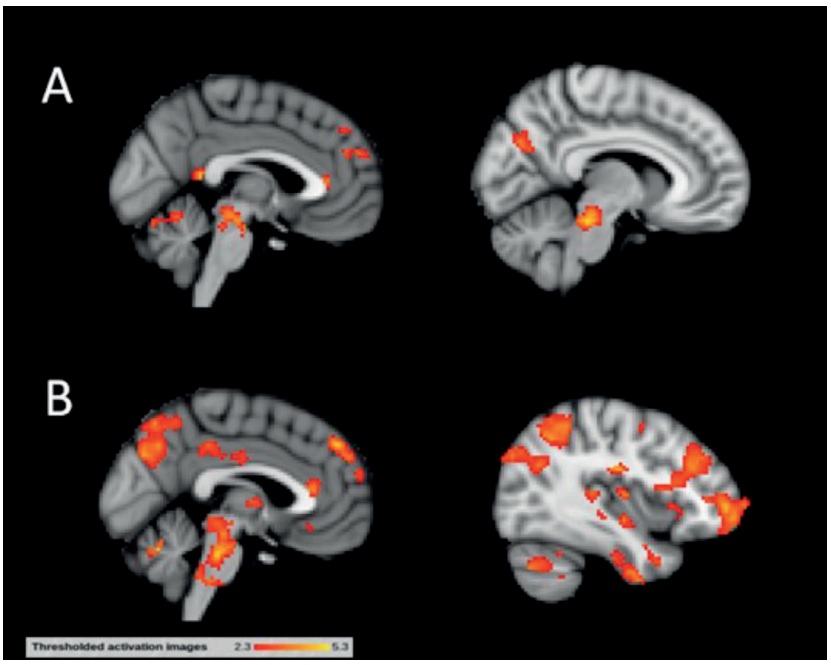

Figure 2. ***A,*** Stroke patients affected by sleep apnea relative to healthy controls. ***B,*** Stroke patients affected by sleep apnea compared to non-apnea-affected stroke cases.

Table VII. rs-fMRI connectivity of left left ventral-posterior-lateral thalamic nucleus of stroke patients affected by sleep apnea as respect to cases not affected.

Brain lobe and region			Side	BA	Talairach coordinates in MNI space			Zmax
					x	y	z	
		Cerebellum	r		44	-68	-30	3,22
		Pons	l		-10	-30	-30	3,17
		Cerebellum	l		-48	-72	-34	2,90
		Thalamus	r		16	-2	4	2,85
		Insula	r		48	20	-4	2,78
Frontal								
	Prefrontal	Anterior prefrontal cortex (MFG)	r	10	20	58	-4	3,17
		Orbito-frontal area (IFG)	l	11	-20	52	-22	3,16
		Premotor and supplementary motor cortices (SFG)	r	6	4	32	52	3,13
		Subgenual area (ACC)	r	25	8	22	-26	2,99
		Frontal eye field	r	8	22	40	46	2,97
		Premotor and supplementary motor cortices (SFG)	l	6	-46	2	10	2,95
		Frontal eye field	l	8	-2	46	40	2,95
		Anterior prefrontal cortex (MFG)	l	10	-16	66	10	2,87
		Pars triangularis (IFG)	l	45	-58	34	-4	2,51
		Dorsolateral prefrontal cortex (MFG)	l	9	-40	38	32	2,59
		Premotor and supplementary motor cortices (SFG)	l	6	-12	-16	56	2,48
		Dorsolateral prefrontal cortex (MFG)	r	9	46	26	28	2,45
Parietal								
	Superolateral	Somatosensory association cortex	l	7	-42	-50	54	3,25
		Somatosensory association cortex	l	7	-4	-66	56	3,23
	Medial/inferior	Gyrus post-centralis- primary somatosensory	r	3	50	-6	56	3,17
	Superolateral	Supra-marginal gyrus	l	40	-58	-38	36	2,82
		Angular gyrus	l	39	-48	-68	28	2,85
Temporal								
	Medial/inferior	Inferior temporal gyrus (ITG)	l	20	-32	-10	-40	2,87
		Inferior temporal gyrus (ITG)	r	20	36	-4	-46	2,72
		Peri-rhinal cortex	r	35	24	-30	-16	2,79
		Gyrus fusiformis	r	37	50	-38	-20	2,67
Occipital								
	Superolateral	Secondary visual cortex	l	18	-8	-78	30	3,15
		Associative visual cortex	r	19	42	-82	28	2,65
Limbic								
		Cingulate cortex (ventral-posterior)	l	23	-10	0	22	3,45
		Cingulate cortex (gyrus para-hippocampal)	r	30	20	-40	-6	2,64
		Cingulate cortex (dorsal-anterior)	l	32	-14	24	30	2,53

