

Reduced sensorimotor inhibition in the ipsilesional motor cortex in a patient with chronic stroke of the paramedian thalamus

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Abstract

Objective: Unilateral or bilateral paramedian infarction in the region of the thalamus and upper midbrain may lead to hypersomnia. To determine whether unilateral infarction of the paramedian thalamus leads to changes in excitability of ipsilesional primary motor hand area (M1).

Methods: We describe a patient with chronic stroke of the right dorsomedian and intralaminar thalamic nuclei, who suffered from mild persistent hypersomnia. We studied the excitability of the right and left M1 with transcranial magnetic stimulation (TMS) in the patient, and in 10 healthy controls.

Results: In contrast to healthy controls, contralateral electrical stimulation of the median nerve failed to induce short-latency afferent inhibition (SAI) in the ipsilesional M1. Other measures of corticomotor excitability and somatosensory evoked potentials were normal.

Conclusions: The selective loss of ipsilateral SAI in a patient with paramedian thalamic stroke suggests that during wakefulness, the intact paramedian thalamus facilitates the excitability of intracortical inhibitory circuits, which process thalamocortical sensory inputs in the ipsilateral M1. This preliminary finding suggests that measurements of SAI may provide a means of probing the integrity of some neural pathways, which are involved in the control of wakefulness and arousal.

Significance: In addition to the established role of the paramedian thalamus in arousal and memory, our observation suggests that thalamocortical projections from the paramedian thalamus contribute to the integration of sensory input at the cortical level during wakefulness.

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Keywords: Transcranial magnetic stimulation; Thalamus; Motor cortex; Arousal; Sleep

1. Introduction

Unilateral or bilateral paramedian infarction in the region of the thalamus and upper midbrain may produce neuropsychological disturbance predominantly affecting arousal and memory. Paramedian thalamic stroke can cause hypersomnia, which has been attributed to disruption

of ascending activating impulses and considered to be produced by deficient arousal during the day (Bassetti et al., 1996).

Several studies have used transcranial magnetic stimulation (TMS) to show that lesions in the thalamus can cause changes in excitability in the ipsilateral primary motor cortex (Classen et al., 1997; Munchau et al., 2002; von Giesen et al., 1994). Here, we evaluated motor cortex excitability and the sleep patterns of a patient 6 months after a right paramedian thalamic stroke. The patient suffered from mild hypersomnia at the time of neurophysiological

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evaluation. We gave focal TMS to the ipsilesional and contralesional primary motor hand area (M1), and assessed several measures of corticomotor excitability (Siebner and Rothwell, 2003). Our aim was to examine whether a lesion of paramedian thalamus has a selective effect on intracortical processing of afferent sensory stimuli in the ipsilesional M1.

2. Methods

2.1. Case report

A 43-year-old right-handed female patient was admitted with right ptosis, paresis and sensory deficit of the left upper limb and severe somnolence. Sensory deficit was evaluated clinically by comparing light touch and pinprick tests with the contralateral side. The patient was a smoker and was on oral anticonceptive treatment. MRI revealed an acute stroke in the territory of the right paramedian artery involving the dorsomedial and centromedian thalamic nuclei, the perilesional oedema also involved the upper portion of the right red nucleus and the fibres of III cranial nerve (MRI not shown). In the following days, the patient fully recovered from right ptosis, left upper limb weakness and sensory loss. Somnolence gradually improved but the patient remained hypersomnic with 12–14 h of sleep behaviour per day.

The patient was re-examined 6 months after the stroke. Initial sensorimotor deficits had fully recovered. Light touch and pinprick tests, two-point discrimination and position sense were normal. No abnormal postures or involuntary movements were present. The only residual symptom was mild hypersomnia. She complained of prolonged night sleep and excessive daytime sleepiness with difficulty in maintaining an alert awake state during times of rest or when little attention was required. The patient was not treated with drugs in the 60 days prior to re-examination. Follow-up included a structural MRI scan of the brain, polysomnography (PSG) and electrophysiological examination.

