BSS
BRAIN STEM SOCIETY

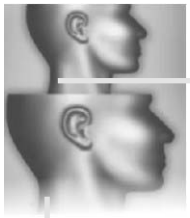
III BRAIN STEM MEETING

ROME

Ambasciatori Palace Hotel

11/12 June 2004

Program and Abstracts



Dear friends,

Time has come and now we find each other here at the Brain Stem Meeting. I am very happy you decided to participate.

Since months I have been concerned with the organisational aspects of the meeting, having to face two formidable problems: the elections of the European Parliament and the Italian Bureaucracy. What may go wrong? Although I did not know what, I was sure something would. Fatally some disaster will arise, grow, and eventually strike, like an inextricable Nemesis.

I am very fond of my La Sapienza University, and would really like you to get a good impression of it. With those two problems constantly in mind (herds of students possibly making sit-ins just in front of the main entrance to Aula Magna, combined with the untimely intervention of some zealous Funzionario who thinks his mission is to put a spoke in the wheel), my health was exposed to major risk.

Hence, for my own safety, we moved to this other beautiful location, in the heart of Rome. Luckily, Rome will undoubtedly entice you with its wonders. Furthermore I am utterly confident of the meeting's scientific contents. Our speakers will raise your interest and trigger the animate discussions that traditionally characterise BSS congresses.

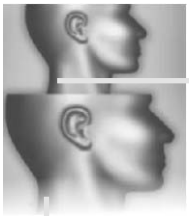
To reinforce the scientific expectancy, I may anticipate that Elsevier has decided to publish in extenso the proceedings of the meeting in a book: "Brainstem Function and Dysfunction".

I hope you will all be able to cope with the questions for the CME-ECM credits. Admittedly a few questions are difficult. I know which speakers prepared the nasty ones, but disclosing their names would only be unfair.

Finally I take the occasion to invite those of you who feel like keeping involved, getting full access to the website, and being promptly informed about our activities and the next meeting, to join the BSS society. But do it now, at the reception desk, before the inextricable Nemesis strikes and makes you change your mind!

Thank you again. I wish you a fruitful meeting and a nice time in Rome.

Giorgio Cruccu (Convener)



CONVENER

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Andrea Truini

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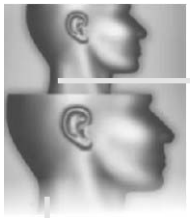

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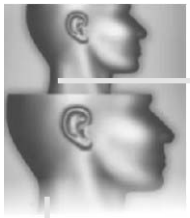


ANATOMY AND PHYSIOLOGY

9.00 Welcome remarks
L. Frati - *Preside I Facoltà di Medicina*
G. Cruccu - *Convener*

Chairpersons: **H.C. Hopf** (Mainz, Germany)
B. Ongerboer de Visser (Amsterdam, The Netherlands)

9.30 Corticobulbar tracts
M. Hallett (Bethesda, USA)

10.00 Somatosensory pathways
R.-D. Treede (Mainz, Germany)

10.30 Head eye-movement control model based on genetically selected neural network
N. Accornero (Rome, Italy)

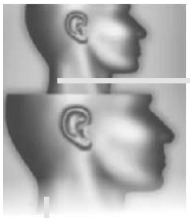
11.00 *Coffee break*

11.30 3D brainstem topodiagnosis. A voxel-based model analysing MR imaging data
J.J. Marx (Mainz, Germany)

12.00 Brainstem functional imaging in experimental animals
C.A. Porro (Udine, Italy)

12.30 Brainstem functional imaging in humans
I. Tracey (Oxford, United Kingdom)

13.00 *Lunch*



PAIN

Chairpersons: **R.-D. Treede** (Mainz, Germany)
J.C. Willer (Paris, France)

14.30 Trigeminal neuropathy. Clinical histological-neurophysiological correlation
G. Cruccu (Rome, Italy)

15.00 Neuropathic facial pain
M. Haanpää (Helsinki, Finland)

15.30 Mechanisms and predictors of chronic facial pain in lateral medullary infarction
S. Fitzek (Jena, Germany)

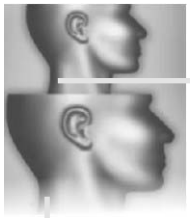
16.00 *Coffee break*

16.30 Interplay between jaw and neck pain pathways and implications for temporomandibular pain disorders
P. Svensson (Aarhus, Denmark)

17.00 Long-term depression of trigeminal nociception: a potential treatment of headache?
J. Ellrich (Aachen, Germany)

17.30 Trigeminal laser evoked potentials in headache
M. Valeriani (Rome, Italy)

18.00 *Elections*



PHYSIOLOGY

Chairpersons: **J.C. Rothwell** (London, United Kingdom)
J. Valls-Solé (Barcelona, Spain)

9.00 Investigation of brainstem descending modulation in animals and humans
D. Bouhassira (Boulogne-Billancourt, France)

9.30 What the vestibulo-spinal system does - and what it doesn't
A.M. Bronstein (London, United Kingdom)

10.00 Auditory startle reaction
M. Kofler (Hochzirl, Austria)

10.30 *Coffee break*

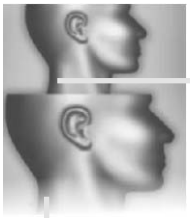
11.00 Exploration of the role of the upper brainstem in motor control
D. Nandi (Oxford, United Kingdom)

11.30 Organization and functional properties of the eyelid motor system
J.M. Delgado-García (Seville, Spain)

12.00 Orbicularis oculi reflexes
A. Esteban (Madrid, Spain)

12.30 Poster discussion

13.30 *Lunch*



MOVEMENT DISORDERS

Chairpersons: **M. Hallett** (Washington, USA)
G. Deuschl (Kiel, Germany)

14.30 Possible role of brainstem-spinal pathways in recovery from stroke
J.C. Rothwell (London, United Kingdom)

15.00 Brainstem dysfunction in PSP
J. Valls-Solé (Barcelona, Spain)

15.30 Brainstem-generated involuntary movements
G. Deuschl (Kiel, Germany)

16.00 *Coffee break*

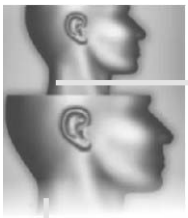
16.30 Neuro-vascular conflict and hemifacial spasm
M. Sindou (Lyon, France)

17.00 New findings in cranial-cervical dystonias
A. Currà (Rome, Italy)

17.30 Presentation of next BSS meeting

18.00 Evaluation of learning process

18.30 Closing remarks



POSTER SESSION

P1 Sensitivity of diffusion weighted MRI and electrophysiological brainstem testing in the diagnosis of acute vertebrobasilar ischemia
J.J. Marx, F. Thömke, A. Mika-Grüttner, S. Fitzek, P.P. Urban, P. Stoeter, M. Dieterich, H.C. Hopf
(Mainz, Germany; Jena, Germany)

P2 Abnormal patterns of breathing during swallowing in multiple sclerosis
P.P. Urban, M. Zahn, S. Schranz, O. Glassl, M. Dieterich
(Mainz, Germany)

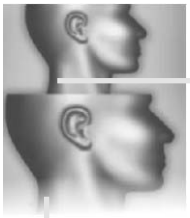
P3 Oculo-jaw synkinesia in Parkinson's disease and MSA-p. Neurophysiological findings
G. Salazar, J. Monells, R. Wix, J. Valls-Solé, E. Tolosa
(Barcelona, Spain)

P4 Unilateral masseter reflex abnormalities with medullary lesions involving the ipsilateral spinal nucleus of the trigeminal nerve
F. Thömke, J.J. Marx, A. Mika-Grüttner, S. Fitzek, P.P. Urban, P. Stoeter, M. Dieterich, H.C. Hopf
(Mainz, Germany; Jena, Germany)

P5 Electrophysiologic study of the motor-motor reflex responses in hemifacial spasm
J. Montero, I. Fernandez-Conejero, S. Yagüe, J. Valls-Solé
(Barcelona, Spain)

P6 Hemifacial spasm and posterior auricular muscle
M. Kiziltan, R. Sahin Ciftci (Istanbul, Turkey)

P7 The diagnostic value of the trigemino-cervical reflex
V. Di Lazzaro, A. Oliviero, E. Saturno, F. Pilato, M. Dileone, P. Tonali
(Rome, Italy)



P8 Dissociation between upper and lower facial muscle responses to median nerve stimulation in patients with mesencephalic lesions
L. León, C. Lazzarini, L. Broglio, M. Pasolini, G. Lauria, J. Valls-Solé (Barcelona, Spain; Brescia, Italy; Milan, Italy)

P9 Clinical and electrophysiological studies in Moebius syndrome
G. Pavesi, L. Cattaneo, E. Chierici, R. Dalla Volta, B. Bianchi, A. Pizzigallo, E. Sesenna (Parma, Italy)

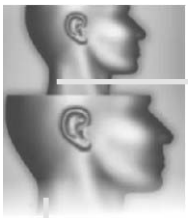
P10 Differences between the effects of electrical and mechanical stimuli on pain perception and laser evoked potentials
M. Veciana, J. Valls-Solé, C. Pech
(Barcelona, Spain; Hochzirl, Austria)

P11 Prepulse modulation of the startle reaction during preparation for movement execution
H. Kumru, J. Valls-Solé, M. Kofler, M.T. Sanegre, J. Castellote
(Barcelona, Spain; Hochzirl, Austria; Valencia, Spain)

P12 Activity induced in the orbicularis oculi muscles by deep brain stimulation in patients with Parkinson's disease
J. Valls-Solé, C. Pech, E. Diéguez, F. Valldeoriola
(Barcelona, Spain; Hochzirl, Austria; Montevideo, Uruguay)

P13 Trigeminocervical reflex and blink reflex in multiple sclerosis
F. Guney, Z. Akpinar, B. Yuruten (Konya, Turkey)

P14 Clinical and neurophysiological evolution of postherpetic nuralgia. Preliminary results
A. Truini, R. Zucchi, M. Haanpää, G. Cruccu
(Rome, Italy; Helsinki, Finland)



GENERAL INFORMATION

REGISTRATION DESK

The registration desk at the meeting venue will be open on 11 and 12 June 2004 from 8.30 to 18.30.

