Received: 2 September 2021 | Revised: 2 May 2022 | Accepted: 3 May 2022

DOI: 10.1111/jsr.13640

RESEARCH ARTICLE

REM sleep and muscle atonia in brainstem stroke: A quantitative polysomnographic and lesion analysis study

Nathalie Tellenbach[1] | Markus H. Schmidt[1] | Filip Alexiev[1,2] | Eva Blondiaux[3] | Fabian Cavalloni[1] | Claudio L. Bassetti[1] | Lukas Heydrich[1] | Panagiotis Bargiotas[1,4]

[1]Department of Neurology, University Hospital (Inselspital) and University of Bern, Bern, Switzerland

[2]Neurology Clinic, St Anna University Hospital, Sofia, Bulgaria

[3]Laboratory of Cognitive Neuroscience, Center for Neuroprosthetics and Brain Mind Institute, Faculty of Life Sciences, Swiss Federal institute of Technology (EPFL), Geneva, Switzerland

[4]Department of Neurology, Medical School, University of Cyprus, Nicosia, Cyprus

Correspondence
Panagiotis Bargiotas, Department of Neurology, Medical School, University of Cyprus, Nicosia, Cyprus.
Email: bargiotas.panagiotis@ucy.ac.cy

Summary

Important brainstem regions are involved in the regulation of rapid eye movement sleep. We hypothesized that brainstem stroke is associated with dysregulated rapid eye movement sleep and related muscle activity. We compared quantitative/qualitative polysomnography features of rapid eye movement sleep and muscle activity (any, phasic, tonic) between 15 patients with brainstem stroke ($N = 46$ rapid eye movement periods), 16 patients with lacunar/non-brainstem stroke ($N = 40$ rapid eye movement periods), 15 healthy controls ($N = 62$ rapid eye movement periods), and patients with Parkinson's disease and polysomnography-confirmed rapid eye movement sleep behaviour disorder. Further, in the brainstem group, we performed a magnetic resonance imaging-based lesion overlap analysis. The mean ratio of muscle activity to rapid eye movement sleep epoch in the brainstem group ("any" muscle activity 0.09 ± 0.15; phasic muscle activity 0.08 ± 0.14) was significantly lower than in the lacunar group ("any" muscle activity 0.17 ± 0.2, $p < 0.05$; phasic muscle activity 0.16 ± 0.19, $p < 0.05$), and also lower than in the control group ("any" muscle activity 0.15 ± 0.17, $p < 0.05$). Magnetic resonance imaging-based lesion analysis indicated an area of maximum overlap in the medioventral pontine region for patients with reduced phasic muscle activity index. For all groups, mean values of muscle activity were significantly lower than in the patients with Parkinson's disease and polysomnography-confirmed REM sleep behaviour disorder group ("any" activity 0.51 ± 0.26, $p < 0.0001$ for all groups; phasic muscle activity 0.42 ± 0.21, $p < 0.0001$ for all groups). For the tonic muscle activity in the mentalis muscle, no significant differences were found between the groups.

In the brainstem group, contrary to the lacunar and the control groups, "any" muscle activity index during rapid eye movement sleep was significantly reduced after the third rapid eye movement sleep phase.

This study reports on the impact of brainstem stroke on rapid eye movement atonia features in a human cohort. Our findings highlight the important role of the human

Lukas Heydrich and Panagiotis Bargiotas act as equivalent co-senior authors.

brainstem, in particular the medioventral pontine regions, in the regulation of phasic muscle activity during rapid eye movement sleep and the ultradian distribution of rapid eye movement-related muscle activity.

KEYWORDS
pons, pontine stroke, rapid eye movement sleep behaviour disorder, rapid eye movement sleep without atonia (RSWA), tonic muscle activity, phasic muscle activity

1 | INTRODUCTION

Rapid eye movement (REM) sleep is a sleep state characterized by autonomic activation, rapid eye movements and fast desynchronized cortical activations in the electroencephalogram, which resemble the cortical waves during wakefulness (Arrigoni et al., 2016). In addition, the REM sleep state is characterized by REM atonia, a condition of suppressed muscle activity (*ma*) in most of the peripheral somatic muscles except those of the inner ear, eye and diaphragm (Saper et al., 2001). The background of atonia during REM sleep can be interrupted by phasic motor activity, including muscle twitches and movements mainly in the cranial muscles (Berry et al., 2017).

In recent years, numerous imaging studies, clinico-electrophysiological and experimental models have highlighted the crucial role of the brainstem in the regulation of REM sleep, REM atonia and REM sleep phasic motor activity (Fuller et al., 2007; Krenzer et al., 2011). In agreement with these experimental data, there are few case reports on dysregulated muscle tone during REM sleep in patients with brainstem lesions (Krenzer et al., 2011; Mathis et al., 2007; Reynolds & Roy, 2011) that further highlight the regulatory role of this brain region on REM sleep and locomotor drive (Boeve et al., 2007). However, the neuroanatomical circuitry for the generation of REM atonia in humans is still not fully understood, and the impact of brainstem stroke on the muscle tone during REM sleep has never been systematically studied before.

In addition, pontine regions contribute not only in the production of REMs but also in the ultradian distribution of REMs within the REM sleep periods, mainly via activation of the pontine tegmentum before the occurrence of REMs (Miyauchi et al., 2009; Weber et al., 2018).

In this study, our aim was to assess quantitative and qualitative features of REM sleep and *ma* during REM sleep and REM-related *ma* (any, phasic, tonic) in patients with brainstem stroke and subjects with lacunar/non-brainstem stroke. Two additional groups of subjects have been used as reference cohorts for REM atonia features: one group of healthy controls (CTRL group); and another group of subjects with Parkinson's disease (PD) and REM sleep behaviour disorder (PDRBD group) with polysomnography (PSG)-confirmed REM sleep without atonia (RSWA). Further, we used a magnetic resonance imaging (MRI)-based lesion mapping approach to explore the association between localization of brainstem stroke with the type and severity of muscle tone dysregulation during REM sleep. We hypothesized that brainstem stroke is associated with dysregulation of muscle tone during REM sleep, possibly with RSWA, and might also have impact on the ultradian rhythmicity of REM sleep.

