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Brainstem reflex circuits revisited

G. Cruccu,[1] G. D. Iannetti,[2] J. J. Marx,[3] F. Thoemke,[3] A. Truini,[1] S. Fitzek,[4] F. Galeotti,[1] P. P. Urban,[3] A. Romaniello,[1] P. Stoeter,[3] M. Manfredi[1] and H. C. Hopf[3]

[1]*Department of Neurological Sciences, 'La Sapienza' University, Rome, Italy,* [2]*Department of Human Anatomy and Genetics and FMRIB Centre, University of Oxford, Oxford, UK,* [3]*Department of Neurology and Department of Neuroradiology, 'Johannes Gutenberg' University, Mainz, Germany and* [4]*Department of Neurology, 'Friedrich Schiller' University, Jena, Germany*

Correspondence to: Prof. Giorgio Cruccu, Dipartimento Scienze Neurologiche, Viale Università 30, 00185 Roma, Italy
E-mail: cruccu@uniroma1.it

Summary

Our current understanding of brainstem reflex physiology comes chiefly from the classic anatomical–functional correlation studies that traced the central circuits underlying brainstem reflexes and establishing reflex abnormalities as markers for specific areas of lesion. These studies nevertheless had the disadvantage of deriving from post-mortem findings in only a few patients. We developed a voxel-based model of the human brainstem designed to import and normalize MRIs, select groups of patients with or without a given dysfunction, compare their MRIs statistically, and construct three-plane maps showing the statistical probability of lesion. Using this method, we studied 180 patients with focal brainstem infarction. All subjects underwent a dedicated MRI study of the brainstem and the whole series of brainstem tests currently used in clinical neurophysiology: early (R1) and late (R2) blink reflex, early (SP1) and late (SP2) masseter inhibitory reflex, and the jaw jerk to chin tapping. Significance levels were highest for R1, SP1 and R2 afferent abnormalities. Patients with abnormalities in all three reflexes had lesions involving the primary sensory neurons in the ventral pons, before the afferents directed to the respective reflex circuits diverge. Patients with an isolated abnormality of R1 and SP1 responses had lesions that involved the ipsilateral dorsal pons, near the fourth ventricle floor, and lay close to each other. The area with the highest probabilities of lesion for the R2-afferent abnormality was in the ipsilateral dorsal–lateral medulla at the inferior olive level. SP2 abnormalities reached a low level of significance, in the same region as R2. Only few patients had a crossed-type abnormality of SP1, SP2 or R2; that of SP1 reached significance in the median pontine tegmentum rostral to the main trigeminal nucleus. Although abnormal in 38 patients, the jaw jerk appeared to have no cluster location. Because our voxel-based model quantitatively compares lesions in patients with or without a given reflex abnormality, it minimizes the risk that the significant areas depict vascular territories rather than common spots within the territory housing the reflex circuit. By analysing statistical data for a large cohort of patients, it also identifies the most frequent lesion location for each response. The finding of multireflex abnormalities reflects damage of the primary afferent neurons; hence it provides no evidence of an intra-axial lesion. The jaw jerk, perhaps the brainstem reflex most widely used in clinical neurophysiology, had no apparent topodiagnostic value, probably because it depends strongly on peripheral variables, including dental occlusion.

Keywords: brainstem infarction; brainstem reflexes; MRI; anatomical–functional correlation

Abbreviations: R1 = early blink reflex; R2 = late blink reflex; SP1 = early masseter inhibitory reflex; SP2 = late masseter inhibitory reflex

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Introduction

Thanks to the functional specificity of the nervous system, classic post-mortem studies designed to correlate a clinical sign with a brain lesion remarkably advanced our understanding of nervous system physiology and pathophysiology. Anatomical–functional correlation studies also traced the central circuits of brainstem reflexes and identified certain

reflex abnormalities as markers of specific areas of lesion. These studies, whether using post-mortem specimens (Aramideh *et al*., 1997; Ongerboer de Visser and Kuypers, 1978, 1979) or neuroimaging (Ongerboer de Visser *et al*., 1990; Fitzek *et al*., 1999, 2001), derived their data from a small number of samples and provided qualitative rather than quantitative, statistically supported results.

Since the 1950s the easiest neurophysiological method for assessing brainstem function has been (Kugelberg, 1952; McIntyre and Robinson, 1959) and still is the electromyographic recording of brainstem reflexes (Ongerboer de Visser and Cruccu, 1993; Hopf, 1994; Kimura *et al*., 1994; Deuschl and Eisen, 1999). This technique is particularly useful in patients with no overt cranial motor nerve impairment. What is lacking is a quantitative approach that could assess the topodiagnostic value of the several brainstem reflexes currently tested in clinical neurophysiology: the early (R1) and late (R2) blink reflex, early (SP1) and late (SP2) masseter inhibitory reflexes, and the jaw jerk.

To approach this problem, using a voxel-based brainstem model that provides maps of statistical probability (Capozza *et al*., 2000; Marx *et al*., 2004), we determined the correlations between reflex abnormalities disclosed by electromyographic recordings and abnormalities seen on MRI in a large cohort of patients with focal ischaemic brainstem lesions. To minimize the risk of highlighting vascular territories rather than the structures within these territories specifically responsible for the clinical dysfunction, we assessed differences between patients with and without a given dysfunction.