2.2. Sleep and daytime sleepiness measurements

Full-night sleep was assessed in the sleep laboratory. Daytime sleepiness was measured the day after PSG using the multiple sleep latency test (MSLT) and the Epworth sleepiness scale (Johns, 1991). The MSLT was performed five times during the day, at 2 h intervals starting at 8 am.

2.3. Electrophysiological measurements

Electrophysiological measurements of sensorimotor function were carried out during wakefulness and compared to normal values obtained in 10 healthy controls with no history of sleep disorders (5 females, two left-handed, age 32.4 ± 8.1 years).

We evaluated motor cortex excitability and the integrity of corticospinal and somatosensory pathways using TMS. Measurements included: (i) the resting and active motor threshold (RMT and AMT), which reflect the intrinsic and extrinsically modulated excitability properties of corticospinal neurons (Hallett, 2000; Ziemann et al., 1996); (ii) central motor conduction time (CMCT), which reflects the integrity of the corticospinal tract (Rossini et al., 1994); (iii) short-latency intracortical inhibition to paired TMS (SICI), long latency intracortical inhibition to paired TMS (LICI) and the cortical silent period (CSP); which are all believed to reflect the excitability of inhibitory GABAergic cortical circuits (Di Lazzaro et al., 2000a, b; Ziemann et al., 1996); (iv) intracortical facilitation (ICF) to paired TMS that is thought to depend on the activity of intracortical glutamatergic excitatory circuits and is also modulated by gabaergic inputs (Kujirai et al., 1993; Ziemann et al., 1998a); and (v) short-latency afferent inhibition (SAI) which is facilitated by cholinergic circuits as demonstrated by the sensitivity to the muscarinic blockade (Di Lazzaro et al., 2000a, b). We also recorded somatosensory evoked potentials (SSEPs) after contralateral median nerve stimulation to demonstrate the functional integrity of the thalamocortical sensory pathway (Mauguiere, 1996).

Electrophysiological measurements were always performed at the same time of the day (between 4 and 6 pm). The study adhered to the guidelines for scientific conduct specified in the Declaration of Helsinki and was approved by the local ethics committee. The patient and controls gave informed consent before participation.

Electrophysiological measurements were conducted 6 months after stroke. The patient was instructed to stay awake with eyes open. Since cortical excitability is largely influenced by drowsiness or sleep, the patient was studied during full wakefulness, which was continuously monitored with two EEG electrodes placed at Cz and Pz (10–20 system). Drowsiness was defined as either slowing of alpha activity (stage 1A) or appearance of theta activity (stage 1B) (Valley and Broughton, 1983). EEG revealed no signs of drowsiness or sleep during the course of the experiment.

TMS was performed with a high power Medtronic Magpro X100 (Medtronic, Minneapolis, MN, USA). A figure-of-eight coil with external loop diameters of 9 cm was held over the motor cortex at the optimum scalp position to elicit motor responses in the contralateral first dorsal interosseous (FDI) muscle. The induced current flowed in a postero-anterior direction and the pulse form was monophasic.

RMT was defined as the minimum stimulus intensity that produced a liminal motor evoked response (about 50 μ V in 50% of trials) at rest. AMT was defined as the minimum stimulus intensity that produced a liminal motor evoked response (about 200 μ V in 50% of trials) during isometric contraction of the tested muscle at about 20% maximum (Rossini et al., 1994). CMCT was calculated by subtracting the peripheral conduction time from cervical roots to muscles