2 | PATIENTS AND METHODS

The protocol for this study was approved by the local ethics committee (KEK Bern 2020–01237).

2.1 | Patients

Demographic, clinical, PSG and MRI data from 15 patients with brainstem stroke (without persisting disorder of consciousness) and 16 patients with lacunar non-brainstem stroke, who underwent PSG in the post-stroke period as part of the standard clinical post-stroke routine, and a group of healthy controls (CTRL group, $N = 15$) were collected from the Bern Sleep–Wake Database (Bargiotas et al., 2019). For the brainstem group, male and female patients with MRI-confirmed stroke in the brainstem region (medulla oblongata, pons, midbrain) were included. For the lacunar non-brainstem group, patients with MRI-confirmed lacunar stroke (outside the brainstem area) were included. Lacunar stroke was defined as small infarcts of 2–15 mm in diameter that lie in the deeper non-cortical parts of the cerebrum (Fisher, 1982). We excluded from both stroke groups patients with PD, multiple system atrophy or Lewy body dementia and other neurodegenerative or neurological disorders associated with alterations in REM-related *ma* (Boeve, 2010).

No patient reported an add-on or withdrawal of a REM-suppressing or REM-increasing medication, shortly before the performance of the PSG.

Subjects with less than 1 hr of total sleep or without REM sleep in the PSG were also excluded from the analysis. The data of the PDRBD group with PSG-confirmed RSWA were collected as part of another, previously published, case series in our centre (Cavalloni et al., 2021). The subjects of the CTRL group were healthy participants recruited as part of another clinical study at the Bern University Hospital (Ethics Commission of the Canton of Bern 2021–00723), and had no history of neurodegenerative disorder or stroke and showed a normal PSG without signs of a sleep-related movement or breathing disorder (e.g. apnea–hypopnea index < 5 per hr, periodic limb movement index < 10 per hr), parasomnias or circadian disturbance.

2.2 | Polysomnography

Standard video PSG was performed during the subacute post-stroke phase as part of the standard clinical post-stroke routine. We used Embla RemLogicTM Software for all recordings. Sleep stages and sleep-associated events were manually scored according to the AASM criteria (Berry et al., 2017), and visual electromyogram (EMG) scoring was performed based on previously described methodology (Frauscher et al., 2012; Lapierre & Montplaisir, 1992).

2.3 | Visual EMG scoring

During PSG, *ma* was measured with EMG using surface electrodes at the chin (submentalis muscle) and bilaterally at the upper (m. flexor digitorum superficialis) and lower (m. tibialis anterior, TA) extremities; phasic activity scoring was based on the chin and upper extremities signals, while tonic activity only on chin signals.

Sleep stages were scored in 30-s intervals according to the AASM criteria (Berry et al., 2017). Because the presence of RSWA might limit the application of the AASM rules, the onset of the REM sleep period was related to the occurrence of the first REM in the electrooculographic channel, and its end on the presence of an awakening, K complexes and spindles or when no REMs were detected in 3 consecutive minutes. A very short or too fragmented REM sleep (< 2 continuous epochs of REM and/or scattered single REM epochs with total amount < 5 min) were excluded (Frauscher et al., 2012; McCarter et al., 2014).

For the PSG recording and RSWA manual scoring methods, the scorer (PB) was blinded to the final diagnosis. We used two previously published EMG-scoring methods to quantify *ma* only in REM sleep, one using 3-s and another using 30-s epochs.

For the analysis of 3-s epochs, we used EMG scoring criteria as previously suggested (Frauscher et al., 2012). In the upper extremity muscles, missing atonia was defined only if phasic EMG activity was present. The phasic activity was defined as a burst with an amplitude of at least double the background EMG voltage and a duration between 0.1 and 5 s. The end of such a burst is defined as soon as the potential returns to the baseline or there is an identifiable interval between two bursts of at least 250 ms.

In the mentalis muscle, missing atonia was defined as any EMG activity occurring in a defined 3-s epoch during REM sleep; EMG activity was considered as any potential lasting longer than 0.1 s, and with an amplitude of at least double the EMG background activity or higher than 10 μV, consisting of the following morphologies.

- Tonic activity, if > 50% of the epoch showed continuous *ma* greater than double the background EMG voltage.
- Phasic activity as defined above.

Any *ma* was defined as any 3-s epoch containing either phasic or tonic activity according to the criteria described above. For the analysis of 30-s epochs, we examined only the tonic activity of the mentalis muscle, as previously suggested (Frauscher et al., 2012). An epoch was considered positive for tonic activity if > 50% of the epoch had *ma* continuously greater than double the background EMG voltage or ≥ 10 μV.

The proportion of all types of *ma* was calculated as a percentage of the total duration of REM sleep and as a percentage of the duration of each REM sleep period.

All increases in EMG tone due to arousals from respiratory events (i.e. hypopnea, apnea) or constantly and simultaneously recurring with electrocardiogram-activity were considered as artefacts, and were excluded from the quantitative scoring of REM-sleep-related EMG activity.

The presence of RSWA was confirmed when the total of epochs in which the respective EMG activity occurs in at least one of the examined muscles exceeded 32% of total REM sleep time (Frauscher et al., 2012).

2.4 | MRI-based lesion analysis

All imaging data were analysed at the time of the original exploration and then reviewed for the purpose of this study by two of the authors (LH and FA) in order to determine the lesion location. For lesion overlap we used MRIcron, which is part of the MRIcron software package (Rorden et al., 2007). Anatomical structures were labelled according to the AAL atlas implemented in MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron). In order to illustrate the maximal overlap of lesions in the group of brainstem stroke using a simple voxel-based lesion overlap analysis, structural lesions were identified by MRI (diffusion-weighted imaging, T1, fluid-attenuated inversion recovery imaging) and were traced manually slice by slice on the T1 template using MRIcron (left-sided lesions were flipped on the right side; Heydrich & Blanke, 2013). The later manual tracing on the template brain was only done when confidence could be achieved for matching corresponding slices between the lesioned brain and the template brain. No patients with unclear lesion boundaries were included in the analysis. Lesion volumes (volume of interest) were determined as the sum of all voxels compromising the traced lesion in all slices, and were spatially smoothed using a 3-mm full-width at half-maximum Gaussian Kernel and a threshold of 0.5.