Subjects and methods

The study was conducted in two European neurological institutions where patients are referred for testing of brainstem reflexes whenever it is useful to ascertain whether or where the brainstem is involved. Starting from March 1997, we collected consecutive patients with an MRI-documented acute brainstem infarction and no clinical or imaging evidence of a major supratentorial lesion. Afterwards, we excluded patients with extra-axial nerve lesions and, because of possible suprasegmental interference with reflex excitability, those with intra-axial ventral lesions involving the corticobulbar tract. One group of 75 patients was tested in the Department of Neurological Sciences, 'La Sapienza' University of Rome, and the other group of 105 in the Department of Neurology, 'Johannes Gutenberg' University of Mainz. Of the total of 180 patients studied, 103 were males and 77 were females, and age ranged from 29 to 88 years (mean 66 years). The subjects' consent was obtained according to the Declaration of Helsinki (BMJ 1991; 302: 1194) and the Ethical Committees of the two institutions approved the study protocol.

Neurophysiological methods

In accordance with the standard methods recommended by the International Federation of Clinical Neurophysiology (IFCN; Deuschl and Eisen, 1999), all participants underwent electromyographic recording of the main brainstem reflexes currently used in clinical neurophysiology: early (R1) and late (R2) blink reflex, early (SP1) and late (SP2) masseter inhibitory reflexes, and the jaw jerk to chin taps (Fig. 1). Examiners were blind to MRI results. Recordings were taken as soon as possible after admission, usually before MRI examination (see below). Although each of the two laboratories used its own normal values (Cruccu and Deuschl, 2000; Hopf *et al*., 1991),

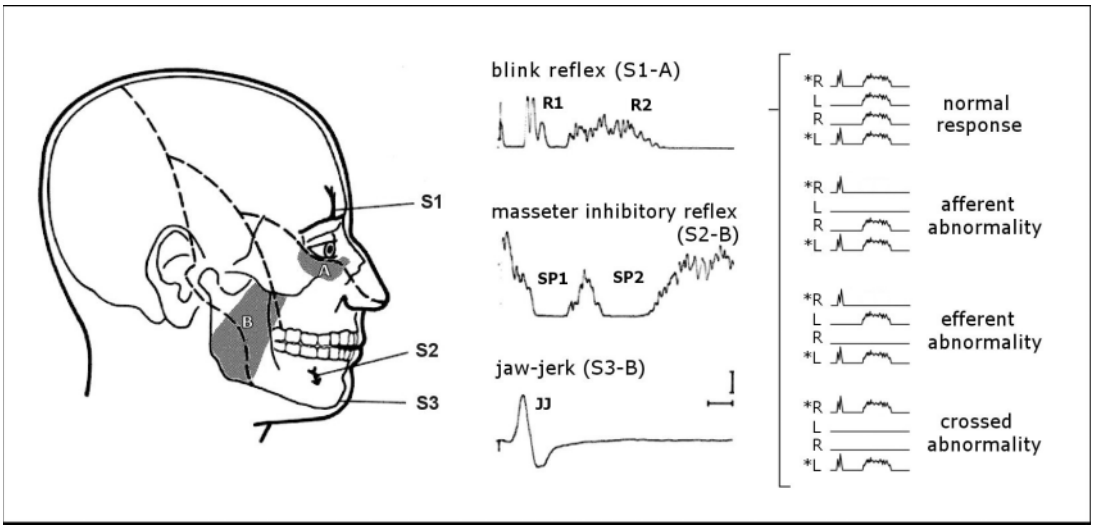

Fig. 1 Scheme of brainstem reflexes. (*Left panel*) Drawing of stimulating and recording sites. S1, electrical stimulation of supraorbital nerve; S2, electrical stimulation of mentalis nerve; S3, chin taps; A, recording from orbicularis oculi muscle; B, recording from masseter muscle. (*Middle panel*) Normal responses. Early (R1) and late (R2) blink reflex; early (SP1) and late (SP2) masseter inhibitory reflex; jaw jerk (JJ). (*Right panel*) Schematic example of R2 abnormality patterns in medullary lesions. In healthy subjects, stimulation (*) of the right side (R) evokes a normal R1 response in the ipsilateral muscle and normal R2 responses bilaterally; stimulation of the left side (L) does the same. In the following abnormality patterns, R1 always remains normal because its circuit does not extend caudally to the medulla. In the right afferent abnormality, R2 is abnormal (in this scheme it is absent) in the right and left muscle after stimulation of the right side and normal after stimulation of the left side. In the right efferent abnormality, R2 is absent in the right muscle and normal in the left, after stimulation of either side. In the crossed abnormality, the responses ipsilateral to stimulation are normal and those contralateral are absent.

general criteria of abnormality adhered to those recommended for clinical practice by the IFCN (Deuschl and Eisen, 1999). Responses were considered abnormal when absent or delayed beyond the normal range. By considering 'uncertain' each response that was not clearly normal or abnormal (see below), we took care not to risk any false-positive or false-negative errors. For reflexes with bilateral responses, abnormalities were classified as 'afferent' (responses in right and left muscles are abnormal after stimulation of one side), 'efferent' (responses in the muscle on one side alone are abnormal after stimulation of either side), or 'crossed' (responses in the muscle ipsilateral to the side of stimulation are normal bilaterally, whereas the contralateral responses are always abnormal regardless of the stimulated side) (Ongerboer de Visser and Cruccu, 1993; Deuschl and Eisen, 1999) (Fig. 1). Two examiners assigned each response to one of four categories: normal, abnormal, uncertain, or not examined (a few patients, especially those who were elderly or in poor general health, did not have all the reflexes examined).