(obtained by magnetic stimulation at cervical level) from the latency of responses evoked by cortical stimulation (Rossini et al., 1994). CSP was elicited whilst subjects held a tonic voluntary contraction of approximately 50% of MVC. Five stimuli at 150% AMT were given. The duration of the silent period was measured from the start of the motor potential to the reappearance of sustained EMG activity. SICI and ICF were studied using a conditioning-test paradigm introduced by Kujirai et al. (1993). Two magnetic stimuli were given through the same stimulating coil to the motor cortex, and the effect of the first (conditioning) stimulus on the second (test) stimulus was investigated. The conditioning stimulus was set at an intensity of 90% of AMT. The test stimulus was adjusted to evoke a MEP in relaxed FDI muscle with an amplitude of approximately 1 mV peak-to-peak. The timing of the conditioning shock was altered in relation to the test shock. Interstimulus intervals (ISIs) of 2 and 3 ms and 10 and 12 ms were investigated. Ten stimuli were delivered at each ISI. The amplitude of the conditioned MEPs was expressed as a percentage of the amplitude of the test MEPs. Inhibition and facilitation of the conditioned responses at the two different ISIs studied was averaged to give grand mean values.

LICI was studied in the following way: two magnetic stimuli were given through the same stimulating coil; both conditioning and test stimuli were set at an intensity adjusted to evoke a MEP in relaxed FDI muscle with an amplitude of approximately 1 mV peak-to-peak (about 110% RMT). An interstimulus interval of 100 ms was investigated. The amplitude of the conditioned MEPs was expressed as a percentage of the amplitude of the test MEPs. SAI was studied using the technique described by Tokimura et al. (Di Lazzaro et al., 2002; Tokimura et al., 2000). The

intensity of the test cortical magnetic shock was adjusted to evoke a muscle response in relaxed FDI with an amplitude of approximately 1 mV peak-to-peak. Conditioning stimuli were single pulses of electrical stimulation applied through bipolar electrodes to the median nerve at the wrist. The intensity of the conditioning stimulus was set at just over motor threshold to evoke a visible twitch of the thenar muscles. The conditioning stimulus to the peripheral nerve preceded the magnetic test stimulus. Interstimulus intervals (ISIs) were determined relative to the latency of the N20 component of the somatosensory evoked potential evoked by stimulation of the median nerve. The active electrode for recording the N20 potential evoked by left median nerve stimulation was attached 3 cm posterior to C3 (10–20 system) (or C4 for right median nerve stimulation) and the reference was 3 cm posterior to C4 (or C3 for right median nerve stimulation). One thousand consecutive potentials were averaged to identify the mean latency of the N20 peak. ISIs were adjusted to individual N20 latency and seven ISIs were tested ranging from N20+2 ms to N20+8 ms. Ten stimuli were then delivered at each ISI. The amplitude of the conditioned MEPs was expressed as a percentage of the amplitude of the test MEPs. The percentage inhibition of the conditioned responses at the seven different ISIs was averaged to obtain a grand mean.

RMT, AMT, SICI, LICI, ICF, SAI, duration of the CSP, CMCT, N20 latency and N20 amplitude were evaluated bilaterally, both in the patient and in controls. Inter-hemispheric differences (dominant hemisphere minus non-dominant hemisphere) were calculated for each measure. In the control group, we calculated mean \pm 2.5 SD to define the upper and lower limits of the normal range for each