2.5 | Statistical analysis

Comparisons were performed by using the Student's *t*-test for unpaired datasets. The effect size between groups was measured using Cohen's *d*. Correlations of clinical independent variables and dependent types of *ma* (tonic, phasic and "any") were analysed using a multivariable regression model. Comparisons between independent groups were performed using the Mann–Whitney–Wilcoxon non-parametric test. For all comparisons, a value of $p \leq 0.05$ was

TABLE 1 Demographic and clinical characteristics of the cohort

	CTRL group	Brainstem group	Lacunar group	*p*
Mean age (years)	58,4	56.0	61.2	n.s.
Gender (number and percentage)				
Female	33%	27%	31%	n.s.
Male	67%	73%	69%	n.s.
Mean NIHSS at admission		2.69	3.79	n.s.
Mean NIHSS at discharge		2.08	1.33	n.s.
No. of patients with NIHSS 0–6		13	12	
No. of patients with NIHSS 7 or higher		2	4	

Abbreviations: CTRL, control; NIHSS, National Institutes of Health Stroke Scale; n.s., non-significant.

considered statistically significant. The Mann–Whitney test was performed to analyse the differences in *ma* types between groups. Analysis of variance (ANOVA) was carried out on different *ma* variables for each REM stage with a group as independent variables.

All statistical operations were conducted using SPSS® and GraphPad Prism® software.

3 | RESULTS

The two stroke groups and the CTRL group were comparable with respect to mean age and gender (Table 1). In the brainstem stroke group, nine patients had a lesion in the pons, four in the medulla oblongata, one in the mesencephalon, and two patients had lesions in multiple brainstem localizations. In the lacunar stroke group, lesions were located in the centrum semiovale, thalamus, internal capsule, striatum and other subcortical areas. Baseline characteristics in both stroke and the CTRL groups are shown in Table 1.

3.1 | REM sleep

In the lacunar stroke group, we identified 40 REM periods, namely 2.5 REM periods per night. The mean duration of REM sleep periods was 19.05 ± 11.5 min and the total REM sleep duration in the group was 762 min. In the brainstem stroke group, we identified 46 REM periods, namely 3.1 REM periods per night. The mean duration of each REM sleep period was 12.8 ± 7.7 min, significantly lower than in the lacunar stroke group, and the total REM sleep duration in the group was 577.5 min. In the CTRL group, we identified 62 REM periods, namely 4,1 REM periods per night. The mean duration of REM sleep periods was 17.9 ± 6.8 min and the total REM sleep duration in the group was 987 min.

3.2 | Muscle activity during REM sleep

The ratio of "any" *ma* to REM sleep epoch in the lacunar stroke group (0.17 ± 0.20) was significantly higher than in the brainstem group (0.09 ± 0.15, $p < 0.05$; Figure 1a).

There was a non-significant trend towards increased ratio of "any" *ma* to REM sleep epoch in the CTRL group (0.15 ± 0.17) compared with the brainstem group (0.09 ± 0.15, $p = 0.06$) as well (Figure 1a). The effect sizes of the differences were medium (Supplementary Table S1).

For both stroke groups and the CTRL group, mean values of "any" *ma* were significantly lower than in the PDRBD group (0.51 ± 0.26, $p < 0.0001$ for all groups; Figure 1a). In the subgroup of pons brainstem stroke, the ratio of "any" *ma* to REM sleep epoch was even lower than in the subgroup of non-pons brainstem stroke (0.05 ± 0.07 versus 0.17 ± 0.21, $p < 0.01$).

The ratio of phasic *ma* to REM sleep epoch in the lacunar stroke group (0.16 ± 0.19) and in the CTRL group (0.14 ± 0.17) was significantly higher than in the brainstem group (0.08 ± 0.14, $p < 0.05$ for both groups; Figure 1b). The effect sizes of the differences were medium (Table S2).

For both stroke groups and the CTRL group, mean values of phasic *ma* in TA were significantly lower than in the PDRBD group (0.42 ± 0.21, $p < 0.0001$; Figure 1b). In the subgroup of pons brainstem stroke, the ratio of phasic *ma* to REM sleep epoch was even lower than in the subgroup of non-pons brainstem stroke (0.04 ± 0.06 versus 0.17 ± 0.20, $p < 0.01$).

The ratio of tonic *ma* to REM sleep epoch, calculated per REM sleep phase, did not differ between the groups (in the brainstem stroke group 0.009 ± 0.033, in the lacunar stroke group 0.007 ± 0.025, in the CTRL group 0.011 ± 0.027, and in the PDRBD group 0.007 ± 0.014, $p > 0.05$; Figure 1c) and between the brainstem subgroups.

In one patient in the lacunar stroke group (7%) and in two patients in the brainstem stroke group (13%), "any" *ma* represented more than 32% of REM sleep duration (69.07% versus 45.75% and 57.19%, respectively), suggesting the presence of RSWA. None of the patients with stroke (either brainstem or lacunar) showed dream enactment or RBD suspicious behaviour.