MRI acquisition

As soon as patients could tolerate the longer-lasting magnetic resonance (MR) scans (mean 8 days after the onset of symptoms), they underwent a standard MRI brain study, followed by a focused brainstem investigation. The MR scans were acquired using 1.5 tesla superconducting systems (Magnetom Vision; Siemens, Erlangen, Germany, and Philips Gyroscan, The Netherlands). High-resolution T1- and T2-weighted brainstem images, before and after intravenous gadolinium, were collected from all patients; in some cases FLAIR (fluid attenuation inversion recovery) images were also available. Slice orientation was parallel (sagittal sections) and perpendicular (axial sections) to the sagittal brainstem cuts of the stereotactic anatomical atlas of Schaltenbrand and Wahren (1977); the slice thickness was 3 mm over a 256×256 matrix. In about half of the patients biplanar EPI T2 and EPI diffusion-weighted (DWI) images were also collected within 48 h after the onset of symptoms, using DWI echo-planar imaging (repetition time 4000 ms, echo time 103 ms) with separately applied diffusion-gradients in the three spatial axes ($b = 1164$ s/mm^3, 128 matrix, 250 ms per slice, 20 slices, thickness 3 mm, eight measurements). The area of infarction was identified and defined independently by two raters.

Three-dimensional mapping and statistics

Given the anatomical–functional right–left symmetry of the brainstem, all left-sided lesions were flipped to the right side, imported and normalized into the brainstem model (Capozza *et al*., 2000; Marx *et al*., 2004) developed using data from topometric and stereotactic atlases (Schaltenbrand and Wahren, 1977; Paxinos and Huang, 1995; Kretschmann and Weinrich, 1998). The brainstem model was subdivided into 5268 volume elements (voxels), ranging from $2 \times 2 \times 2$ mm to $2 \times 2 \times 4$ mm. After MRIs had been imported and normalized into the brainstem model, each voxel of the model was assigned a value of 0, 0.5 or 1; value 1 stood for a voxel certainly involved in the area of MR abnormal signal, value 0 for a voxel certainly uninvolved, and value 0.5 for a voxel only partly involved or disagreed by the two raters. Statistical analysis of the pooled patient data aimed to identify which of the 5268 voxels were significantly affected. For within-group, one-sample analysis the system used χ^2 or Kolmogorov–Smirnov tests. The system signalled and interrupted the χ^2 analysis when it found a voxel that failed to meet the numerical conditions for a reliable χ^2 test, and was allowed to switch to the Kolmogorov–Smirnov. For each voxel, the statistical probabilities of finding an affected voxel in the population were calculated against a hypothetical mean value for the probability of finding a chance lesion, provided by the average number of affected voxels in our population. For two-sample statistical analysis between two groups of patients (those with and those without a given reflex dysfunction) we used the Mann–Whitney *U* test. The significance of the results of any statistical test performed was colour-coded in each voxel, and displayed at its proper location in the brainstem model, creating a 3D statistical map. From the 3D visualization, 2D slices could be extracted along any of the three main section planes and be further elaborated to smooth the boundaries of the areas containing significantly affected voxels (Fig. 2).

Results

In a preliminary analysis, controlling for differences between patients from Rome and Mainz, no main clinical (including age and sex), neurophysiological (abnormality frequency of each reflex response) or anatomical (distribution of lesions in the brainstem) variable was statistically significant.

Early blink reflex (R1)

The R1 response was examined in 176 patients and found normal in 125, uncertain in 1 and abnormal in 50 (28% abnormality frequency). One-sample analysis of the patients with an abnormal R1 yielded many significant voxels ($P < 0.01$), depicting (but also exceeding) the whole reflex circuit in the pons (trigeminal afferents and principal nucleus, facial nucleus and efferents), as commonly described (Ongerboer de Visser and Cruccu, 1993; Kimura *et al*., 1994; Hopf, 1994). The differential two-sample analysis between patients with abnormal and normal R1 strongly contracted the area containing significantly affected voxels ($P < 0.001$) to a dorsal–medial pontine region just caudal to the trigeminal principal nucleus, medial to the trigeminal spinal nucleus pars oralis and ventral to the facial nerve loop around the abducens nucleus (Fig. 3).

Early masseter inhibitory reflex (SP1)

The SP1 response was examined in 160 patients and found normal in 99, uncertain in 7 and abnormal in 54 (34%). Similarly to R1, the two-sample analysis of patients with and without SP1 abnormality showed a smaller though more significant area ($P < 0.001$) than that detected by one-sample analysis: the most significant voxels were in the dorsal–medial pons, slightly more lateral and rostral (extending rostrally to the area of the main trigeminal and masticatory nuclei) than the region described for R1, but widely overlapping it (Fig. 3). Although 13 patients with abnormal R1 had a normal SP1 and 23 with abnormal SP1 had a normal R1, a direct comparison between R1 and SP1 abnormality yielded no significantly different voxels.