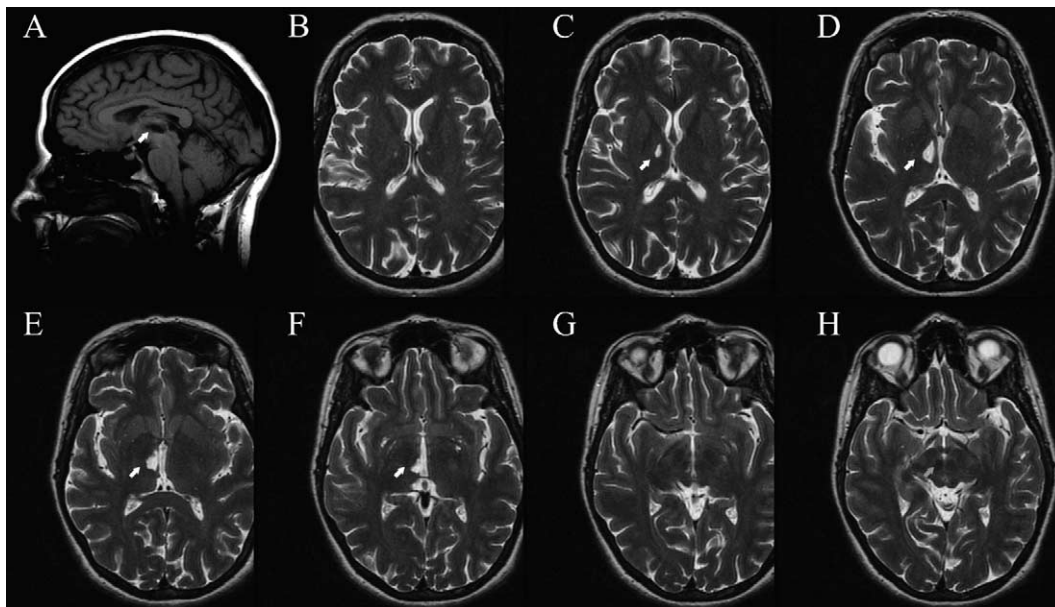


Fig. 1. T1 weighted sagittal MRI (A) shows a chronic lesion in the right thalamus. T2 weighted axial MRI (C–F) shows the cranio-caudal extension of the chronic lesion in the right thalamus involving dorsomedial and centromedian nuclei (white arrows). T2 weighted axial MRI (B, G and H) shows the upper and lower scans without pathological signals (H: grey arrow indicates the normal red nucleus).

neurophysiological parameter and the inter-hemispheric differences (ID).

3. Results

At 6-month follow-up, structural T1 and T2-weighted MRI showed a chronic lesion in the right thalamus involving dorsomedial and centromedian nuclei (Figs. 1 and 2). The results of PSG are summarized in Table 1. PSG did not show any major abnormality of sleep. In particular,

PSG revealed no apnoea or periodic limb movements during sleep. The MSLT revealed a sleep latency of 8.4 min (normal value > 10 min, pathologic sleepiness < 5 min, dubious between 5 and 10 min). We observed no epoch of REM sleep within the first 10 min during five consecutive tests. The patient reached a score of 12 on the Epworth sleepiness scale (normal value < 10), indicating mild hypersomnia.

Table 2 summarizes the electrophysiological results. RMT, AMT, SICI, ICF, duration of the CSP, CMCT, N20 latency and N20 amplitude were within normal limits. LICI