3.3 | Ultradian distribution of REM-related muscle activity

We assessed time dynamics and ultradian distribution of REM-related "any" *ma* over REM sleep phases between the two stroke and the

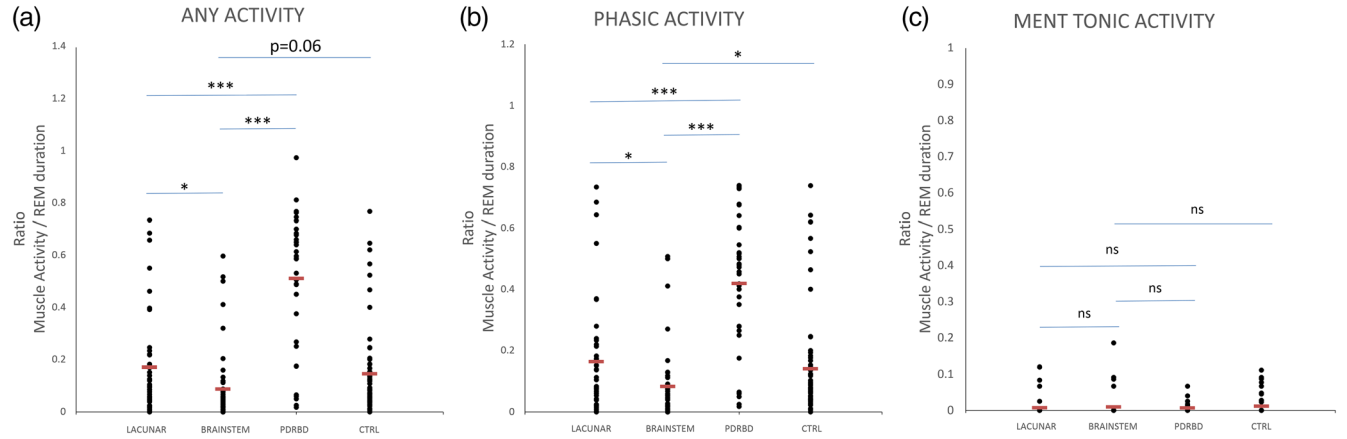

FIGURE 1 Rapid eye movement (REM) atonia index for "any" activity (a), phasic activity (b) and tonic activity in mentalis muscle (c) in patients with LACUNAR non-brainstem stroke (LACUNAR), in patients with BRAINSTEM stroke (BRAINSTEM), in the control group (CTRL), and in patients with Parkinson's disease (PD) and polysomnography (PSG)-confirmed REM sleep behaviour disorder (PDRBD). The horizontal line indicates the mean of each group. Each circle represents a patient. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