Five patients had a selective SP1 abnormality of the crossed type. The analysis versus the patients with the standard SP1

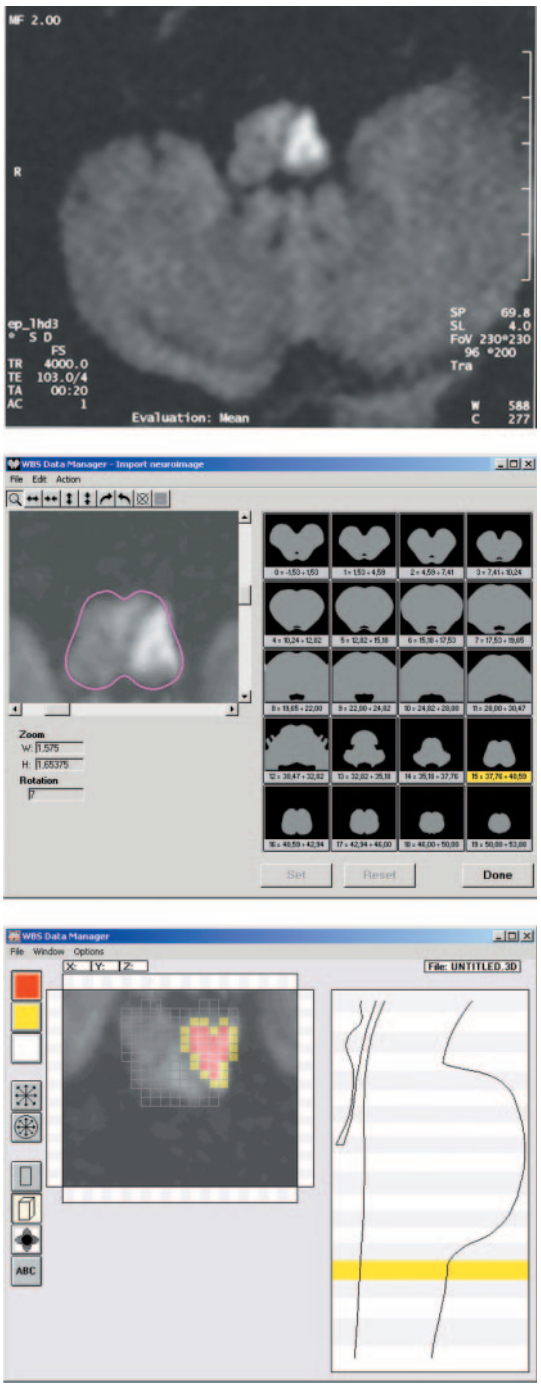

Fig. 2 Method of importing MR scans into the voxel-based model and lesion reconstruction. (*Top panel*) MR axial section at medullary level. (*Middle panel*) The same image is zoomed, scaled, rotated and non-linearly warped, to be normalized to the proper level of the model. All the other possible axial or sagittal sections that include areas of abnormal signal are similarly imported and normalized. (*Bottom panel*) Each imported section is flipped top–bottom (to comply with the anatomical atlas representation) and is flipped left–right if the area of abnormal signal is left-sided. Voxels are assigned a colour code and a numerical value according to their position relative to the area of abnormal signal (see Subjects and methods). Finally, the system, considering the spatial information in the available sections, reconstructs by interpolation the volume of the 'lesion'.

afferent abnormality identified a distinct area of significance ($P < 0.002$) in the median–paramedian pontine tegmentum rostral to the level of the trigeminal root entry and main trigeminal nucleus.

Late blink reflex (R2)

The R2 response was examined in 176 patients and found normal in 116, uncertain in 4 and abnormal in 56 (32% abnormality frequency). Of the patients with R2 abnormalities, 39 had an afferent and 28 an efferent abnormality (15 of these having both afferent and efferent abnormalities); only four patients had a purely crossed abnormality.

One-sample analysis of patients with an R2 afferent abnormality identified significant voxels depicting the whole afferent pathway from its entry into the pons, descending along the trigeminal spinal complex to the level of the inferior olive and caudal pole of the hypoglossal nucleus. The two-sample analysis between patients with and without this reflex abnormality showed a smaller though more significant (from $P < 0.02$ to $P < 0.001$) area of affected voxels in the dorsal–lateral medulla at the level of the inferior olive, nucleus ambiguus, and the exit of the ninth and tenth nerves (Fig. 4). No significant voxels were found below the level of the caudal pole of the hypoglossal nucleus and exit of the tenth nerve rootlets.

Because the efferent type of abnormality may be secondary to lesions that involve either the pontine course of the seventh nerve or the pontomedullary interneuronal pathways (Ongerboer de Visser and Kuypers, 1978; Aramideh *et al*., 1997), for the first group we collected all the patients who had the R2 efferent abnormality but also an abnormal R1, and for the second group we collected those who had the R2 efferent abnormality and a normal R1. In the first group (nine patients) the significant voxels ($P < 0.01$) were distributed along the course of the seventh nerve or nucleus in the pons, as expected. In the second group (10 patients), significant voxels were only found in a small though highly significant area ($P < 0.001$) in the lateral medulla, at the same rostral–caudal level as the R2 afferent abnormality. Although this significant area appeared slightly more medial than that for the R2 afferent abnormality, a direct comparison between the two groups (patients with the R2 efferent abnormality versus those with the R2 afferent abnormality) failed to reach statistical significance. Neither the afferent + efferent (15 patients) nor the pure crossed (four patients) type of R2 abnormality yielded significant voxels.