The registration fee includes:
- Name badge for participation in all sessions
- Congress kit
- Final Program with Abstracts (1 copy)
- Coffee breaks and lunches
- Special price for social dinner
- Certificate of attendance

MESSAGES

Messages for participants will be displayed on the board next to the registration desk.

BADGE

The badge is the official meeting document and should be worn at all time in order to gain entry into the meeting room and ECM-CME credits.

OFFICIAL LANGUAGE

English is the official language of the meeting. No simultaneous translation is provided.

ECM-CME CREDITS

Accreditation for ECM-CME has being requested to the EU Office and to the Italian Health Ministry.

SLIDE/POWERPOINT

Speakers are kindly requested to hand in their presentation to the technicians at least one hour before the beginning of the session.

POSTERS

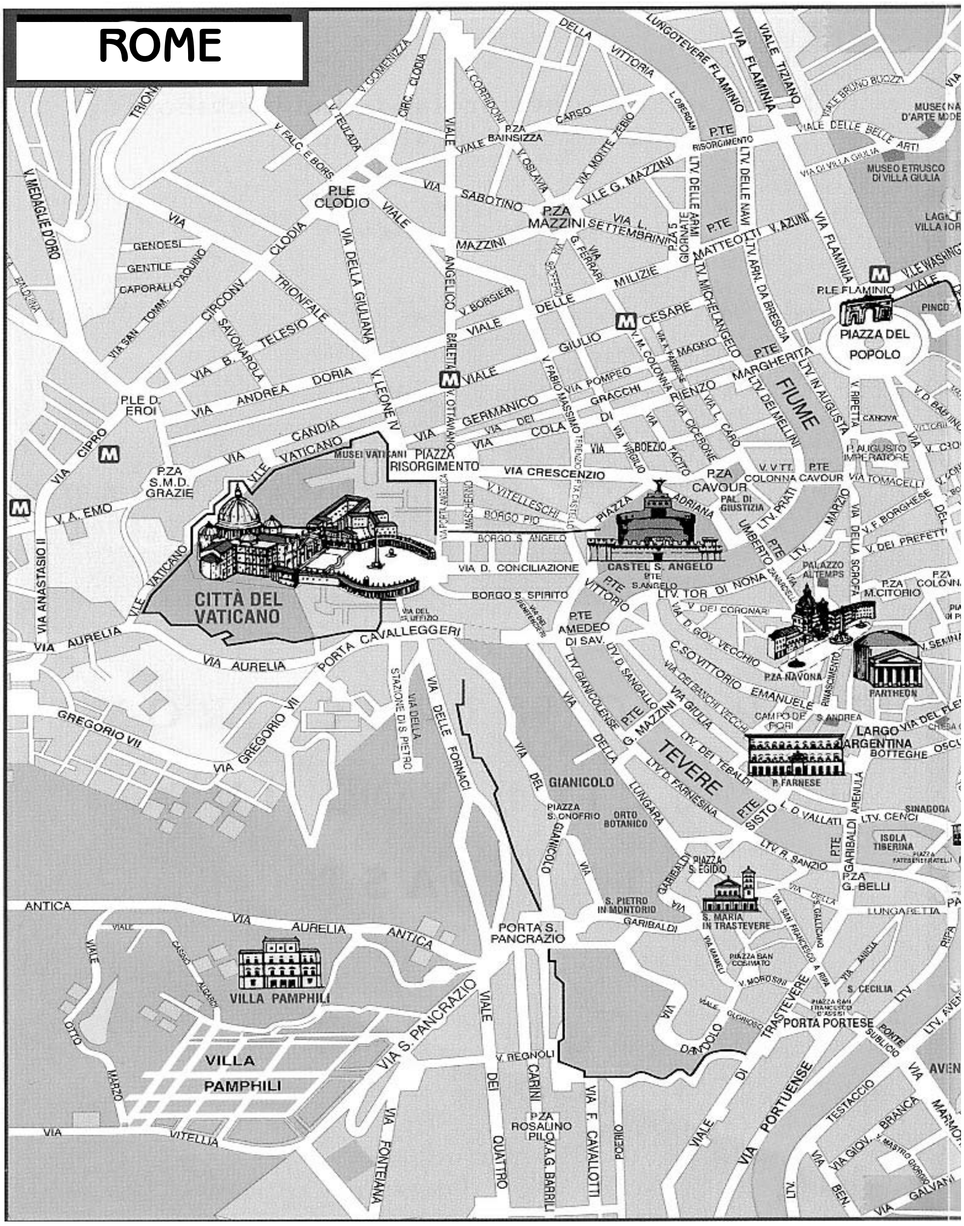
Posters should remain on display for the whole meeting. Authors are invited to mount their poster on Friday 11 June in the morning and are requested to attend their poster during the discussion (Saturday 12 June from 12.30 to 13.30). Posters should be removed on Saturday 12 June from 16.00.
(Poster boards are marked with poster reference number)

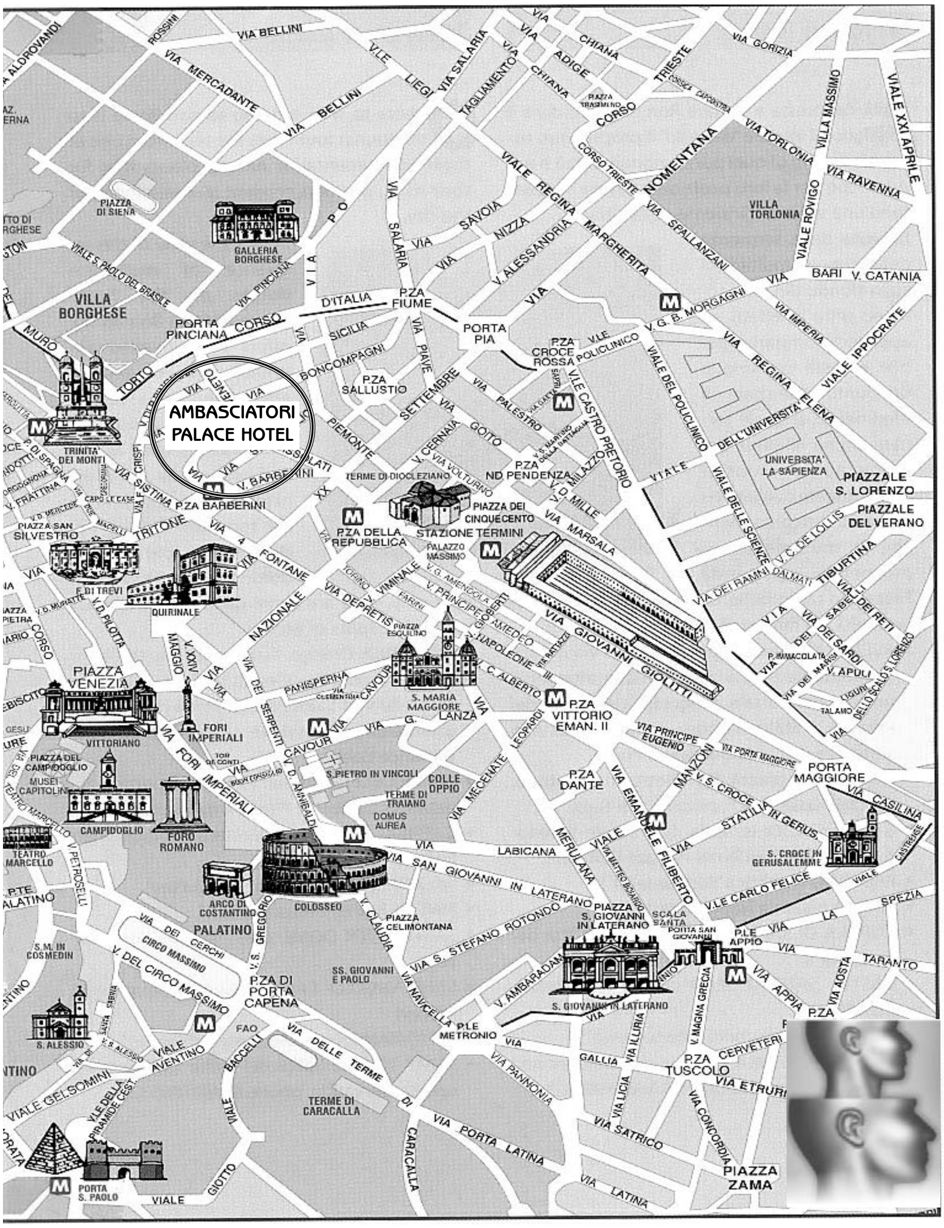
MEETING VENUE

Ambasciatori Palace Hotel

Via Vittorio Veneto, 62 - 00187 Rome (Italy)

Phone: +39-06-47493




AMBASCIATORI
PALACE HOTEL
VILLA BORGHESE
GALLERIA BORGHESE
PIAZZA DI SIENA
PORTA PINCIANA
CORSO D'ITALIA
P.ZA FIUME
PORTA PIA
P.ZA CROCE ROSSA
P.ZA SALLUSTIO
TRINITA' DEI MONTI
P.ZA BARBERINI
TERME DI DIOCLEZIANO
PIAZZA DEI CINQUECENTO
STAZIONE TERMINI
P.ZA DELLA REPUBBLICA
QUIRINALE
PIAZZA VENEZIA
VITTORIANO
FORI IMPERIALI
PIAZZA DEL CAMPIDOGLIO
MUSEI CAPITOLINI
CAMPIDOGLIO
FORO ROMANO
COLOSSEO
ARCO DI COSTANTINO
PALATINO
CIRCO MASSIMO
P.ZA DI PORTA CAPENA
TERME DI CARACALLA
S. ALESSIO
PORTA S. PAOLO
S. MARIA MAGGIORE
P.ZA VITTORIO EMAN. II
P.ZA DANTE
PIAZZA S. GIOVANNI IN LATERANO
S. GIOVANNI IN LATERANO
S. CROCE IN GERUSALEMME
PORTA MAGGIORE
PIAZZALE S. LORENZO
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UNIVERSITA' LA SAPIENZA
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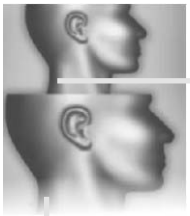
P.ZA TUSCOLO
P.LE METRONIO
P.LE APPIO
TEATRO MARCELLO
S.M. IN COSMEDIN
DOMUS AUREA
TERME DI TRAIANO
COLLE OPPIO
S.PIETRO IN VINCOLI
SS. GIOVANNI E PAOLO
PIAZZA CELIMONTANA
VIA NOMENTANA
VIALE REGINA MARGHERITA
VIA XX SETTEMBRE
VIA NAZIONALE
VIA CAVOUR
VIA GIOVANNI GIOLITTI
VIA MARSALA
VIA MERULANA
VIA SAN GIOVANNI IN LATERANO
VIA APPIA
VIA PORTA LATINA
VIA DELLE TERME DI CARACALLA
VIALE AVENTINO
VIA DEI FORI IMPERIALI
VIA SALARIA
VIA PO
VIA BELLINI
VIA TIBURTINA
VIALE XXI APRILE



GENERAL INFORMATION

SOCIAL DINNER

The social dinner will take place on Friday 11 June at the "Taverna de' Mercanti" in the heart of Trastevere.
Registered participants who have regularly booked the requested number of seats will receive the tickets upon registration to the meeting.
(Restaurant Address: Piazza de' Mercanti 3a - phone: +39-06-5881693)

WEATHER AND CLOTHING

In June temperatures are around 25-28°C during the day, and 20-25°C during the night.