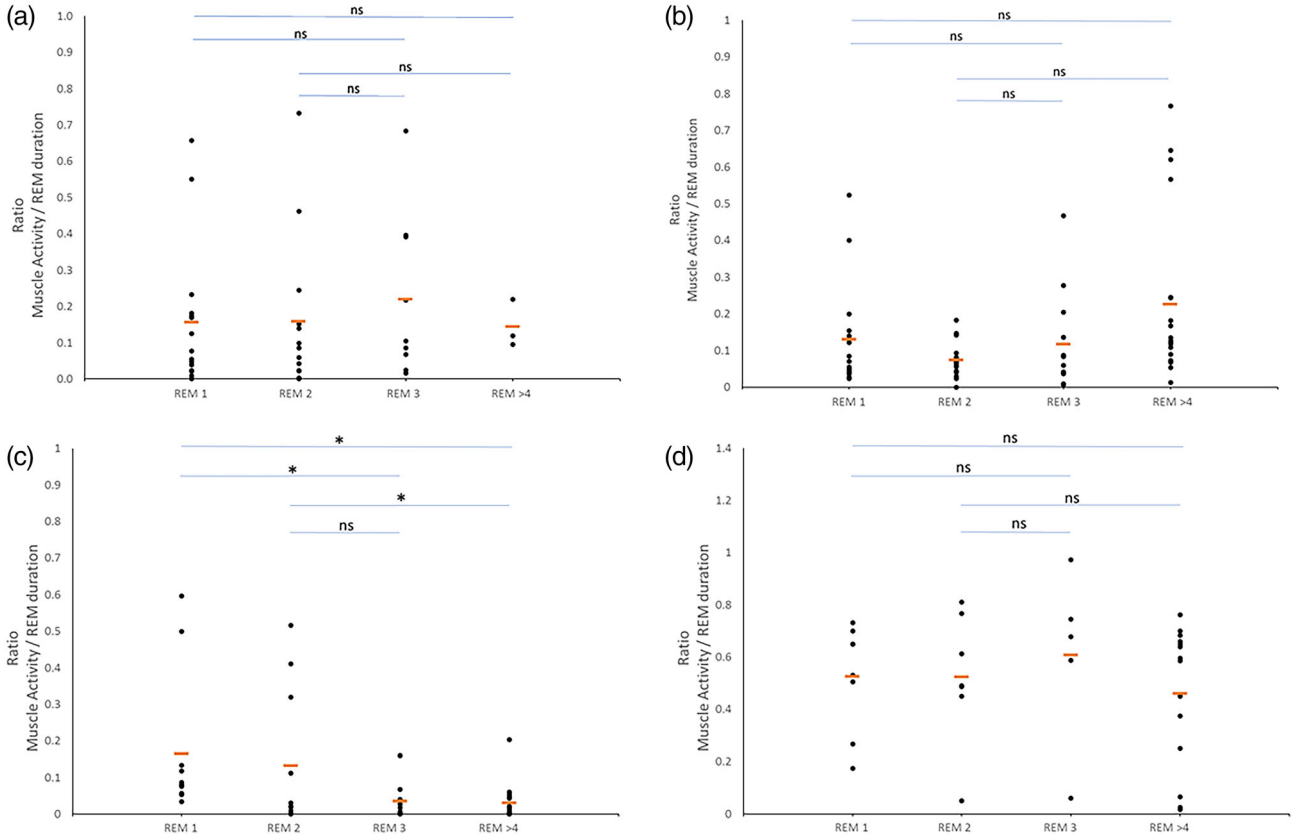

FIGURE 2 Ultradian distribution of rapid eye movement (REM) atonia index for "any" activity over REM periods in patients with lacunar non-brainstem stroke (a), in control (CTRL) group (b), in patients with brainstem stroke (c), and in patients with Parkinson's disease (PD) and polysomnography (PSG)-confirmed REM sleep behaviour disorder (PDRBD) (d). In the lacunar group (a), the CTRL group (b) and the PDRBD group (d), no significant differences were found between REM phases (ANOVA, $p > 0.05$) in respect to "any" activity. In the brainstem group (c), "any" activity is significantly reduced after the third REM phase. ANOVA p-values are presented for REM phases (ANOVA). The mean REM duration did not differ significantly between the phases. In the lacunar group (a), sleep phase mean duration (in min), REM 1: 15.4; REM 2: 23.5; REM 3: 16.2; REM > 4: 17.6. In the brainstem group (b), sleep phase mean duration (in min), REM 1: 10.6; REM 2: 9.5; REM 3: 13.6; REM > 4: 9.1. In the CTRL group (c), sleep phase mean duration (in min), REM 1: 21; REM 2: 15.3; REM 3: 16.9; REM > 4: 10.5. In the PDRBD group (d), sleep phase mean duration (in min), REM 1: 14.4; REM 2: 10.2; REM 3: 17.6; REM > 4: 7.8, $^{*}p < 0.05$

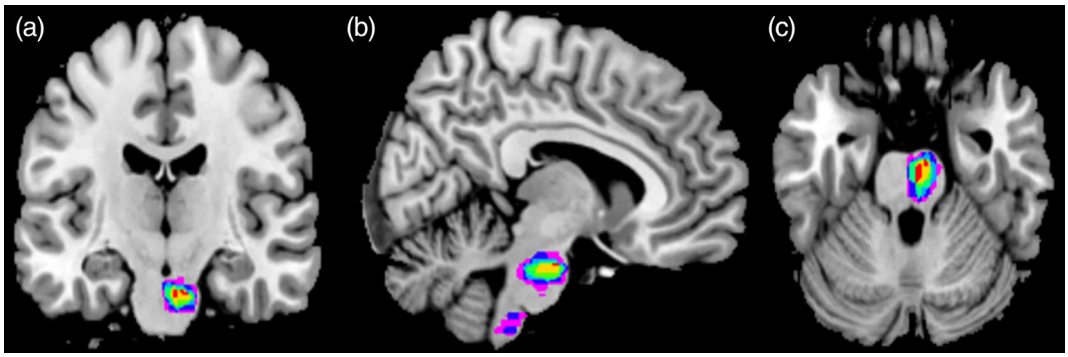

FIGURE 3 Lesion overlap in brainstem stroke in coronal (a), sagittal (b) and axial (c) view. The lesion overlap map highlighted one region in medioventral pons (centred on MNI coordinates **x** = 4, **y** = −21, **z** = −27) and another region in the base of pons more ventral and lateral compared with the first one (centred on MNI coordinates **x** = 8, **y** = −16, **z** = −26). The number of overlapping lesions is illustrated by colour, from violet ($n = 2$), dark blue ($n = 3$), light blue ($n = 4$), turquoise ($n = 5$), green ($n = 6$), yellow ($n = 7$) to red ($n = 8$; maximal lesion overlap). Another cluster was found in the ventrolateral medulla oblongata (centred on MNI coordinates **x** = 7, **y** = −34, **z** = −48), involving five out of 15 patients with brainstem stroke

control groups. In the lacunar stroke group, the mean muscle atonia index did not differ between REM phases (for REM 1 phase, 0.16 ± 0.19; for REM 2 phase, 0.16 ± 0.21; for REM 3 phase, 0.22 ± 0.21; for REM > 4 phases, 0.14 ± 0.07; Figure 2a). Similarly, in the CTRL group, the mean muscle atonia index did not differ between REM phases (for REM 1 phase, 0.13 ± 0.15; for REM 2 phase, 0.07 ± 0.05; for REM 3 phase, 0.12 ± 0.13; for REM > 4 phases, 0.23 ± 0.23; Figure 2b). In the brainstem stroke group, the mean muscle atonia index was significantly reduced towards the second half of the night (for REM 1 phase, 0.17 ± 0.19; for REM 2 phase, 0.13 ± 0.19; for REM 3 phase, 0.04 ± 0.05; for REM > 4 phases, 0.03 ± 0.06; Figure 2c). In the PDRBD group, the mean muscle atonia index did not differ between REM phases (for REM 1 phase, 0.53 ± 0.20; for REM 2 phase, 0.52 ± 0.25; for REM 3 phase, 0.61 ± 0.34; for REM > 4 phases, 0.46 ± 0.27; Figure 2d). In all groups, the ultradian distribution of REM-related "any" activity was independent of the REM phase duration (Figure 2).

3.4 | Lesion overlap

Lesion overlap analysis highlighted two main clusters in the pons, involving nine out of 15 patients with brainstem stroke; one in the ventromedial pontine area (one centred on MNI coordinates **x** = 4, **y** = −20, **z** = −27, and another one in the base of pons more ventral and lateral compared with the first one, centred on MNI coordinates **x** = 8, **y** = −16, **z** = −26; Figure 3a–c). One patient had a lesion in the corticospinal tract but lower than the overlap. Another cluster was found in the ventrolateral medulla oblongata (centred on MNI coordinates **x** = 7, **y** = −34, **z** = −48), involving five out of 15 patients with brainstem stroke (Figure 3b). The MRI-based lesion analysis indicated that for the subgroup of pons brainstem stroke with the lowest phasic *ma* index, the area of maximum stroke overlap was in the medioventral pontine region (red region in Figure 3a–c).