Late masseter inhibitory reflex (SP2)

The SP2 response was examined in 160 patients and found normal in 81, uncertain in 35 and abnormal in 44 (27%). One-sample analysis showed no significant voxels. Only two-sample analysis between patients with and without SP2 abnormality yielded (weakly, $P < 0.05$) significantly affected voxels; these were located in the same lateral medullary

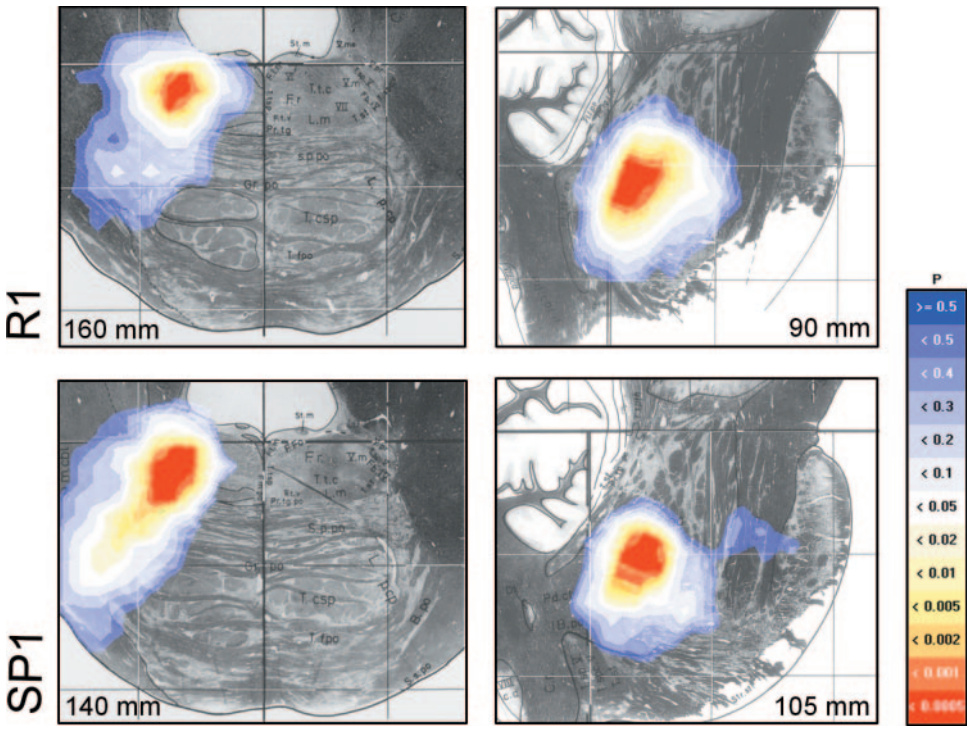

Fig. 3 R1 blink reflex and SP1 masseter inhibitory reflex. Axial (left) and sagittal (right) pontine sections. Statistical results of the comparison between patients with an abnormal (n = 50) and those with a normal (n = 125) early blink reflex (R1) and comparison between patients with an abnormal (n = 54) and those with a normal (n = 99) early masseter inhibitory reflex (SP1). The level of probability is colour-coded. Blue indicates non-significant areas, white the minimum level of significance ($P < 0.05$) and red the highest level of significance. Although the core of significance for R1 appears slightly more caudal and medial than that for SP1, a direct comparison between patients with an abnormal R1 but a normal SP1 (n = 13) and those who had a normal R1 but an abnormal SP1 (n = 23) yielded no significant voxels.

region significant for R2. The crossed abnormality, found in only four patients, was not significant.

Jaw jerk

The jaw jerk was examined in 154 patients and found normal in 93, uncertain in 23 and abnormal in 38 (25%). One-sample analysis showed occasionally significant, isolated voxels, scattered throughout the brainstem, with a more dense area at the level of the trigeminal root entry, which was confirmed by two-sample analysis between patients with a normal and an abnormal jaw jerk ($P < 0.01$). No significant voxel was located in the mesencephalic dorsal medial tegmentum, where the proprioceptive trigeminal nucleus lies.

All reflexes

The one-sample analysis of all the patients who had at least two reflexes abnormal yielded an area of weak significance at the level of the trigeminal root entry. Two-sample analysis between the patients with abnormality of the three short-latency reflexes (R1, SP1 and jaw jerk) and those without yielded an area of strong significance ($P < 0.001$) still in the same region, almost depicting the course of the presynaptic afferents in the pons (Fig. 5).

Discussion

In this study investigating brainstem reflexes in patients with focal ischaemic brainstem lesions, we provide quantitative statistical data to verify the common notions about reflex circuits derived from previous pathological studies. Our method for statistically analysing neuroimaging data is innovative because, accounting for the data variability within our patient sample, it shows to what extent the results can be considered valid for the general population, and because, assessing differences between patients with and without a given dysfunction, it minimizes the risk of highlighting vascular territories rather than the structures specifically responsible for the clinical dysfunction. This method and the large cohort of patients enabled us to report new information on the anatomical circuits of brainstem reflexes and their topodiagnostic value.