ELECTRICITY

Electrical current in Italy is 220 volts, 50-cycle AC. Italian outlets only accept round prong plugs. Appliance designed to operate on 110/120 volts needs a voltage converter and a plug adapter.

BANKING

Euro is the official Italian currency. Money can be easily exchanged at all main banks. Traditional banking hours are Monday through Friday, from 8.20 AM to 1.20 pm and 2.30 to 3.30 PM. Banks are closed on Saturday and Sunday.
Some automatic exchanging machine are located outside the major banks to provide 24-hour service. Many hotels and shops accept credit cards and the main foreign currencies, although the exchange rate can be slightly less favourable.

INSURANCE

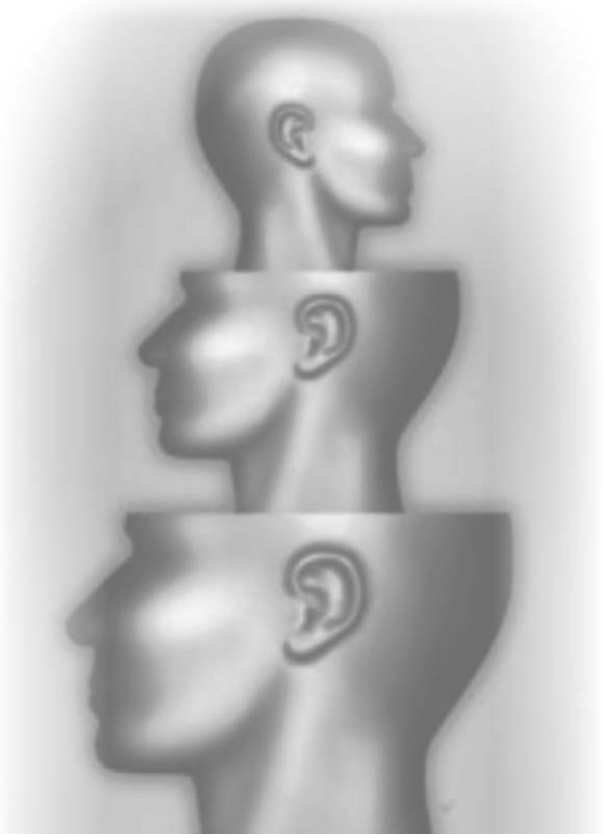
In registering for the III Brain Stem Meeting, participants agree that neither the Organizing Committee nor the Organizing Secretariat assume any liability whatsoever. Participants are requested to make their own arrangements for both health and travel insurance.

CANCELLATION AND REFUNDS

No refund (registration, dinner, hotel accommodation and booking fee) will be allowed for cancellations received after 5 March, 2004.

Friday 11 June

ANATOMY AND PHYSIOLOGY



CORTICOBULBAR TRACTS

M. Hallett
Human Motor Control Section, NINDS, Bethesda, MD, USA

The general principle for cortical control of cranial nerve motor nuclei 5, 7, 9, 10, 11 and 12 is that there is predominant contralateral influence and variable, but important, ipsilateral influence as well.

The best understood situation is the 7th nerve, thanks in part to anatomical studies in the primate by Morecraft et al. (2001). Perioral muscles, prototypical for the lower face, are innervated largely contralaterally from the primary motor cortex, premotor cortex and caudal cingulate. For upper face muscles, orbicularis oculi are innervated mostly by rostral cingulate but there are contributions also from primary motor cortex, supplementary motor area, caudal cingulate area and lateral premotor cortex, all bilaterally. Such a pattern explains the upper face sparing in typical middle cerebral artery stroke. Recovery from stroke in any location is explained by at least a minimal projection from all cortical face areas to all parts of the face. Early transcranial magnetic stimulation studies of the face area of primary motor cortex suggested cortical projections to the 7th nerve nucleus with a latency of approximately 10 ms, but these studies were confounded by possible contamination by R1 of the blink reflex. More recent studies show a projection from the midline frontal region consistent with the rostral cingulate with a latency of 6-8 ms [Sohn et al. 2004]. Activation in the rostral cingulate area can also be seen in fMRI studies with voluntary eye closure (Hanakawa et al. unpublished).

Muscles innervated by cranial nerves 5, 9, 10, 11 and 12 are also mainly innervated contralaterally. In the case of midline muscles such as those of swollowing, innervation is also asymmetric with apparently random dominance of side. As has been well demonstrated for swollowing and for the tongue, rapid improvement after stroke is due to enhancement of the influence from the uninjured side. Latencies for responses after transcranial magnetic stimulation are commonly about 6 to 7 ms.

Morecraft RJ, Louie JL, Herrick JL, Stilwell-Morecraft KS: *Cortical innervation of the facial nucleus in the non-human primate: a new interpretation of the effects of stroke and related subtotal brain trauma on the muscles of facial expression.* Brain 2001; 124: 176-208.

Sohn YH, Voller B, Dimyan M, et al: *Cortical control of voluntary blinking: a transcranial magnetic stimulation study.* Clin Neurophysiol 2004; 115: 341-7.

SOMATOSENSORY PATHWAYS

R.-D. Treede
Institute of Physiology and Pathophysiology, Johannes Gutenberg-University, Mainz, Germany

Somatosensory pathways in the brainstem may be divided into those that ascend from the spinal cord and carry information on stimulation of skin and deep tissues in the trunk and limbs, and the trigeminal system pathways that carry information on stimulation of the face. The ascending tracts are divided according to somatosensory submodalities: touch and proprioception are mediated by the dorsal column pathway to the cuneate and gracile nuclei in the lower brainstem, which project via the medial lemniscus to the ventrobasal thalamus; pain and temperature sensations are mediated by the spinothalamic tract which occupies a more lateral position throughout the brain stem than the medial lemniscus. Therefore, these two systems are vulnerable to separate distinct lesion patterns within the brainstem. The trigeminal system can also be divided according to submodalities: tactile sensations are mediated by a rostral pathway through the principal sensory nucleus, whereas temperature and pain sensations are mediated by the caudal parts of the trigeminal nuclear complex. Although medio-lateral differences in lesion patterns may influence the pattern of sensory loss in the face, the vast extension of the trigeminal nuclei in the rostro-caudal direction leads to different clinical and electrophysiological findings according to the rostro-caudal level of the lesion. This presentation will outline the location of somatosensory pathways within the brain stem, the sensory patterns associated with different lesion sites, and clinical neurophysiological assessment tools for these pathways.

Supported by DFG grant Tr 236/13-3.

HEAD EYE-MOVEMENT CONTROL MODEL BASED ON GENETICALLY SELECTED NEURAL NETWORK

N. Accornero, M. Capozza
Department of Neurosciences, University of Rome "La Sapienza", Italy

AIM To verify experimentally whether genetic algorithms can assemble neural networks that control the visual reflex movements of a simplified eye-head model simulated on a computer.
METHOD The simplified eye-head model is a 2-D model: an antagonist muscle pair allows the head to rotate on a horizontal plane, and two other antagonistic pairs simulates the action of the medial and lateral eye muscles so that each eye can rotate within the internal orbit. The two linear retinas, each one with a fovea, pick up the image of a target that moves randomly in front of the eyes.
The neural net receives visual input information from both retinas and proprioceptive information from the head and eye muscles, and generates output data that activate these same muscles. No set of examples needs to be constructed in advance nor is an external supervisor needed to calculate errors.
RESULTS After the automatic selection of many population of networks, the system proved capable of accomplish the desired motor control efficiently and could generate rapid conjugated and unconjugated movements (saccades) and slow movements (pursuit) as a function of the target position and movement.
CONCLUSIONS This study confirms that on a par with biological processes, artificial connectionist systems can efficiently control movement without explicitly implementing mathematical or physical rules. The only selective pressure on the population of neural networks was to foveate binocularly on the moving target.

3D BRAINSTEM TOPODIAGNOSIS. A VOXEL-BASED MODEL ANALYSING MR IMAGING DATA

J.J. Marx, G.D. Iannetti**, F. Thömke, S. Fitzek***, P.P. Urban, P. Stoeter*, M. Dieterich, G. Cruccu**, H.C. Hopf

*Department of Neurology and *Department of Neuroradiology, University of Mainz, Germany*

***Department of Neurosciences, University of Rome "La Sapienza", Italy*

****Department of Neurology, University of Jena, Germany*

Using a new method of statistically based three dimensional (3D) brainstem mapping that allows to import and normalise MR images, we identified brainstem areas responsible for specific clinical and electrophysiological abnormalities in patients with acute brainstem infarction.

PATIENTS AND METHODS From 1996 to 2001 180 patients with acute and isolated MR documented brainstem infarction were prospectively recruited at the Department of Neurological Sciences, University of Rome "La Sapienza" and the Department of Neurology, University of Mainz. EPI-diffusion-weighted MRI and hr T1- and T2-weighted imaging (slice thickness 3 mm) were performed using a 1.5 Tesla superconducting system. Lesions were normalized according to anatomical landmarks and their brainstem outlines and imported into a 5268-voxel, 3D-brainstem model developed using data from topometric and stereotactic atlases. The 3D model enables to select groups of patients with and without a given clinical or electrophysiological dysfunction, to compare them statistically, and to identify which voxels are significantly affected. Finally, the significance of the statistical test result is colour-coded in each voxel, and displayed at its proper location in the brainstem model producing a 3D statistical parametric map of lesion probability.