Legend: Peak locations and significance of brain areas with increased connectivity with the left ventral-posterior-lateral thalamic nucleus during resting state fMRI in 6 patients affected also by sleep apnea compared to 6 stroke patients not affected by sleep apnea. Data are reported according to the brain lobes and regions, and then ordered by significance.
Abbreviations: Zmax= maximum Z scores. MFG= middle frontal gyrus; IFG=inferior frontal gyrus; SFG=superior frontal gyrus; ACC=anterior cingulate cortex; ITG=inferior temporal gyrus.

found that after stroke *"connector hubs will most rapidly synchronize following an external perturbation"*. Our interpretation is that stroke might have determined a higher activation at rest of brain areas controlling the response to both internal and external threatening stimuli, secondary influencing those modulating breathing during sleep. This result is congruent with the data emerged from PSG, which documents a greater number of arousals per hour of sleep in patients with SA.

The brain actively generates and maintains arousal through multiple grossly redundant autochthonous arousal systems that evoke awakening from sleep in response to sensory stimulation. Anyone neural system is not necessary and may be sufficient for maintaining wakefulness. Among them, thalamus-cortical projections play a critical role[65-69]. Physiologically, neocortical neurons' threshold of arousability increases or decreases as sleep becomes deeper or lighter, up

to the point of a thalamus-cortical functional disconnection during slow wave sleep[70-74]. In particular, in a concurrently recorded electroencephalographic-fMRI study, the cingulo-insular-thalamic network has been proposed to maintain tonic alertness[75,76]. Functional MRI studies in awaken healthy humans have shown that ventral-posterior-lateral thalamic nuclei are activated during chemo-stimulation, together with cerebellum, cingulate and insular cortices[8,77]. In a fMRI study with included diffusion tractography, Pattinson et al[9] observed that, during chemo stimulation, the ventral group of thalamic nucleus strongly connects with the frontal cortex, the amygdala, and the ACC. To summarize, evidences exist that thalamic connections with frontal, cingulated, and insular cortices, implicated in alertness and in encoding external and internal stimuli, contribute also to the ventilatory response to chemical stimuli, govern the access to the cortex of information coming from the respiratory system, and integrate respiratory signals to and from the respiratory nuclei of medulla.

Clinical evidence for thalamic involvement in sleep disordered breathing after stroke has been documented previously[78,79]. Our data are in line with previous findings and raise the question whether this hyper-functional connectivity makes the patient more easily arousable. The only case with a thalamic lesion enhances the results, which are focused on the hyper functional connectivity between the thalamus and all the other cerebral regions, rather than on hypo-connectivity.

It can be argued that some of the brain lesions documented in our series are secondary to a pre-existed OSA. MRI studies in patients with newly diagnosed OSA have in fact shown damages in brain areas deputed to the control of breathing, such as in the medulla, basal ganglia, hippocampus, corpus callosum, corona radiate, cingulate gyrus, ventral-lateral frontal cortex, and cerebellum[80,81]. In our series, cases affected by SA did not differ from those not affected by factors predisposing to OSA, including being overweight, one's BMI, or diurnal somnolence. In line with previous reports[82,83], location of the brain lesions did not correlate with the presence of the SA[84], reducing the possibility of a causal relationship between the site damaged and the breathing disturb during sleep observed in our patients. Even though it cannot be completely ruled out SA since before stroke, in this series of cases it is unlikely that SA pre-existed the cerebrovascular event.

The main limitation of our study consists of the small sample size that did not allow to investigate possible differences in thalamic connectivity depending on the hemispheric lateralization[85]. Nonetheless, to our best knowledge, this is the first case-control study investigating thalamic functional hyper connectivity in patients with and without SA after stroke, compared to HC.

Conclusions

Our preliminary data suggest that, in post-stroke SA cases, are present functional changes in thalamic brain networks that allow modulating participation of the cerebral cortex to both external/internal stimuli. This over-activation might have determined their propensity toward arousal state, and SA may represent the chemoreflex response consequent to the hyper thalamus-cortical and subcortical connectivity above detailed. Further studies are needed to confirm these results that may change the diagnostic and therapeutic approach to patients with SA after stroke.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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