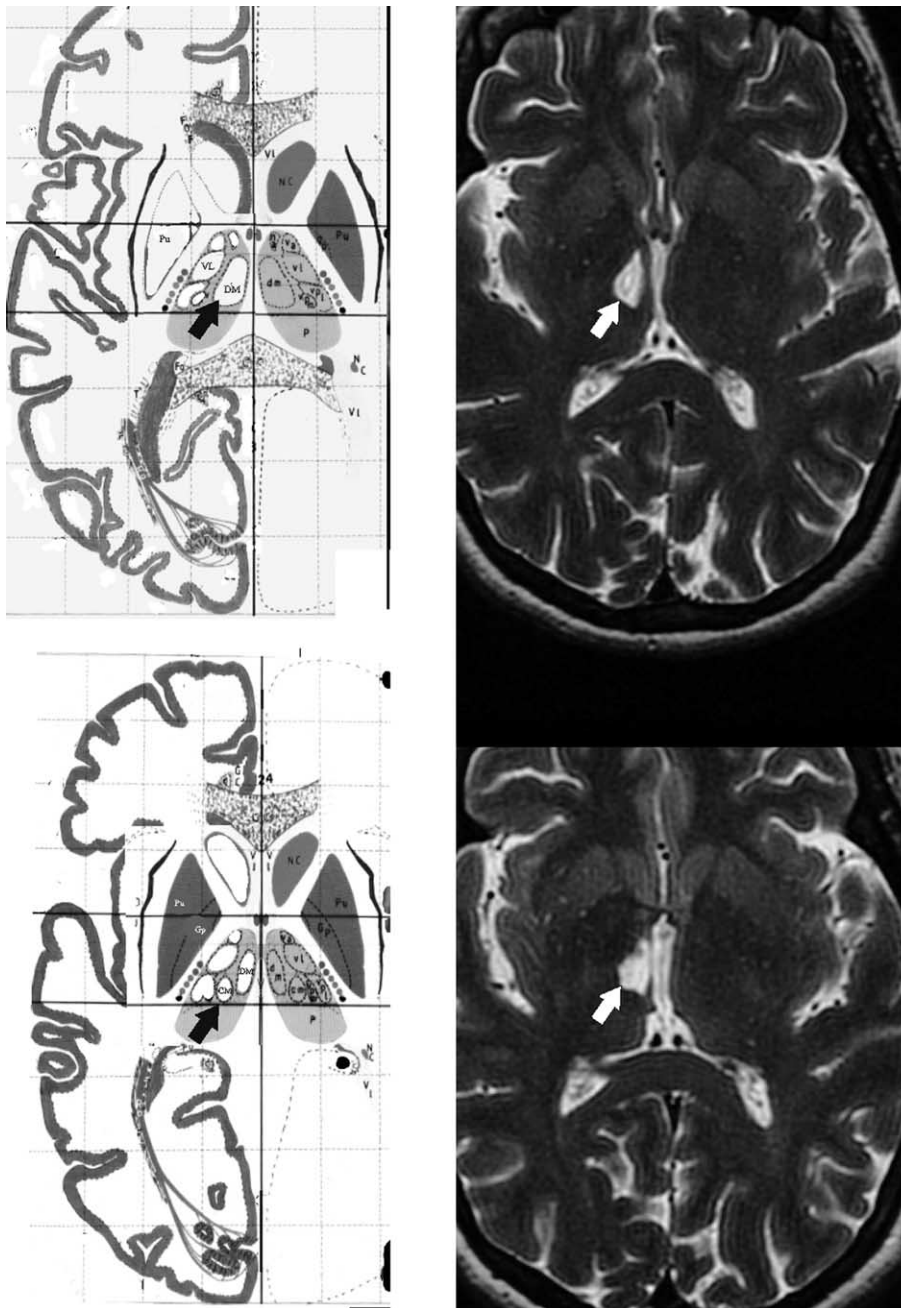


Fig. 2. Atlas image (modified from Talairach and Tournoux, 1988) showing the location of the dorsomedial nucleus (black arrow) and a T2 weighted axial MRI, showing the lesion of the dorsomedial and centromedian nuclei (white arrow). DM, dorsomedial nucleus; CM, centromedian nucleus.

Table 1
Polysomnographic parameters of the patient

Polysomnographic parameters	
<i>Macrostructure</i>	
Sleep onset latency	11.0 min
Sleep efficiency on time in bed	97.0%
Sleep period time	503 min
Total sleep time	493 min
Number of REM periods	4
REM latency	1 h 22 min
<i>Sleep stages percentages</i>	
REM	22.0%
Stage 1	13.0%
Stage 2	39.0%
Stage 3	18.0%
Stage 4	8.0%
<i>Wake parameters</i>	
Total number of awakenings	2
Awakenings > 2 min	0
Apnea–hypopnea index	0 events/h

showed a tendency to be more pronounced in the affected hemisphere (AH) than in the unaffected hemisphere (UH) while SICI showed a tendency to be reduced in the AH when compared with the UH.