RESULTS A first mapping analysis in 31 patients with ischemic Horner's syndrome allowed us to identify a crucial affected area in the ventrolateral medullary tegmentum, corresponding to an adrenergic cell group that contributes to the descending sympathoexcitatory pathway according to tracing studies in human autopsy material. In a correlation study on the main brainstem reflexes currently used in clinical neurophysiology (blink reflex, masseter inhibitory reflex, jaw jerk) we were able to confirm statistically the reflex circuits suspected from pathological studies, and produce new information about the caudal medullary level of the polysynaptic responses.

CONCLUSIONS Our method constitutes a new approach to in vivo brainstem mapping. It provides reliable topodiagnostic evaluations by analysing statistically neuroimaging data of patients with and without a given dysfunction and thus confirms and extends on statistical ground the common notion, moving from anecdotic pathological observations to population studies.

BRAINSTEM FUNCTIONAL IMAGING IN EXPERIMENTAL ANIMALS

C.A. Porro
Dipartimento di Scienze e Tecnologie Biomediche, University of Udine, Italy

Autoradiographic techniques for investigating local glucose metabolic rates have demonstrated enhanced metabolic activity during prolonged noxious stimulation in unanesthetized rats in several brainstem regions, extending from the caudal medulla to the meso-diencephalic junction, for which a role in nociceptive or anti-nociceptive mechanisms has been suggested. They include portions of the bulbar, pontine and mesencephalic reticular formation, namely the dorsal medullary reticular n., n. gigantocellularis (pars ventralis), n. paragigantocellularis, n. reticularis pontis caudalis and oralis and deep mesencephalic gray matter, as well as the lateral parabrachial region and raphe nuclei. At the mesencephalic level, metabolic increases were found both in the ventro-lateral and dorsal subdivisions of the periaqueductal gray matter, in the intermediate and deep layers of the superior colliculus, and in the anterior pretectal nucleus. Bilateral increases of metabolic activity were also found in the lateral reticular nucleus and interpositi deep cerebellar nuclei.

The extent of noxious-evoked metabolic changes in brainstem structures appears to be considerably less than the ones observed at the spinal level, and blunts over time in parallel with changes in pain-related behaviour. In pentobarbital-anesthetized rats, noxious-evoked increases were found only in some regions of the medulla, whereas no change with respect to controls was detected in any pontine or mesencephalic structure. These studies provide a detailed spatio-temporal mapping of nociceptive processing in brainstem circuits.

BRAINSTEM FUNCTIONAL IMAGING IN HUMANS

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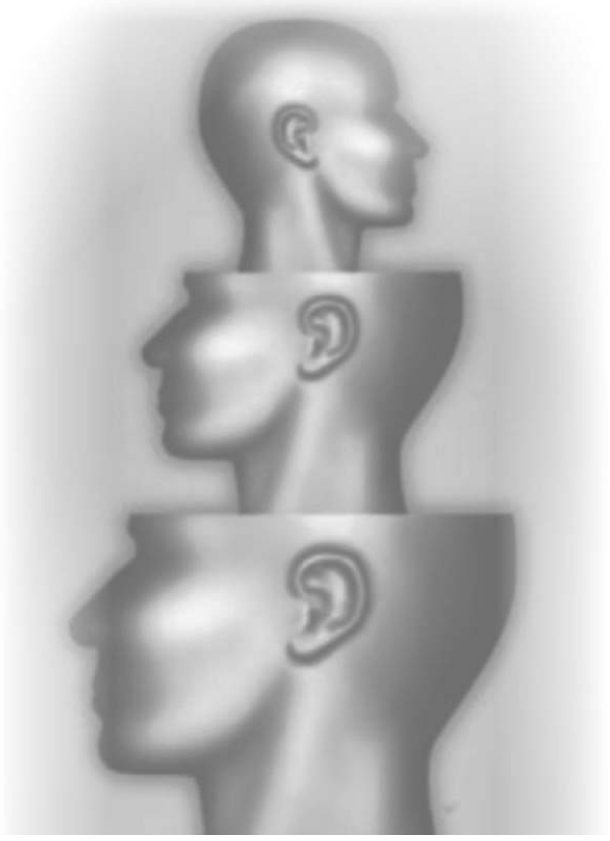
Functional Magnetic Resonance Imaging (FMRI) has been widely applied in various whole-brain imaging studies, where the spatial resolution of data collection is approximately 3 x 3 x 5 mm prior to any spatial smoothing during image analysis (which can worsen the spatial resolution to 5 x 5 x 5 mm). Several studies, particularly those focussing on pain processing, have observed activations within the brainstem however the ability to unequivocally localise these functional activations to specific brainstem structures has not been feasible due to the relatively low spatial resolution of data collection. In order to better image function within the brainstem it is necessary to collect data at a higher spatial resolution as well as optimise structural image data collection parameters to provide better contrast within the brainstem, as conventional whole-brain structural sequences do not give high quality contrast images for brainstem structures. We have been actively developing methods to address these issues. In this talk I will summarise developments in data collection from the human brainstem with specific examples taken from our interest in identifying the key regions of the brainstem that are involved in pain processing.

Pain is an unpleasant sensory and emotional experience usually triggered by stimulation of peripheral nerves and often associated with actual or potential tissue damage. It is well known that pain perception for patients and normal subjects can be modulated by psychological factors, such as attention, stress, and arousal. Our understanding of how this modulation occurs at a neuroanatomical level is poor. In the first study to be described, we neuroanatomically defined a key area active in response to pain, that is modulated by attention to the painful stimulus. High-resolution functional magnetic resonance imaging was used to define brain activation to painful heat stimulation applied to the hand of nine normal subjects within the periaqueductal gray region. Subjects were asked to either focus on or distract themselves from the painful stimuli, which were cued using colored lights. During the distraction condition, subjects rated the pain intensity as significantly lower compared with when they attended to the stimulus. Activation in the periaqueductal gray was significantly increased during the distraction condition, and the total increase in activation was predictive of changes in perceived intensity. This provides direct evidence supporting the notion that the periaqueductal gray is a site for higher cortical control of pain modulation in humans [Tracey et al., J. Neuroscience 2002].

The second study to be described during my presentation presents FMRI data from a human model of neuropathic pain with the aim of identifying key components of the brainstem that might play a facilitatory role in central sensitisation. We found activation within the nucleus cuneiformis (NCF), in response to punctate stimulation. This phylogenetically ancient brainstem structure has not been found active in humans to date, although several animal studies have shown its importance in chronic pain. Further studies to be describe extend our observations of this nucleus, and other brainstem structures relevant to visceral pain processing.

Friday 11 June

PAIN



TRIGEMINAL NEUROPATHY. CLINICAL-HISTOLOGICAL-NEUROPHYSIOLOGICAL CORRELATION

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Unilateral trigeminal neuropathy is often secondary to focal compression. Isolated, bilateral trigeminal neuropathy is either associated to connective tissue diseases, or has no apparent cause: idiopathic trigeminal neuropathy (ITN) [Spillane and Wells 1959].
We studied seven patients with ITN, four male and three female, aged 60-71 years, onset of sensory disturbances at 46-63 years, disease duration 3-18 years. Three patients had constant burning pain, one constant burning pain and allodynia, one paroxysmal shooting pain, and two had no pain complaints. All had bilateral paresthesias and hypesthesia (4 also had intraoral paresthesias). All subjects underwent neurophysiological recording of the trigeminal reflexes and trigeminal laser-evoked potentials (LEPs). The early component of the trigeminal reflexes (the R1 blink reflex and SP1 masseter inhibitory reflex) were markedly abnormal or absent in all patients. The LEPs related to the small-myelinated afferent input (Ad-LEPs) were abnormal or absent in 5 patients. In three patients we also studied the LEPs related to the unmyelinated afferent input (C-LEPs) [Cruccu et al. 2003], and found them normal in all. Four subjects underwent biopsy of the supraorbital nerve; all had severe axonal loss (simil-wallerian degeneration) of all myelinated-fibre groups, with sparing of unmyelinated fibres.
Histological findings demonstrated a selective degeneration of myelinated fibres only. Neurophysiological findings indicated that degeneration followed a progressive gradient from large to small myelinated fibres. Because one patient had paroxysmal pain without any sign of demyelination and four had constant burning pain with complete sparing of C afferents, our findings in ITN are in contrast with common views about pathophysiology of paroxysmal and constant burning pains.

Cruccu G, Pennisi E, Truini A, et al: *Unmyelinated trigeminal pathways as assessed by laser stimuli in humans.* Brain 2003; 126: 2246-56.
Spillane JD, Wells CE: *Isolated trigeminal neuropathy. A report of 16 cases.* Brain 1959; 82: 391-416.

NEUROPATHIC FACIAL PAIN

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Neuropathic facial pain is a pain condition caused by a lesion or dysfunction of the nervous system. The peripheral lesions are often traumatic, iatrogenic or inflammatory, whereas the most common central causes are vascular lesions and multiple sclerosis. The most common forms of facial neuropathic pain are trigeminal neuropathies (focal or associated to diffuse disease), postherpetic neuralgia, trigeminal neuralgia (idiopathic or symptomatic) and central post-stroke pain (mostly in Wallenberg syndrome). Under the unclear labels of burning mouth syndrome and atypical facial pain some patients may have neuropathic pain mechanisms.

The examination of a pain patient aims at clarifying the underlying disease and understanding whether the pain is nociceptive, neuropathic, psychogenic, or a combination of such. In case of neuropathic pain, abnormal sensory findings should be neuroanatomically logical, compatible with a definite lesion site. The various components of neuropathic pain syndrome such as continuous pain, paroxysmal pain and stimulus-evoked pains are recorded. Meticulous neurological examination is mandatory, and depending on the case, laboratory tests may be needed. In particular, trigeminal reflexes are considered the best tool to differentiate all forms of pain secondary to neurological lesions from idiopathic or non-neuropathic conditions. Laser evoked potentials are providing important pathophysiological information.