4 | DISCUSSION

Current evidence implicates the brainstem in the regulation of REM sleep and REM atonia. Therefore, we hypothesized that brainstem stroke is associated with dysregulation of muscle tone during REM sleep and possibly with RSWA. We assessed quantitative and qualitative features of REM sleep and *ma* (any, phasic, tonic) during REM sleep in patients with brainstem and non-brainstem (lacunar) stroke, and compared them with data from healthy controls and from patients with PD with RBD. In addition, we explored the association between localization of brainstem stroke with the type and severity of muscle tone dysregulation during REM sleep. In contrast to our hypothesis, brainstem stroke was associated with preserved REM atonia and, in addition, the levels of phasic *ma* in the brainstem group, particularly in those with stroke in the ventromedial pons, was significantly lower than in the lacunar stroke group and the control group. In particular, an area in the ventromedial pons was involved in all patients with low levels of phasic *ma*. We found no difference between the groups in respect to tonic *ma*; however, tonic activity was generally very low, thereby differences might have been missed. In addition, there are several reports that only tonic activity might not be such a reliable marker for RSWA as phasic or "any" *ma* (Khalil et al., 2013). REM sleep was significantly reduced in the brainstem stroke group. Finally, we found differences in the overnight distribution of REM atonia between the groups.

In recent years, numerous imaging and clinico-electrophysiological studies in animal models have highlighted the crucial role of the brainstem in the regulation of REM atonia and locomotor drive (Fuller et al., 2007; Krenzer et al., 2011). Several brainstem regions including the red nucleus, the lateral dorsal tegmental nucleus and the pedunculopontine nucleus may be involved in the regulation of REM atonia (Fuller et al., 2007). In particular, the sublaterodorsal tegmental nucleus (SLD), located in the dorsal part of the pons, has been identified as the critical region for the control of REM atonia. In agreement with these experimental data, a few human reports

suggested a strong correlation between structural damage at the dorsal pons, in particular those affecting the SLD region, and the development of RSWA and subsequently RBD (Mathis et al., 2007; St. Louis et al., 2014; Xi & Luning, 2009). However, in our study, we did not confirm the increased *ma* during REM and the development of RSWA in patients with brainstem stroke. In contrast, ischaemic lesions in the pons, particularly in the ventromedial pons, were associated with more profound REM atonia and reduced phasic EMG activity during REM sleep, without affecting the EMG signal of tonic atonia. This could be suggestive of a pontine REM sleep network in the human mesopontine areas, outside the region expected to represent the SLD, that contains REM-off populations and is suppressed as a result of the ischaemic lesion. Indeed, REM periods per patient were slightly higher in the brainstem group; however, the significant decrease in the mean and total duration of REM sleep in the brainstem group, compared with the lacunar and control groups, do not support this hypothesis. On the other hand, across REM sleep, tonic muscle atonia is periodically interrupted by phasic activity in the form of muscle twitches and jerks. This myoclonic activity is mediated by a glutamatergic input, and by the activation of glutamate receptors in spinal postural and cranial motor neurons (Burgess et al., 2008). Cortical mechanisms have been implicated in the generation of this activity; however, recent evidence suggests that additional sources of muscle jerks and twitches during REM are brainstem motor structures, mainly ventromedial pontine and medullar regions (Blumberg & Plumeau, 2016). Therefore, it could be hypothesized that the ischaemic lesion in the ventromedial brainstem in combination with the lesion in the pontine area where descending corticospinal projection fibres are located (both regions typically affected in the brainstem group in our study), leads to reduced phasic *ma* during REM and more consolidated REM atonia via direct impact on the sources of REM sleep muscle twitches.

Moreover, we assessed REM characteristics in the study cohorts. In our study, all patients in both stroke groups exhibited REM periods. Although the mean number of REM periods per recording was slightly higher in the brainstem group, the mean and total REM duration were significantly lower than in the lacunar stroke group, confirming previous reports (Carroll & Landau, 2014). The available literature of humans with brainstem lesions and alterations in REM sleep is relatively scarce and consists only of a limited number of case series reports of contradictory results (Carroll & Landau, 2014). Differences in the type and the exact localization of the lesions within the brainstem may explain apparent discrepancies in the results. To the best of our knowledge, this is the first study that assessed the ultradian distribution of REM atonia and provided evidence for time-of-night effects for REM-related *ma* in humans with brainstem lesions. We found that in the brainstem group, the degree of REM atonia did depend on the time of night and was not equally distributed in periods of REM sleep over the night. EMG activity during later REM sleep periods is expected to increase, and according to some authors this can be attributed to increasing REM duration (Sasai-Sakuma et al., 2014). Indeed, in both the lacunar and the control groups, there was a trend of increased EMG activity. On the contrary, in the brainstem group, EMG activity is significantly reduced towards the second half of the night, and this reduction was unrelated to the duration of REM sleep. It remains unclear how brainstem pathology affects the distribution of REM atonia across REM phases. From a theoretical perspective, evidence suggests REMs and twitching in REM sleep: (a) are associated with the ponto-geniculo-occipital (PGO) spikes, distinctive wave forms that are typically identified as propagating activity between the pons, thalamus and cortex; and (b) follow a well-defined temporal trajectory across REM sleep that is coordinated by a variable γ-aminobutyric acid (GABA) and glycine drive (Brooks & Peever, 2016), and increase towards the end of the night (Miyauchi et al., 2009). Thus, a brainstem/pons lesion could impact the generation of PGO spikes leading to reduced twitching and more profound REM atonia at the second half of the night, thus altering the ultradian distribution of phasic REM microstate. However, this hypothesis needs further investigation.

In the stroke groups, two subjects (65- and 53-year-old males) in the brainstem group (both mesencephalic strokes) and one subject (75-year-old male) in the lacunar group (thalamic stroke) exhibited increased muscle tone during REM, suggestive of RSWA. In our study, all subjects with RSWA were males, aged > 40 years, and it remains open if the increased muscle tone was associated with stroke itself or even stroke localization. There are previous reports for the presence of elevated isolated RSWA in adults, in particular men aged > 40 years, without clinical features of RBD (Feemster et al., 2019). Intriguingly, there is increasing evidence about the role of isolated RSWA as a precursor of RBD or even as an early biomarker of synuclein-mediated neurodegeneration (Stefani et al., 2015). Whether stroke in specific brain regions poses similar risks remains to be investigated.