Anatomical–functional information

R1 and SP1

The circuit for the early R1 blink reflex is relatively well known in humans (Kimura *et al*., 1994; Marx *et al*., 2001), whereas our knowledge about the circuit for the early SP1 masseter inhibitory reflex relies on a single study (Ongerboer de Visser *et al*., 1990). Our quantitative correlation study

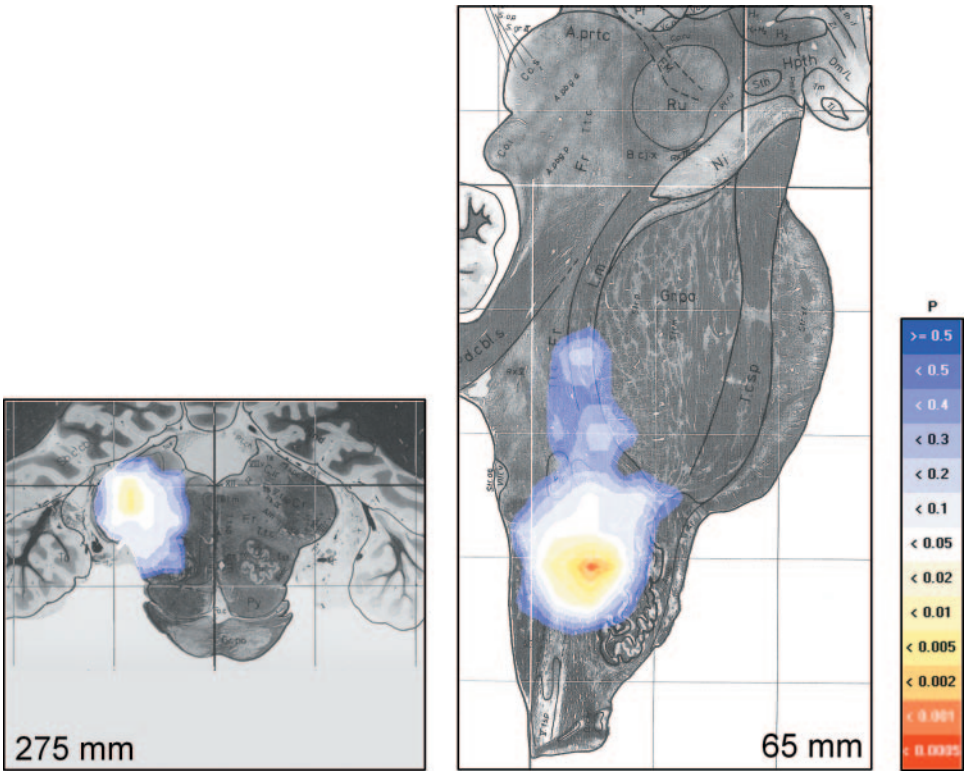

Fig. 4 R2 afferent abnormality. Axial (left) and sagittal (right) sections. Statistical results of the comparison between patients who had an afferent abnormality of the R2 blink reflex (n = 39) and those who had a normal R2 (n = 116). The level of significance is colour-coded (see legend to Fig. 3). Note that the core of significance is in the lateral medulla at the level of the nucleus ambiguus, the exit of the ninth and tenth nerve rootlets, and the inferior olive, and that the minimally significant area (colour-coded in white) does not extend below the caudal pole of the olivary nucleus.

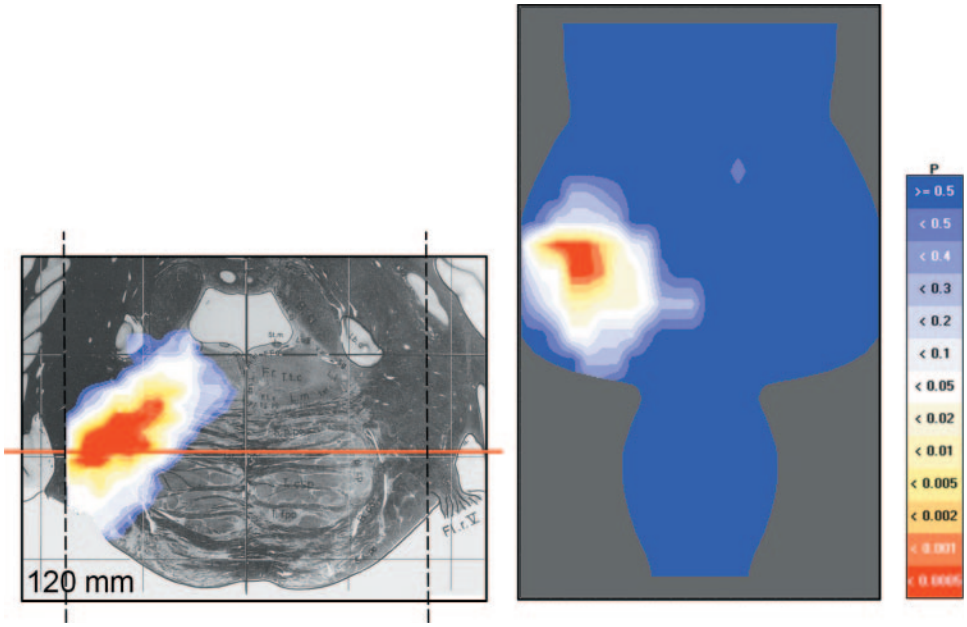

Fig. 5 Early responses [R1, SP1 and jaw jerk (JJ)]. Axial section of the atlas (left) and coronal section of the model (right). Statistical results of the comparison between patients in whom R1, SP1 and JJ were abnormal (n = 25) and those in whom they were normal (n = 54). The level of significance is colour-coded (see legend to Fig. 3). The horizontal red line on the axial section indicates the level displayed in the coronal section. The vertical dashed lines define the lateral limits of the field of view of the model. Note that the significant area depicts the intrapontine course of trigeminal primary afferents.

grossly confirmed the circuits for both R1 and SP1 as previously accepted. But although the SP1 circuit is thought to be restricted to the mid-pons and that of R1 must extend more caudally to reach the facial nucleus, both reflexes had the most significant voxels in the dorsal mid-pons, close to the floor of the fourth ventricle and the main trigeminal sensory nucleus, with small differences between the two.