In healthy controls, the magnitude of SAI showed a tendency towards a stronger SAI in the dominant hemisphere (DH) compared with the non-dominant hemisphere (NDH), but both hemispheres showed a clear SAI. In contrast to healthy controls, the amount of SAI markedly differed between hemispheres in the patient (Table 2). While SAI in the contralesional M1 was normal, the patient showed a complete loss of SAI in the ipsilesional M1 (Fig. 3). Sensory stimulation had even a facilitatory effect on the MEP amplitude at longer ISIs (Fig. 3).

Table 2
Neurophysiological findings in the patient and in 10 control subjects

Test	Control subjects					Patient		
	DH	NDH	ID (DH–NDH)	ID lower limit	ID upper limit	UH (DH)	AH (NDH)	ID (UH–AH)
RMT (%)	61.8 (4.4)	62.2 (3.3)	–0.4 (3)	–8	7.2	60	58	2
AMT (%)	46.9 (6.9)	47 (4.8)	–0.1 (8.2)	–20.6	20.4	44	43	1
CSP (ms)	146.3 (42.5)	156.3 (28.8)	–10 (47)	–128	108	108	101	–7
SICI (%)	40.5 (8.9)	43.1 (24.5)	–2.6 (20)	–53.5	48.3	24.3	52.6	–28.3
ICF (%)	131.4 (42.5)	123.6 (20.8)	7.8 (45.2)	–105.3	120.8	106.1	121.8	–15.7
LICI (%)	35.2 (22.6)	35.7 (20)	–0.4 (27.7)	–69.8	68.9	64.5	17.8	46.7
SAI (%)	53.9 (22.1)	64.2 (17.9)	–10.4 (11.7)	–39.6	18.9	54.2	125.6	–71.4
N20 lat/amp (ms/ μ V)	19/2.8 (0.6/0.8)	19/2.9 (0.6/0.6)	0/–0.1 (0.6/0.8)	–1.6/–1.9	1.6/2.1	17.8/2.4	17.9/2.4	–0.1/0
CMCT (ms)	5.9 (0.6)	5.8 (0.6)	0.1 (0.2)	–0.4	0.6	5.7	5.6	0.1

DH: dominant hemisphere; NDH: non-dominant hemisphere; ID: interside difference; UH: unaffected hemisphere; AH: affected hemisphere; SICI: mean SICI at 2 and 3 ms ISIs; ICF: mean ICF at 10 and 12 ms ISIs; LICI: mean LICI at 100 ms ISI; SAI: mean SAI at N20+2–8 ms ISIs; RMT and AMT %: % of maximum stimulator output; SICI, ICF, LICI and SAI %: % of test response; CMCT: central motor conduction time; (): standard deviations; bold: out of normal limits.

4. Discussion

In the waking state, we observed a selective attenuation of the SAI in the ipsilesional M1 6 months after a thalamic stroke that had destroyed the dorsomedian and intralaminar nuclei. The reduction of SAI was evenly distributed across all ISIs, resulting in a loss of SAI at short ISIs and an abnormal sensorimotor facilitation at longer ISIs. Previous work has shown that an electrically induced afferent volley from the median nerve can produce short-latency facilitation (Deletis et al., 1992) and inhibition (Tokimura et al., 2000) of the corticomotor output to the stimulated limb. In our patient, a loss of thalamocortical input from the dorsomedian and intralaminar nuclei onto intracortical circuits was associated with a shift in the balance between short-latency sensorimotor inhibition and facilitation towards a stronger facilitation. TMS measurements showed that the change in motorcortical excitability was restricted to the conditioning effect of afferent somatosensory stimuli. There was no evidence for a damage of the corticospinal output tract or additional abnormalities in the excitability of the M1. EEG monitoring excluded the possibility that the changes in sensorimotor excitability were confounded by an altered state of vigilance during the electrophysiological measurements. Sensory testing, SSEP measurements and structural MRI showed that the somatosensory thalamocortical pathways and the sensory nuclei of the thalamus were not affected by the paramedian thalamic stroke. Taken together, our findings suggest that during wakefulness, SAI is under the control of neuronal networks located in the paramedian thalamus.