The treatment is directed to the underlying disease and the disturbing components of the neuropathic pain syndrome. Currently we have a number of drugs and surgical interventions of proven efficacy for trigeminal neuralgia. In ophthalmic postherpetic neuralgia, however, the available therapies are insufficient for many patients.

MECHANISMS AND PREDICTORS OF CHRONIC FACIAL PAIN IN LATERAL MEDULLARY INFARCTION

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The purpose of our study was to identify clinical predictors and anatomical structures involved in patients with pain after dorsolateral medullary infarction. Eight out of 12 patients (67%) developed poststroke pain within 12 days to 24 months after infarction. The pain occurred in the ipsilateral face (6 patients) and/or the contralateral limbs and trunk (5 patients, 3 of which also had facial pain). Ipsilateral facial pain was significantly correlated with lower medullary lesions including the spinal trigeminal tract and/or nucleus as documented by MRI. The R2 blink reflex component was abnormal only in patients with facial pain. Likewise, pain and temperature sensation in the ipsilateral face was decreased in all patients with facial pain but not in patients without pain. Ipsilateral touch sensation in the face was also decreased in all patients with facial pain, but the MRI lesions did not involve the principal sensory nucleus of the fifth cranial nerve, and the R1 blink reflex latencies were normal. Although facial pain was correlated with lesions of the spinal trigeminal tract and/or nucleus, none of the lesions involved the subnucleus caudalis, which contains most nociceptive neurons. These findings suggest that facial pain after medullary infarction is due to lesions of the lower spinal trigeminal tract (axons of primary afferent neurons) leading to deafferentation of spinal trigeminal nucleus neurons.

INTERPLAY BETWEEN JAW AND NECK PAIN PATHWAYS AND IMPLICATIONS FOR TEMPOROMANDIBULAR PAIN DISORDERS

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Deep craniofacial tissues such as the masseter and neck muscles represent common sites for acute and chronic pain. Temporomandibular disorders (TMDs) are currently viewed as a family of related pain conditions in the jaw muscles, temporomandibular joint and associated structures. The pain is often poorly localized and referred, and indeed is often associated with pain in the neck muscles as well as the jaw muscles. Furthermore, there are also clinical reports that pain in cervical musculoskeletal tissues may be referred to cranial structures including the jaw muscles.

There is good evidence for a close interaction between the human craniofacial and cervical neuromuscular systems. For example, head posture and jaw clenching clearly influence the electromyographic (EMG) activity in both jaw muscles and cervical muscles in both humans and experimental animals. Several animal studies have demonstrated reflex connections between afferents supplying the trigeminal region and neck muscles. Studies in animals also have documented considerable convergence of craniofacial and cervical afferents onto trigeminal brainstem and upper cervical nociceptive neurons as well as EMG changes in neck or jaw muscles following cervical or craniofacial deep noxious stimuli, and have implicated these effects as fundamental mechanisms underlying pain localization and referral and neuromuscular adaptation in these two closely associated regions. However, there have so far been limited experimental pain studies exploring the possible association between jaw and cervical muscle pains in humans and their effects on the neuromuscular function of muscles in the craniofacial and cervical regions. A series of experimental pain studies have recently revealed the close interplay between the jaw and neck systems in different conditions: 1) the lower jaw in its "resting position" and during different head positions, 2) during maximal jaw clenching efforts, 3) during recordings of short-latency jaw-stretch reflexes and 4) exteroceptive suppression periods. The results provide strong evidence of the reciprocal interactions between jaw and neck muscle pain and the reflex expression of neuromuscular activity in both jaw and neck regions. This underpins the close interplay between these two regions that is also manifested in the clinical literature revealing the spread or referral of pain between the craniofacial and cervical regions.

LONG-TERM DEPRESSION OF TRIGEMINAL NOCICEPTION. A POTENTIAL TREATMENT OF HEADACHE?

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Electric low-frequency stimulation (LFS) of spinal dorsal root nociceptive fibers induced a sustained depression (1 hour) of activity in substantia gelatinosa neurons in-vitro. This long-term depression (LTD) of spinal nociception was only exceptionally demonstrated under in-vivo conditions in rat. Thus, the significance of LTD for memory in pain pathways has been questioned. In some experiments the following hypothesis was addressed: Noxious LFS of trigeminal afferents induces LTD of sensorimotor and nociceptive processing in man.
In 27 healthy volunteers three different electrophysiological experimental series were conducted. The masseter inhibitory reflex (MIR) was elicited by electric stimulation of the mental nerve area with a small cathode (2 mm diameter) and a large anode (9 mm diameter). During clenching the teeth with at least 90% of maximum strength the painful electric pulse elicited a reflex with an early MIR1 (12 ms) and a late MIR2 (45 ms) in both masseter muscles. The blink reflex (BR) was evoked by painful rectangular pulses applied to the forehead via a custom-made concentric electrode consisting of a small central cathode (0.5 mm diameter) and a large ring anode (30 mm diameter). This stimulation elicited a bilateral BR with a latency of 36 ms. Applying the same technique a cortical vertex potential (SEP) consisting of an N2 (115 ms) and P2 component (185 ms) was evoked by noxious electric stimulation of the forehead in the third experimental series. Signals were recorded before (20 min) and after (60 min) a 20 min stimulation pause (BR, SEP) or a 20 min period of LFS (MIR, BR, SEP). Noxious LFS was applied via the same electrodes with the same painful stimulus intensities as used for eliciting the reflexes and cortical potentials. LFS consisted of 1200 rectangular pulses with a frequency of 1 Hz.
Noxious LFS of trigeminal afferents induced LTD of the MIR, the BR and the SEP for at least one hour. Noxious LFS of mental nerve afferents caused a significant depression of the early MIR1 and the late MIR2. Whereas the onset latency (+25%), the duration (-42%) and the integral (+68%) of the MIR2 were strongly modulated after LFS, only the integral (+35%) of the MIR1 significantly changed. LFS of supraorbital nerve afferents decreased the BR integral by 50% and increased the latency by about 10% on both sides. The SEP N2-P2 amplitude decreased after LFS of the forehead to about 70% of the baseline. The perception ratings significantly reduced after LFS in all three experimental series. BR and SEP remained unchanged under control conditions.
The experiments documented a sustained depression (1 hour) of orofacial sensorimotor and nociceptive processing in healthy man indicating that LTD may also play a role in human synaptic plasticity. Some results suggested central mechanisms of LTD. A sustained inhibition may also be important for a neurostimulation therapy of orofacial pain and headache.

TRIGEMINAL LASER EVOKED POTENTIALS IN HEADACHE

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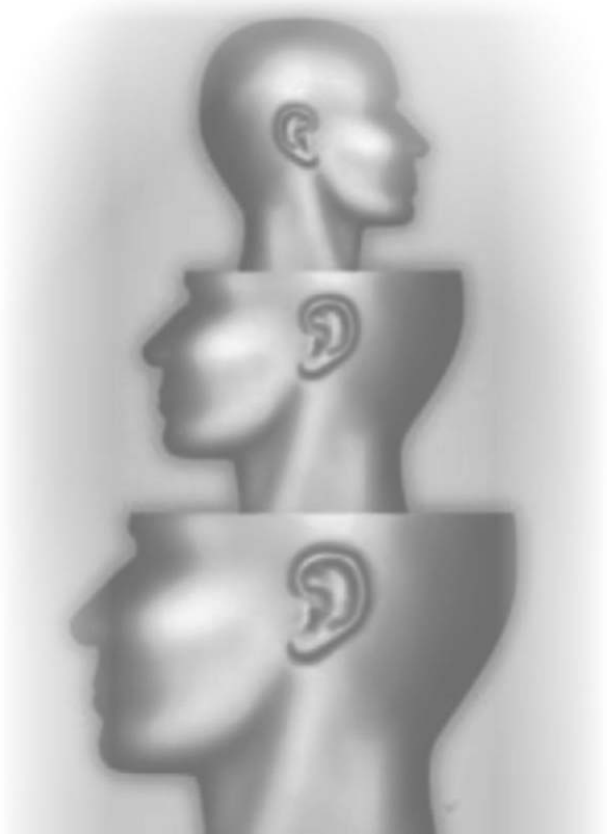
In spite of the large number of neurophysiologic studies dealing with headache, the function of the brain areas specifically devoted to nociception has only recently explored. This has been allowed by the introduction of the new technique of laser evoked potentials (LEPs) in both the clinical practice and research field. Indeed, painful laser pulses delivered on the hairy skin are able to activate the thin myelinated (Ad) and the unmyelinated (C) fibers without any concurrent activation of the larger non-nociceptive afferents [Bromm and Treede, 1984]. To investigate the trigeminal nociceptive pathways, laser stimuli must be delivered onto the facial skin [Cruccu et al., 1999]. Trigeminal LEPs have been used to study the episodic migraine without aura (MO) during both the intercritical phase and the acute attack, chronic migraine (CM), and chronic tension-type headache (CTTH). In all these kinds of headache, the trigeminal LEP amplitudes and latencies were found within the normal limits, thus suggesting the absence of any damage of the nociceptive pathways. MO patients show a reduced habituation to experimental pain during the intercritical phase [Valeriani et al., 2003]. Indeed, the progressive amplitude reduction of the trigeminal LEPs after successive stimuli is significantly lower in MO patients, than in CTTH patients and healthy subjects. This result demonstrates that the well-known phenomenon of the scarce habituation after repetitive sensory stimuli in MO involves also the nociceptive pathways. During the migraine attack, trigeminal LEPs increase their amplitude, as a proof of the nociceptive pathway sensitization in MO [de Tommaso et al., 2002]. De Tommaso et al. (2003a) showed a lower dependence of the trigeminal LEP amplitude from the stimulus intensity in CM patients than in control subjects. Compared to healthy subjects, CM patients show also a lower LEP amplitude decrease when subject's attention is diverged from the laser pulse. All these findings suggest an abnormal brain processing of cutaneous pain in CM. It is remarkable to notice that in migraine patients the same results observed with LEPs after trigeminal stimulation were obtained also after hand skin stimulation, as if the demonstrated abnormal pain processing were a generalised phenomenon in the nociceptive system, not limited to the face representation. In CTTH patients, the LEP amplitude after stimulation of facial or pericranial skin sites is higher, compared to healthy subjects, and it is directly related to the pericranial tenderness [de Tommaso et al., 2003b]. The authors attributed the LEP amplitude increase to a focalization of patient's attention onto the cutaneous sites of pericranial tenderness.