Analysis of the SP1 crossed abnormality depicted a clear area of significance in the median–paramedian pontine tegmentum. Interestingly, this area was ventral and rostral to the level of the main trigeminal and masticatory nuclei, suggesting that the axon collateral to the inhibitory interneuron crossing the midline takes a rostral and ventral loop to reach the contralateral jaw-closing motoneurons. In lower mammals, the SP1 circuit consists of a single inhibitory interneuron (located in an area close to the masticatory nucleus) that receives the afferent input from the nearby ipsilateral trigeminal root afferents and sends collaterals to the jaw-closing motoneurons on both sides. The collaterals are thought to cross the midline in close proximity to the two masticatory nuclei (Holstege and Kuypers, 1977; Holstege *et al*., 1977). We are aware of only two patients reported in the literature: one patient had a crossed abnormality of SP1 and the other of both SP1 and SP2; both patients had large lesions (one inflammatory, one haemorrhagic), located in the paramedian pons, and extending from mid-pons to upper pons (Ongerboer de Visser *et al*., 1990).

R2

The anatomical–functional organization of the late R2 blink reflex is the most studied of all brainstem reflexes. Our study grossly confirmed previous reports (Kimura and Lyon, 1972; Ongerboer de Visser and Kuypers, 1978; Aramideh *et al*., 1997; Fitzek *et al*., 1999). It also identified the caudal border for the R2 circuit. The significant voxels caudal to the core of the circuit (lateral medulla at the level of the nucleus ambiguus and exit of the ninth and tenth nerve rootlets) extended down to the caudal pole of the hypoglossal nucleus, i.e. rostral to the pyramidal decussation and the pars caudalis of the trigeminal spinal nucleus (which extends from the pyramidal decussation to the C3 spinal segment). Although the R2 circuit is thought to reach the subnucleus caudalis, the caudal limit of the circuit has never been clearly defined (Valls-Solé *et al*., 1996) and in the four patients who had a post-mortem examination the lesion never extended below the level of the olivary/hypoglossal nerve nuclei (Ongerboer de Visser and Kuypers, 1978; Aramideh *et al*., 1997), indicating that the lesion was rostral to the subnucleus caudalis. Our quantitative finding in 39 patients with afferent-type R2 abnormalities further differentiates the blink reflex from the corneal reflex. The latter is purely nociceptive, and is mediated by Aδ afferents that in monkeys project onto nociceptive-specific neurons in lamina I and outer II of the subnucleus caudalis (the first central relay of thermal-pain inputs from the face); the R2 blink reflex is mainly mediated by non-nociceptive Aβ afferents that project to mechanosensitive neurons in the medullary laminae III–IV (the afferents for both reflexes also send collaterals to wide-dynamic-range neurons in a medullary reticular area equivalent to the spinal lamina V) (Price *et al*., 1976; Yokota *et al*., 1979; Marfurt and Echtenkamp, 1988; Cruccu *et al*., 1991; Sessle, 2000). Our data suggest that—in humans—the eyeblink after innocuous stimuli is mediated at the level of the inferior olive, i.e. by the subnucleus interpolaris.

Excluding the patients with intrapontine lesions of the seventh nerve, we found no differences between the R2 afferent, afferent + efferent, and efferent defects. The core of the lesion responsible for the latter was expected to lie more medially in the medullary reticular formation. Previous studies suggested that the axons of the interneurons relaying the afferent input to the contralateral facial motoneurons cross the midline and then ascend from the medulla to the pons just medial to those relaying the ipsilateral input (Ongerboer de Visser and Kuypers, 1978; Aramideh *et al*., 1997). Probably the two sets of interneurons run too close to each other to allow resolution by our voxel-based system (2 mm), which cannot match the anatomical detail of pathological studies. In contrast, the lack of significance for the crossed type of R2 abnormality probably depends on the small number of samples. Also in previous studies on the blink reflex in patients with brainstem lesions, abnormal patterns other than the common afferent type were rarely observed: three out of 13 in the study by Ongerboer de Visser and Kuypers (1978) and one out of 14 in the study by Valls-Solé and colleagues (1996).

SP2

Lesions of the SP2 circuit reached a lower level of significance than the other brainstem reflexes, possibly for the same reasons that weaken the significance of the jaw jerk. Two-sample analysis nevertheless detected a significant area in the same region of highest significance for the R2 blink reflex, i.e. in the lateral portion of middle (referring to the rostral–caudal axis) medulla. In a previous study, the SP2 circuit was located at the pontomedullary junction (Ongerboer de Visser *et al*., 1990). Of the five patients with SP2 abnormalities, three had focal lesions in the lower pons and two at the pontomedullary junction. In another study, eight patients with SP2 abnormalities had lesions in the upper or middle medulla (Valls-Solé *et al*., 1996). In the 44 patients with SP2 abnormalities studied here the significant area reached as caudally as the middle medulla, thus confirming the conclusions of Valls-Solé and colleagues.