This study has some limitations. It is a pilot retrospective study, and we assessed an unselected and relatively small group of patients with brainstem stroke. Therefore, only a few brainstem areas are affected. We cannot exclude that in a larger set of subjects with brainstem stroke, where a wider range of brainstem loci would be affected, the impact of brainstem on REM atonia might differ. Therefore, the results of this pilot study should be interpreted with caution, and must be confirmed and validated in larger samples.

Our findings add further to our understanding of the role of the human brainstem – particularly of the mesopontine areas – in the regulation of muscle tone during REM sleep and in the ultradian distribution of REM-related *ma*. This provides further support to the animal-to-human translation of the functional significance of the brainstem for the regulation of REM sleep. Larger, prospective clinical and experimental studies are needed to fully understand the complex pathways in different brain regions involved in muscle tone regulation during REM sleep.

AUTHOR CONTRIBUTIONS

N. T.: performance of data collection and analysis, interpretation of data, writing of the report; M. S.: contribution in data interpretation, critical revision of the report for intellectual content; F. A.: contribution in data collection, critical revision of the report for intellectual content; E. B.: performance of data analysis and writing; F. C.: contribution in data collection, critical revision of the report for intellectual content; C. L. B.: contribution in study concept and design, critical revision of the report for intellectual content; L. H.: contribution in

study concept and design, study supervision, performance of data analysis, interpretation of data, significant contribution in report writing; P. B.: conceptualization of the study concept and design, study supervision, acquisition of data, performance of data analysis, interpretation of data, significant contribution in report writing.

ACKNOWLEDGEMENT

The authors thank Prof. Hannes Mathis for assisting in data collection.

CONFLICT OF INTEREST

All authors have no specific conflict of interest with respect of present work and have nothing to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Panagiotis Bargiotas https://orcid.org/0000-0001-6502-8942

REFERENCES

Arrigoni, E., Chen, M. C., & Fuller, P. M. (2016). The anatomical, cellular and synaptic basis of motor atonia during rapid eye movement sleep. *The Journal of Physiology*, *594*(19), 5391–5414. https://doi.org/10.1113/JP271324

Bargiotas, P., Dietmann, A., Haynes, A. G., Kallweit, U., Calle, M. G., Schmidt, M., Mathis, J., & Bassetti, C. L. (2019). The Swiss *narcolepsy* scale (SNS) and its short form (sSNS) for the discrimination of narcolepsy in patients with hypersomnolence: A cohort study based on the Bern sleep-wake database. *Journal of Neurology*, *266*(9), 2137–2143. https://doi.org/10.1007/s00415-019-09365-2

Berry, R. B., Brooks, R., Gamaldo, C., Harding, S. M., Lloyd, R. M., Quan, S. F., Troester, M. T., & Vaughn, B. V. (2017). AASM scoring manual updates for 2017 (version 2.4). *Journal of Clinical Sleep Medicine*, *13*(5), 665–666. https://doi.org/10.5664/jcsm.6576

Blumberg, M. S., & Plumeau, A. M. (2016). A new view of "dream enactment" in REM sleep behavior disorder. *Sleep Medicine Reviews*, *30*, 34–42. https://doi.org/10.1016/j.smrv.2015.12.002

Boeve, B. F. (2010). REM sleep behavior disorder: Updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and futu. *Annals of the New York Academy of Sciences*, *1184*(1), 15–54. https://doi.org/10.1111/j.1749-6632.2009.05115.x

Boeve, B. F., Silber, M. H., Saper, C. B., Ferman, T. J., Dickson, D. W., Parisi, J. E., Benarroch, E. E., Ahlskog, J. E., Smith, G. E., Caselli, R. C., Tippman-Peikert, M., Olson, E. J., Lin, S.-C., Young, T., Wszolek, Z., Schenck, C. H., Mahowald, M. W., Castillo, P. R., Del Tredici, K., & Braak, H. (2007). Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. *Brain*: *A. Journal of Neurology*, *130*(Pt 11), 2770–2788. https://doi.org/10.1093/brain/awm056

Brooks, P. L., & Peever, J. (2016). A temporally controlled inhibitory drive coordinates twitch movements during REM sleep. *Current Biology*, *26*(9), 1177–1182. https://doi.org/10.1016/j.cub.2016.03.013

Burgess, C., Lai, D., Siegel, J., & Peever, J. (2008). An endogenous glutamatergic drive onto somatic Motoneurons contributes to the stereotypical pattern of muscle tone across the sleep–wake cycle. *Journal of Neuroscience*, *28*(18), 4649–4660. https://doi.org/10.1523/JNEUROSCI.0334-08.2008

Carroll, C., & Landau, M. E. (2014). Effects of pontine lesions on REM sleep. *Current Neurology and Neuroscience Reports*, *14*(7), 460. https://doi.org/10.1007/s11910-014-0460-x

Cavalloni, F., Debove, I., Lachenmayer, M. L., Krack, P., Pollo, C., Schuepbach, W. M. M., Bassetti, C. L. A., & Bargiotas, P. (2021). A case series and systematic review of rapid eye movement sleep behavior disorder outcome after deep brain stimulation in Parkinson's disease. *Sleep Medicine*, *77*, 170–176. https://doi.org/10.1016/j.sleep.2020.11.025

Feemster, J. C., Jung, Y., Timm, P. C., Westerland, S. M., Gossard, T. R., Teigen, L. N., Buchal, L. A., Cattaneo, E. F. D., Imlach, C. A., Mccarter, S. J., Smith, K. L., Boeve, B. F., Silber, M. H., & St Louis, E. K. (2019). Normative and isolated rapid eye movement sleep without atonia in adults without REM sleep behavior disorder. *Sleep*, *42*(10), zsz124. https://doi.org/10.1093/sleep/zsz124

Fisher, C. M. (1982). Lacunar strokes and infarcts: A review. *Neurology*, *32*(8), 871. https://doi.org/10.1212/WNL.32.8.871