Saturday 12 June

PHYSIOLOGY



INVESTIGATION OF BRAINSTEM DESCENDING MODULATION IN ANIMALS AND HUMANS

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It has long been established that brainstem descending controls can modulate both motor and sensory processes in the spinal cord. In particular, numerous experimental studies performed during the last two or three decades have contributed to characterize the descending modulation of nociceptive neurones of the spinal dorsal horn. These works have emphasized the role of the periaqueductal gray and rostroventral medulla (ie the PAG-RVM axis), but other structures are also involved in this modulation. These structures exert both tonic and phasic descending inhibition or facilitation of the activity of spinal or trigeminal nociceptive neurones. The physiological mode of activation of these descending controls has not been clearly defined. However it has been shown, both in animals and humans, that noxious stimuli can trigger some descending inhibitory controls named difuse noxious inhibitory controls (DNIC) acting specifically on spinal and trigeminal wide dynamic range (WDR) neurons. The responses of WDR neurons are inhibited in an intensity-dependent and long-lasting manner by nociceptive stimuli applied, outside their excitatory receptive fields (ie heterotopic areas of the body). In man, heterotopic noxious stimuli inhibit the spinal nociceptive flexion (RIII) reflex, which reflects the spinal transmission of nociceptive signals. In both animals and humans, these phenomena are sustained by a spino-bulbo-spinal loop with an ascending part located in the anterolateral quadrant of the spinal cord.
Although it is widely accepted that endogenous modulatory systems affect sensations of pain, the way in which they are brought into play and their consequences on nociceptive behaviour have rarely been addressed in the context of tissue injury. In a series of electrophysiological studies we investigated the alteration of both phasic (ie DNIC) and tonic descending controls in animal models of inflammatory or neuropathic pains (1, 2, 3). We showed that descending modulatory systems exhibit functional plasticity during the course of inflammation. Such changes are stage dependent and alter both the excitability and receptive field size of spinal nociceptive neurones.
In a recent study, recordings of the RIII nociceptive flexion reflex were performed in patients with peripheral nerve injury in order to analyze the alterations of descending modulation (4). It was shown that light stimulation (ie brushing, or light pressure) in an area of mechanical allodynia (ie pain triggered by normally non painful light stimuli) located on the upper limb, could inhibit the RIII reflex recorded from the lower limb. Thus, DNIC seem to be exacerbated under such pathological conditions.
As a whole, these data suggest that alterations of descending modulation could play a significant role in the pathophysiology of clinical pain syndromes. The dynamic aspects of these changes suggest that they might be involved in the evolution from acute to chronic pain and contribute to the variability of clinical syndromes.

1. Danziger N, Weil-Fugazza J, Le Bars D, Bouhassira D: *Alteration of descending modulation of nociception during the course of monoarthritis in the rat.* J Neurosci 1999; 19: 2394-2400.
2. Danziger N, Weil-Fugazza J, Le Bars D, Bouhassira D: S*tage-dependent changes in the modulation of spinal nociceptive neuronal activity during the course of inflammation.* Eur J Neurosci 2001; 13: 230-240.
3. Danziger N, Gautron M, Le Bars D, Bouhassira D: *Activation of diffuse noxious inhibitory controls (DNIC) in rats with an experimental peripheral mononeuropathy*. Pain 2001; 91: 287-96.
4. Bouhassira D, Danziger N, Attal N, Guirimand F: *Comparison of the pain suppressive effects of clinical and experimental painful conditioning stimuli.* Brain 2003; 126: 1068-78.

WHAT THE VESTIBULO-SPINAL SYSTEM DOES - AND WHAT IT DOESN'T

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This presentation will review our experimental work into vestibulo-spinal function in man. The strategy used was to compare results in normal subjects with those of bilateral labyrinthine defective subjects (LDS). Initial experiments showed that head stability during pseudo-random whole-body oscillation was impaired in LDS [Bronstein AM. Acta Otolaryngol 1988; 105: 1-6] proving that vestibulo-spinal mechanisms are functionally useful. In subsequent work we investigated EMG responses to free fall. When the whole person falls in the supine position, a similar generalised EMG response is observed in normal and LDS. This indicates that the labyrinth is not essential for the free-fall startle [Bisdorff et al. EEG and Clin Neurophysiol 1994; 93: 409-16]. In other experiments subjects lay supine with the head off the couch, so that only the head was allowed to 'drop' [Ito et al J Physiol 1995; 489 : 911-6]. Activation of neck muscles during whole-body free-fall startle occurs at 50 ms whereas if the head alone 'drops' latencies are approximately 50% shorter. LDS show delayed neck EMG latency during head drop. These experiments show that free-fall can activate different pathways, presumably poly-synaptic reticular mechanisms during free-fall startle and more direct vestibulo-spinal pathways during head drop.

CNS disease impairs vestibulo-collic mechanisms in various ways. Some patients with Progressive Supranuclear Palsy (PSP) show an exagerated stability of the head in space. This leads to visible head-on-trunk deviations (torticollis) when these patients turn while walking [Bisdorff et al. Mov Disord 1997; 12: 328-36]. This apparent increase in vestibulo-collic activity is explained by the lack of resetting head-eye saccadic movements secondary to the reticular nuclei damage in PSP. In spasmodic torticollis (ST), head drop experiments have shown that the basic short latency response is preserved. However, the long latency response normally observed when subjects are instructed to voluntarily resist the head drop, is delayed and hypoactive in ST. This finding show a vestibulo-voluntary interaction during active head righting reflexes and that CNS disease can affect higher control mechanisms but spare more basic vestibulo-collic responses [Munchau et al. Brain 2001; 124: 47-59].

Recently we have investigated the 'broken escallator phenomenon', ie the odd feeling and unsteadiness reported when people mount an escallator which is stationary [Reynolds and Bronstein. J Neurophysiol 2004; 9: 92-100]. In these experiments, subjects walk first on a stationary motorised sled ('BEFORE'), then on the moving sled ('MOVING') and again onto the stationary sled ('AFTER' trials - with full warning that the sled will not move). As expected LDS were unsteady on the MOVING trials due to the lack of vestibulo-spinal activity. In the AFTER condition, despite full knowledge that the sled will be stationary, both normal subjects and LDS showed an aftereffect including a postural overshoot. We expected this postural aftereffect to be larger in LDS, as vestibulo-spinal reflexes would be good candidates to limit or 'break' the postural aftereffect. However, this was not the case as the size of the postural aftereffect was similar in both subject groups. These results confirm the prominent role of the vestibulo-spinal system during external postural perturbations (eg as in MOVING trials). When the perturbation is internally generated, as in the AFTER trials, the CNS relies less on sensory (vestibular) feed-back and more on feed-forward mechanisms to maintain balance [Bunday et al in preparation].

AUDITORY STARTLE REACTION

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The auditory startle reaction to an unexpected loud stimulus is considered to be a brainstem reflex. The pattern of auditory startle responses (ASRs) in various muscles is integrated in the nucleus reticularis pontis caudalis which receives direct and indirect input from the cochlear nucleus, and projects via bulbobulbar neurons to cranial nerve nuclei and via the reticulospinal tract to spinal motoneurons. The basic reflex pattern consists of a generalized flexion response which is most prominent around the face, neck and shoulders, and progressively less marked in the lower half of the body. ASRs are variable and subject to complex influences. With repeated stimulation ASRs habituate rapidly with the exception of an auditory blink reflex (startle blink). Age and gender are two important physiological parameters affecting ASR characteristics such as probability, latency, magnitude and habituation. We performed a study of the auditory startle reaction in 54 healthy non-medicated volunteers (27 males and 27 females), divided into three different groups: 17 subjects below 30 years of age (9 males, 8 females), 20 subjects between 30 and 50 years of age (9 males, 11 females), and 17 subjects older than 50 years of age (9 males, 8 females). The analysis of age-related differences showed that ASR probability was significantly lower in younger subjects than in older subjects, particularly in extremity muscles. ASR probability did not differ significantly among age groups in facial and neck muscles. Median ASR latencies were significantly shorter in all muscles combined of younger versus older subjects. The largest latency differences among age groups were observed in extremity muscles. The magnitude of ASR - measured as the area under the curve - tended to grow with age, with a significant increase in facial and neck muscles. The analysis of gender-related differences showed that ASR probability was significantly lower, and the area of the response was significantly smaller, in men than in women. Median ASR latencies were significantly shorter in all muscles combined of men versus women, despite significantly larger body height of men. The observed age- and gender-related differences might be due to variations of central processing in the brainstem centers involved in the ASR generation, and should be taken into consideration when testing ASRs in health and disease.

EXPLORATION OF THE ROLE OF THE UPPER BRAINSTEM IN MOTOR CONTROL

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This presentation is a brief overview of the work performed in our primate laboratory and in the clinical Movement Disorders Unit in recent years. As the title suggests the studies pertaining to the region of the upper brainstem are emphasized. The studies are grouped into two broad sections.

The first set of experiments explores the pedunculopontine nucleus (PPN) and the effects of manipulating it on motor behaviour. The PPN is a nuclear structure in the rostral brainstem with principal afferents from the basal ganglia and major efferents to the thalamus, basal ganglia, spinal and brainstem motor centers. This structure has also been implicated in the akinesia seen in patients with Parkinson's disease.

We implanted a macroelectrode in the unilateral PPN of a macaque using contrast ventriculography. This was then connected to a subcutaneous implantable pulse generator (IPG) to permit sustained deep brain stimulation (DBS) of the PPN at different frequencies and amplitudes in a freely behaving monkey. We established that this procedure did not alter the normal motor activities of the animal. We found that low frequency (< 30 Hz) DBS of the PPN induced some positive motor effects like contralateral proximal limb tremor while high frequency (> 45 Hz) DBS rendered the animal akinetic.