Jaw jerk

We found no brainstem region significantly associated with an abnormal jaw jerk. Clearly this does not mean that the jaw jerk does not have its own definite circuit. Experimental studies in

animals and autopsy findings in humans have demonstrated that the afferents for the jaw jerk are axons of first-order sensory neurons that have their cell body in the mesencephalic trigeminal nucleus and send collaterals that connect monosynaptically with the jaw-closing motoneurons in the pons (McIntyre and Robertson, 1959; Darian-Smith, 1973). Reflex abnormalities were mainly reported in patients with mesencephalic infarction (Ongerboer de Visser and Goor, 1976; Hopf and Gutman, 1990; Hopf *et al*., 1991). Our statistical analysis may have failed to highlight these pathways for several reasons. One is the greater variability of vascular territories involving the jaw-jerk circuit, e.g. the 'non-critical' anteromedial region most frequently affected in middle mesencephalic infarcts (Kumural *et al*., 2002). Admittedly, our method does not completely ignore the vascular supply or areas generally favoured by brainstem infarction. Main lesion spots within the vascular territories show up only if a specific anatomical area is involved in many patients with the same specific functional deficit. A lesion spot will not show up if the same deficit can arise from different sites of lesion spread over a long reflex circuit. Another possible explanation is the usual method of eliciting the jaw jerk in clinical applications, i.e. with a hand-held neurological hammer. The jaw jerk is strongly influenced by age, ability to cooperate, level of muscle relaxation, position of the mandible, and dental occlusion (Kimura *et al*., 1994; Cruccu and Deuschl, 2000). In patients with temporomandibular disorders and no neurological disease it may be very asymmetrical or even unilaterally absent (Cruccu *et al*., 1997). Hence, some of the abnormalities found in German and Italian patients might not have been secondary to the brainstem lesion and might thus have biased the statistical analysis. In experimental settings using special mechanical devices or bypassing the receptors with the direct stimulation of Ia afferents (Cruccu *et al*., 2001), most of the peripheral influences are controlled or minimized.

Diagnostic information

The early R1 blink reflex was always clearly normal or abnormal (R1 was considered uncertain in only one of 176 patients). R1 is therefore easy to assess and interpret, probably because of its narrow latency jitter and narrow interindividual range, and insensitivity to suprasegmental influences (Deuschl and Eisen, 1999; Cruccu and Deuschl, 2000). The early SP1 masseter inhibitory reflex also had a relatively low number of uncertain responses: seven out of 160 patients. Although SP1, being mediated by only one interneuron, would be expected to be even more stable than R1, it is an inhibitory response that must be assessed during voluntary contraction. Hence its latency is more difficult to measure (and somehow more arbitrary) than that of excitatory responses; in practice, SP1 has slightly higher variance and a wider range of normal latencies than R1 (Deuschl and Eisen, 1999; Cruccu and Deuschl, 2000).

The reflexes with the highest frequencies of abnormal findings were SP1, R2 and R1 (34, 32 and 28%, respectively). The brainstem areas housing their reflex circuits are frequently affected in vascular brainstem disorders. In patients with extra-axial lesions, R2 is less sensitive than R1 and SP1, presumably because it is mediated by a large number of afferents (providing it with an abundant biological reserve) and a polysynaptic chain of interneurons (causing an unstable latency that is subject to suprasegmental influences) (Cruccu and Deuschl, 2000). But in patients with intra-axial lesions its abnormality frequency is as high as that of the short-latency responses because its brainstem circuit is far more complex and extends caudally in the medulla.

From the topodiagnostic point of view R1 is equivalent to SP1. Hence, in patients who are known to have an intra-axial lesion, it is sufficient to test one of the two reflexes, probably R1 because it has a lower number of uncertain responses and does not require the subject's active collaboration. A practical note in patients with suspected brainstem infarction is that, despite disturbed consciousness and even coma, R1 stands, being suppressed only by direct dysfunction of the pons.

Although infrequent findings, an R2 abnormality of the purely efferent type with a normal R1 or an SP1 crossed abnormality have a high topodiagnostic value, implicating precise, anatomically well defined, mid-medullary or upper pontine areas.

The two reflexes that had the highest number of uncertain responses were SP2 (35/160) and jaw jerk (23/154). The reason why SP2 engendered numerous uncertain responses is probably the same as that we invoked to explain why SP1 was less stable than R1. Another factor is SP2's multisynaptic circuit. The reason why the jaw jerk, a monosynaptic, short-latency and excitatory reflex not influenced by supratentorial or cerebellar dysfunction (Hopf *et al*., 2000), did so must be sought elsewhere. One possibility is that the stimulus is not a graded and reproducible electrical pulse. Another is that it depends on the cooperation of the patient and mandibular function (Cruccu *et al*., 1997; Cruccu and Deuschl, 2000).

An interesting piece of topodiagnostic information yielded by this study is that the abnormality of several reflexes in the same patient, particularly of the short-latency reflexes, points at the region where the trigeminal primary afferents enter the pons before dividing to reach their respective circuits. But the same finding, i.e. the suppression of the short-latency responses, is very common in extra-axial lesions, particularly posterior fossa tumours and vascular anomalies compressing the trigeminal sensory root (Cruccu and Deuschl, 2000). Hence it does not *per se* demonstrate a brainstem dysfunction.

Finally, although our method does minimize the influence of vascular territories (indeed, the areas with the highest probabilities of lesion for an abnormal R1 or SP1 do not respect vascular territories; Fig. 3), our maps have the vascular territory as a covariable which cannot be dealt with statistically. A confirmation of our results may come from checking the same responses in other conditions that are independent of vascular territories.

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