SAI starts only a few milliseconds after the arrival of the somatosensory input at the cortex, and implies a relatively direct pathway from sensory input to motor output (Tokimura et al., 2000). SAI has been shown to depend upon the activity of cholinergic circuits

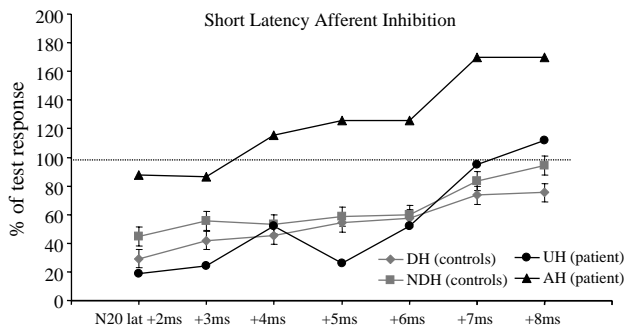


Fig. 3. SAI time course at different interstimulus intervals in both the patient and in controls. The loss of SAI was consistent across all ISIs. At late ISIs the mean amplitude of the conditioned response was evenly facilitated. DH, dominant hemisphere; NDH, non-dominant hemisphere; UH, unaffected hemisphere; AH, affected hemisphere.

as demonstrated by its sensitivity to the muscarinic blockade (Di Lazzaro et al., 2000a, b). The dorsomedial nucleus and intralaminar nuclei (thalamic paramedian structures) are under control of excitatory projections from pontomesencephalic cholinergic neurons (pedunculopontine and laterodorsal tegmental cholinergic nuclei) through muscarinic receptors (Jones, 2003; Steriade, 2004). These pontomesencephalic cholinergic neurons have no direct projection to the cortex but they do have a prominent indirect effect on the functional state (and excitability) of cortical neurons as they activate thalamocortical neurons (Steriade, 2001; Steriade, 2004). At the time of this neurophysiological study (i.e. 6 months after stroke), the only residual symptom was mild hypersomnia probably due to the interruption of the pontomesencephalic-(paramedian) thalamo-cortical pathway. The pontomesencephalic-(paramedian) thalamo-cortical pathway is thought to be important for arousal, and cholinergic projections (during wakefulness) are also thought to facilitate the responsiveness of cortical neurons to sensory stimuli (e.g. promoting sensory-motor inhibition, see Jones, 2003) (Jasper and Tessier, 1971; Jones, 2003). Our results indicate that during wakefulness, the intact paramedian thalamus exerts a facilitatory effect on the excitability of intracortical inhibitory circuits. This supports the concept that the pontomesencephalic-(paramedian) thalamo-cortical pathway also plays a prominent role in regulating intracortical sensory (motor) processing. We propose that the measurement of SAI can be used to test how this pathway related to arousal modulates the integration of sensory input at the cortical level. We found a marked loss of SAI, while only mild hypersomnia was evident at the time of the neurophysiological study. The unilateral lesion and the sparing of other arousal systems could explain this discrepancy.

It is interesting to note that SAI was slightly more pronounced in the DH in healthy controls: further

studies focused on this asymmetry could confirm this result and provide information about its functional role and the relationship with handedness. The slight asymmetry of CSP between DH and NDH in healthy subjects confirms previous reports (Garvey et al., 2003; Priori et al., 1999). Our patient had symmetric CSPs, which showed a tendency to be slightly shorter respect to the healthy group. Thalamic lesions had been reported associated with shorter or prolonged CSP depending on the lesion location (Classen et al., 1997; Liepert et al., 2005; Munchau et al., 2002). Further studies can clarify the exact relationship between CSP and the thalamus.

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