In another set of experiments, a stainless steel cannula (internal diameter 0.75 mm) was implanted into the unilateral PPN of a macaque (n = 2) using similar stereotactic techniques and microinjections of gamma-aminobutyric acid (GABAA) antagonist bicuculline, agonist muscimol and control saline were administered sequentially. Automated activity counts, blinded clinical rating scores and videotape records, were employed to establish the reduction in activity with muscimol. The animals were then rendered Parkinsonian with intravenous 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP). The intracerebral injections were repeated. It was found that bicuculline significantly improved the motor behaviour of the Parkinsonian monkey. The effect of bicuculline microinjection in the PPN matched that of oral administration of L-dopa.

Just recently, we have repeated the PPN DBS experiments in another macaque using a custom made fine DBS electrode (0.7 mm) and continued the stimulation studies in the MPTP-induced Parkinsonian state. We have found that PPN DBS significantly improves the activity counts and combining it with oral L-Dopa improves function more than the drug given alone.

The clinical studies, which constitute the other main body of work, have focused on the effect of DBS of the zona incerta (ZI) in the control of intractable inten-

tion tremor, commonly seen in multiple sclerosis tremor (MST), and also in essential tremor (ET) and some cases of post-traumatic tremor (PTT). We have used field potential (FPs) and EMG recording and visually-guided computer controlled arm tracking tasks (VGT) to objectively monitor the results of the DBS treatment. We have found that complex intention tremor involving both proximal and distal joints responds best with simultaneous stimulation of the thalamus (VIM/VOP) and the ZI.

Our studies seem to add evidence to the view held by many previous groups that the brainstem plays a particularly important role in proximal and axial motor control.

ORGANIZATION AND FUNCTIONAL PROPERTIES OF THE EYELID MOTOR SYSTEM

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We have studied the profile, metric, and frequency-domain properties of spontaneous, passive, reflex, and learned eyelid movements. Those studies were carried out (with a comparative purpose) in cats, rabbits, rats and mice. Moreover, we have studied the location of neural centers involved in eyelid responses using the attenuated rabies virus as a retrograde trans-neuronal tracer. We have recorded and analyzed the functional properties of muscles involved in eyelid responses (mainly the orbicularis oculi muscle) and those of their innervating motoneurons, located in the facial motor complex. Finally, we have also recorded and analyzed the firing properties of pre-motor neurons (located in brain stem, cerebellum, and motor cortex) involved in eyelid motoric. Eyelids have a negligible mass and muscles involved in their movements are devoid or a true stretch-reflex response. Besides, the orbicularis oculi muscle is organized topographically, and have motor units specialized in some of the particular motor functions referred above. Facial motoneurons seem to encode eyelid velocity, but not eyelid position, the latter being determined by eye position signals present in levator palpebrae motoneurons. Facial motoneurons fire phasically during reflex responses, but tonically during learned (classically-conditioned) eyelid responses, suggesting a different neural origin of both motor commands. Reflex responses of trigeminal origin are generated both at the trigeminal nucleus and at the nearby reticular formation. It is still not determined the precise origin of learned eyelid responses, although many cerebral areas seem to be involved in this process. On the other hand, the cerebellum (vermal and paravermal cortices and selected areas of the fastigial, interpositus, and dentate nuclei) is apparently involved in the reinforcement of reflex and learned eyelid responses, but not in their generation. The hippocampus encodes apparently higher cognitive functions related to the predictive value of stimuli used as a conditioning signal (i.e., the conditioned stimulus) and/or to their salience or relevance. Wide cortical (entorrinal, parietal, temporal) areas seem to participate in the generation of learned eyelid responses. Facial motoneurons can be experimentally obliged to reinnervate the orbicularis oculi muscle; in this situation, every facial motoneuronal pool seems to carry specific motor commands that cannot be modified by the experience in adult mammals.

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ORBICULARIS OCULI REFLEXES

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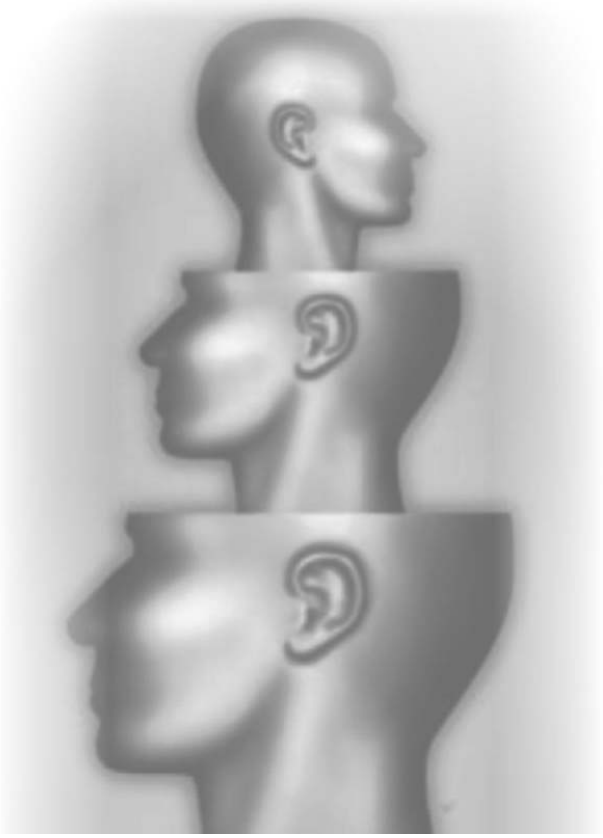
This presentation is focused on the blink reflex (BR) elicited by the electrical stimulation of the trigeminal supraorbital nerve, the most controlled and reliable model of the orbicularis oculi (OO) reflexes in clinical neurophysiology. BR is a trigemino-facial reflex of cutaneous nature recorded on the OO muscles, conformed by three components; the first two, named R1 and R2, of rather well-known characteristics, and the third one, R3, of increasing interest. R1 and R2 are built up by the same MUPs, the later in a repetitive pattern. There are many reasons for supporting that the afferent volley in both components is conveyed by different types of nerve fibres, the R2 predominantly by thin myelinated, high threshold A-delta fibres. This response, however, has a lower electrical excitability threshold which would likely be explained by a functional reverberating central circuitry. The trigeminal afferent limb reaches the facial efferent one by means of a long and quite complex central pathway located at the brainstem bulbopontine level; other proposed brainstem structures playing a role in the anatomo-physiology of the reflex will also be considered. The anatomical substrate and criteria of the rich topographical BR impairment semiology will be commented. The method of suppression-recovery of the BR to paired stimuli measures the basal excitability of the reflex; it is critically reviewed and a reliable analysis is proposed. The relationship between the BR and the spontaneous blinking has been considered, and the existence of a primary blink inhibitory reflex on levator palpebrae muscles, previous to the BR active responses of the orbicularis, is suggested. Strategic position of the neural structures of the BR, in an area involved in the gating of the various sensory-motor systems and the relative simplicity of its evaluation with common methodology used in clinical neurophysiology, makes of the BR an essential tool to establish diagnosis and to offer a pathophysiological insight into an important number of human neurological disorders.

Saturday 12 June

MOVEMENT DISORDERS



POSSIBLE ROLE OF BRAINSTEM-SPINAL PATHWAYS IN RECOVERY FROM STROKE

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A large amount of work has been published on the role of the corticospinal system in voluntary movement. Although undoubtedly important, it is often forgotten that the primary message from work such as that of Lawrence and Kuypers (1968) is that complete bilateral section of the corticospinal tract results in relatively little permanent deficit in voluntary movements. The implication is that other descending systems must be able to produce a large proportion of the repertoire of volitional motor output. Only fractionated movements of the fingers seem to be exclusively controlled by the corticospinal system. The present experiments examined whether cortical input to reticulospinal systems might be one mechanism that preserves motor function after damage to corticospinal projections

Cortical input to the reticulospinal system can be demonstrated by interacting volitional and startle evoked movements ("start-react" paradigm). If subjects are prepared to move in a simple reaction time task, then presentation of a startle input will trigger release of the prepared voluntary movement at half the usual latency of a voluntary reaction. Since this is the usual latency of the startle response, it is possible that a copy of some of the prepared commands to move are stored in the reticulospinal system and released by the startle input.

We have used this approach to investigate whether 10 patients with stroke can modulate the amplitude of the startle reflex under conditions when they try to move voluntarily to a startle input. We found that in all cases, patients who had very little or no voluntary movement on the affected side could nevertheless modulate the amplitude of the startle reflex in the start-react paradigm. The resulting EMG response was at least 50% larger than that from the expected sum of the response to startle alone and voluntary movement alone, and was modulated according to the nature of the voluntary movement that the subjects had been prepared to make. We suggest that this may indicate an intact volitional input to brainstem startle centres that could potentially contribute to recovery of voluntary movement.

BRAINSTEM DYSFUNCTION IN PSP

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Neurophysiological studies can help in the assessment of patients with parkinsonism, with the documentation and quantitation of certain signs that may be specific or predominant in one disease and less common or not found in others. In accordance to the distribution of the pathological lesions and the main clinical signs, the most interesting neurophysiological tests to perform in patients with progressive supranuclear palsy (PSP) are those examining brainstem functions and reflexes.

Clinical evidence of eye movement difficulties are not always present when other clinical features lead to the suspicion of PSP. At this time, recording of eye movements by electrooculography might be of some help. Characteristic abnormalities are slowness of vertical eye movements, absent Bell's phenomenon, and square wave jerks. Often, patients with PSP have vertical gaze paralysis with preserved reflex eye movements. The horizontal eye movements may be slow. The analysis of microsaccades can be helpful in distinguishing patients with PSP and those with other parkinsonisms.

Mentalis muscle reflex responses to electrical stimulation of the median nerve are the electrophysiological equivalent of the palmomental reflex. They can be often observed in patients with PSP as well as in patients with other degenerative disorders and even in a few normal subjects if the stimulus is of sufficient intensity. Mentalis muscle responses are usually accompanied by other facial responses. In most patients, electrical stimulation of the median nerve induces a response in the orbicularis oculi at a latency slightly shorter than that observed in the mentalis muscle. However, a distinctive abnormality has been reported in patients with PSP in whom the mentalis muscle response is not accompanied by the orbicularis oculi response. This observation points to a specific disorder of the integration of sensory inputs on their way to activate facial motoneurons of the orbicularis oculi but not those of the mentalis muscle, revealing the likely existence of two different pathways activated by the same stimulus.