Frauscher, B., Iranzo, A., Gaig, C., Gschliesser, V., Guaita, M., Raffelseder, V., Ehrmann, L., Sola, N., Salamero, M., Tolosa, E., Poewe, W., Santamaria, J., Högl, B., & SINBAR (Sleep Innsbruck Barcelona) Group. (2012). Normative EMG values during REM sleep for the diagnosis of REM sleep behavior disorder. *Sleep*, *35*(6), 835–847. https://doi.org/10.5665/sleep.1886

Fuller, P. M., Saper, C. B., & Lu, J. (2007). The pontine REM switch: Past and present. *The Journal of Physiology*, *584*(Pt 3), 735–741. https://doi.org/10.1113/jphysiol.2007.140160

Heydrich, L., & Blanke, O. (2013). Distinct illusory own-body perceptions caused by damage to posterior insula and extrastriate cortex. *brain*: *A. Journal of Neurology*, *136*(Pt 3), 790–803. https://doi.org/10.1093/brain/aws364

Khalil, A., Wright, M.-A., Walker, M. C., & Eriksson, S. H. (2013). Loss of rapid eye movement sleep Atonia in patients with REM sleep behavioral disorder, narcolepsy, and isolated loss of REM Atonia. *Journal of Clinical Sleep Medicine*, *09*(10), 1039–1048. https://doi.org/10.5664/jcsm.3078

Krenzer, M., Anaclet, C., Vetrivelan, R., Wang, N., Vong, L., Lowell, B. B., Fuller, P. M., & Lu, J. (2011). Brainstem and spinal cord circuitry regulating REM sleep and muscle atonia. *PLoS One*, *6*(10), e24998. https://doi.org/10.1371/journal.pone.0024998

Lapierre, O., & Montplaisir, J. (1992). Polysomnographic features of REM sleep behavior disorder: Development of a scoring method. *Neurology*, *42*(7), 1371–1374. https://doi.org/10.1212/wnl.42.7.1371

Mathis, J., Hess, C. W., & Bassetti, C. (2007). Isolated mediotegmental lesion causing narcolepsy and rapid eye movement sleep behaviour disorder: A case evidencing a common pathway in narcolepsy and rapid eye movement sleep behaviour disorder. *Journal of Neurology*, *Neurosurgery*, *and Psychiatry*, *78*(4), 427–429. https://doi.org/10.1136/jnnp.2006.099515

McCarter, S. J., St Louis, E. K., Duwell, E. J., Timm, P. C., Sandness, D. J., Boeve, B. F., & Silber, M. H. (2014). Diagnostic thresholds for quantitative REM sleep phasic burst duration, phasic and tonic muscle activity, and REM atonia index in REM sleep behavior disorder with and without comorbid obstructive sleep apnea. *Sleep*, *37*(10), 1649–1662. https://doi.org/10.5665/sleep.4074

Miyauchi, S., Misaki, M., Kan, S., Fukunaga, T., & Koike, T. (2009). Human brain activity time-locked to rapid eye movements during REM sleep. *Experimental Brain Research*, *192*(4), 657–667. https://doi.org/10.1007/s00221-008-1579-2

Reynolds, T. Q., & Roy, A. (2011). Isolated cataplexy and REM sleep behavior disorder after pontine stroke. *Journal of Clinical Sleep Medicine*: *JCSM*, *7*(2), 211–213.

Rorden, C., Karnath, H.-O., & Bonilha, L. (2007). Improving lesion-symptom mapping. *Journal of Cognitive Neuroscience*, *19*(7), 1081–1088. https://doi.org/10.1162/jocn.2007.19.7.1081

Saper, C. B., Chou, T. C., & Scammell, T. E. (2001). The sleep switch: Hypothalamic control of sleep and wakefulness. *Trends in Neurosciences*, *24*(12), 726–731. https://doi.org/10.1016/s0166-2236(00)02002-6

Sasai-Sakuma, T., Frauscher, B., Mitterling, T., Ehrmann, L., Gabelia, D., Brandauer, E., Inoue, Y., Poewe, W., & Högl, B. (2014). Quantitative

assessment of isolated rapid eye movement (REM) sleep without atonia without clinical REM sleep behavior disorder: Clinical and research implications. *Sleep Medicine*, *15*(9), 1009–1015. https://doi.org/10.1016/j.sleep.2014.02.010

St. Louis, E. K., McCarter, S. J., Boeve, B. F., Silber, M. H., Kantarci, K., Benarroch, E. E., Rando, A., Tippmann-Peikert, M., Olson, E. J., & Mauermann, M. L. (2014). Lesional REM sleep behavior disorder localizes to the dorsomedial pons. *Neurology*, *83*(20), 1871–1873. https://doi.org/10.1212/WNL.0000000000000978

Stefani, A., Gabelia, D., Högl, B., Mitterling, T., Mahlknecht, P., Stockner, H., Poewe, W., & Frauscher, B. (2015). Long-term follow-up investigation of isolated rapid eye movement sleep without Atonia without rapid eye movement sleep behavior disorder: A pilot study. *Journal of Clinical Sleep Medicine: JCSM*, *11*(11), 1273–1279. https://doi.org/10.5664/jcsm.5184

Weber, F., Hoang Do, J. P., Chung, S., Beier, K. T., Bikov, M., Saffari Doost, M., & Dan, Y. (2018). Regulation of REM and non-REM sleep by periaqueductal GABAergic neurons. *Nature Communications*, *9*(1), 354. https://doi.org/10.1038/s41467-017-02765-w

Xi, Z., & Luning, W. (2009). REM sleep behavior disorder in a patient with pontine stroke. *Sleep Medicine*, *10*(1), 143–146. https://doi.org/10.1016/j.sleep.2007.12.002

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Tellenbach, N., Schmidt, M. H., Alexiev, F., Blondiaux, E., Cavalloni, F., Bassetti, C. L., Heydrich, L., & Bargiotas, P. (2022). REM sleep and muscle atonia in brainstem stroke: A quantitative polysomnographic and lesion analysis study. *Journal of Sleep Research*, e13640. https://doi.org/10.1111/jsr.13640