Patients with PSP have absent or severely reduced auditory startle reactions. This may be due to neuronal loss in the cholinergic neurons of the lower pontine reticular formation, including those of the pedunculo-pontine tegmental nucleus and the nucleus reticularis pontis caudalis. Another function of the pedunculopontine tegmental nucleus is the control of prepulse inhibition of the startle reaction. This has also been examined in patients with PSP using somatosensory and auditory

stimuli. With both types of stimulation, the degree of prepulse inhibition was significantly reduced in comparison to control subjects.
Table 1 summarizes the findings observed in the study of brainstem reflexes and functions in patients with PSP in comparison to those reported in patients with other forms of parkinsonism.

Table 1: Characteristics of some brainstem reflexes in patients with parkinsonism.

TEST	**IPD**	**PSP**	**PSP**	**CBD**
Blinking frequency	reduced	extremely reduced	variable	normal
Excitability recovery	enhanced	enhanced	enhanced	normal
Blinking to auditory stimuli	normal	reduced	normal	normal
Blinking to nerve stimuli	normal	reduced	normal	normal
Auditory prepulse inhibition	reduced	reduced	?	?
Somatosensory prepulse inhibition	normal	reduced	normal	?

IPD = Parkinson's disease; PSP = Progressive supranuclear palsy;
MSA = Multiple system atrophy (strionigral degeneration);
CBD = Cortico basal degeneration;
? = Data unknown.

BRAINSTEM-GENERATED INVOLUNTARY MOVEMENTS

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Many abnormal movement are considered to be produced by brainstem structures. All these conclusions are mainly based on clinical observations, limited imaging data or complex electrophysiological tests.
Pathoanatomic or structural imaging data can only provide lesions or abnormal structures but may unfortunately not confirm the origin of the hyperkinesia. Myoclonias, mainly the reticular myoclonus has been demonstrated to have its origin in the brainstem. Several forms of tremor are mostly likely due to brainstem structures like essential tremor, Holmes tremor, palatal tremor and orthostatic tremor. Some cranial dystonias have been observed following lesions of the midbrain. The evidence will be reviewed for and against a brainstem-origin of these abnormal movements.

NEURO-VASCULAR CONFLICT AND HEMIFACIAL SPASM

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PURPOSE Anatomical findings and surgical results in a series of 144 patients affected with HemiFacial Spasm (HFS) and treated with Microsurgical Vascular Decompression (MVD) are reported.
METHODS MVD was performed through a keyhole retromastoid approach, under monitoring of Brainstem Auditory Evoked Potentials (BAEP) for controlling Auditory Nerve function, and Facial EMG for studying Lateral Spread Evoked Motor Responses (LSEMR). Procedure consisted of dissecting the VIIth nerve free from the conflicting vessel(s) and of maintaining vessel(s) by interposition of Teflon® prosthesis.
RESULTS The offending vessels were: the postero-inferior cerebellar artery in 59% of cases, the antero-inferior cerebellar artery in 54%, the vertebrobasilar artery in 20%. Multiple conflicts were found in 32%. The result was considered excellent when there was no residual spasm, good if only "minimal twiching" persisted, that is when relief was > 90%, poor for spasm relief of 30% to 90%, and failure when relief was < 30%. The effect of MVD was satisfying (excellent or good) in 100 patients (69%) on discharge at 10th day, and in 123 patients (85.5%) after 1 to 20 year follow-up (mean 5.6 years). 42 of the 123 patients (34%) experienced a delayed cure (up to 3½ years in one case). Spasm recurrence was noticed in 9 cases of the 100 patients with satisfying effect on discharge. The following permanent neurological complications were encountered: facial palsy 1 case, hearing deficit 7 cases (of whom 5 were complete), IX-X deficit 1 case. There was neither death nor ischaemic complication at brainstem or cerebellum in the series. Most of hearing complications occurred before using intraoperative BAEP monitoring (3 cases of the 5 with complete cophosis). Local complications were: 1 meningitis, 10 CSF leakage requiring either a series of lumbar punctures or lumbar external drainage, and 3 wound infection and/or delayed woundhealing requiring surgical treatment.
CONCLUSIONS Our data are consistent with those of the literature: high rate of long-term success and low complication rate. We do not recommend early re-operation in patients with initial failure or poor result; as a matter of fact delayed effect is frequent. Intraoperative BAEP monitoring is mandatory to prevent hearing morbidity [Polo et al.]. Intraoperative monitoring of facial EMG LSEMR is not necessary, due to lack of reliability for predicting long-term efficacy [Hatem et al.].

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NEW FINDINGS IN CRANIAL-CERVICAL DYSTONIAS

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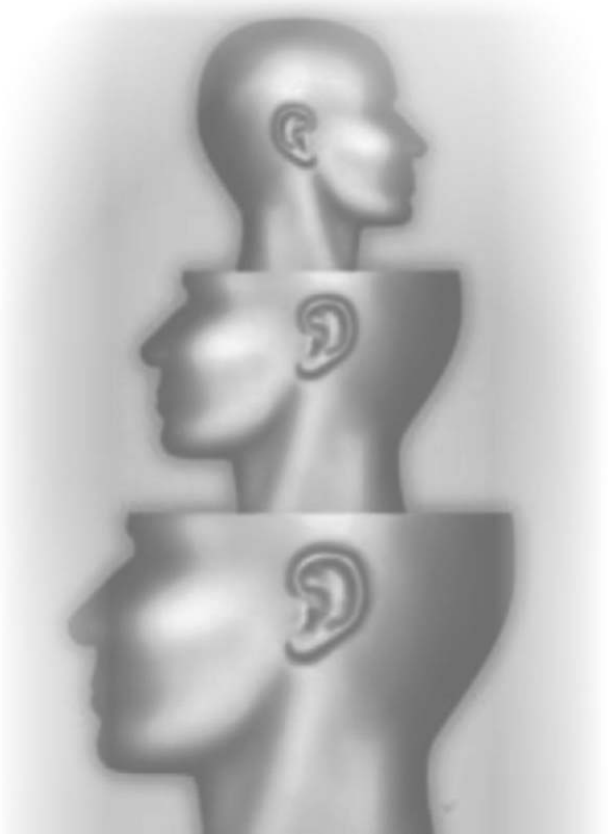
Neurophysiological studies in patients with cranial and cervical dystonia disclose abnormalities at the level of the brainstem, the spinal cord, and the cortex. Most evidence suggests an abnormal modulatory signal rather than a primary disorder of spinal and brainstem interneurones, or cortical circuitry. Clinical studies and animal models point toward altered basal ganglia motor output, acting either indirectly by engagement of cortical motor areas via the thalamus, or directly by descending influences to brainstem and spinal cord motor machinery.

In dystonia, effects on the motor system are paralleled by changes in somatosensory function. Clinical and neurophysiological studies emphasize the role of sensory feed-back in the generation, maintenance or suppression of dystonic movements also in cranial and cervical dystonia. The disorganisation of the primary sensory and motor representations at the cortical level together with the increased somatosensory responsiveness of neurons in the basal ganglia suggest that the basic defective process in dystonia is the sensorimotor integration.

Altered motor control due to abnormal sensory information and defective sensorimotor integration raises the question whether the disordered functions seen in patients with dystonia are intrinsic abnormalities of the underlying disease process or they represent maladaptative reorganization to abnormal motor performance. Early findings of altered excitability of brainstem reflex pathways in patients with dystonia but without blepharospasm supports the view of intrinsic deficits, but recent animal models and clinical studies suggest that a maladaptive role for plasticity may be invoked in some patients with cranial dystonia. Phenomenology of dystonia possibly results from the interaction at the basal ganglia and the cortical motor areas between intrinsic deficits and deficits that are due to the effects of plastic reorganisation.

Saturday 12 June

POSTER SESSION



P1 SENSITIVITY OF DIFFUSION WEIGHTED MRI AND ELECTROPHYSIOLOGICAL BRAINSTEM TESTING IN THE DIAGNOSIS OF ACUTE VERTEBROBASILAR ISCHEMIA

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**Department of Neurology, University of Jena, Germany*

BACKGROUND To evaluate the sensitivity of diffusion weighted MRI (DWI) and electrophysiological brainstem testing in the diagnosis of clinically suspected acute vertebrobasilar ischemia.

PATIENTS AND METHODS From 1997 to 2002 we prospectively recruited 243 consecutive patients presenting with acute signs and symptoms suspective of vertebrobasilar ischemia. All patients underwent biplane EPI-T2 and EPI-DWI within 24 hours after onset of symptoms and high resolution T1-/ T2-weighted MRI using a 1,5 Tesla system within 7 days. Within 7 days, a battery of electrophysiological brainstem tests was applied (blink reflex, masseter inhibitory reflex, jaw jerk, AEPs, MEPs with investigation of cortico-orofacial and cortico-lingual projections, SSEPs with investigation of brainstem generated far field potentials, electrooculography and investigation of the oculo-auricular phenomenon). Electrophysiological abnormalities were interpreted as acute if they improved in follow-up investigations.

RESULTS In 32 of 243 patients imaging studies and complementary investigations revealed a diagnosis other than brainstem or cerebellar infarction. DWI showed acute ischemic changes in 74.4% of the remaining 211 patients with best final diagnosis of vertebrobasilar infarction. High resolution MRI was not able to detect significantly more acute infarctions than DWI alone. 83.9% of patients had acute electrophysiological pathology. Jaw jerk (58.2%), electrooculography (57.4%) and blink reflex (53.7%) were most commonly affected. When combining the results of DWI and electrophysiological testing the detection rate of acute lesions was significantly higher than that from DWI alone (92.4% versus 74.4%, $p < 0.05$).

CONCLUSIONS DWI and electrophysiological testing are complementary tools in the diagnosis of acute ischemic lesions in the vertebrobasilar territory. DWI allows quick demonstration of aetiology and the site of brainstem or cerebellar infarction. Electrophysiological testing can demonstrate an intra-axial pathology even in patients with normal MR imaging, which may influence further patient management. The tests can be done economically, especially to monitor the time course of functional deficits.

P2 ABNORMAL PATTERNS OF BREATHING DURING SWALLOWING IN MULTIPLE SCLEROSIS

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BACKGROUND The temporal coordination of respiration and swallowing is provided by an extended pontomedullary neuronal network. Recent data suggest a high prevalence of dysphagia and recurrent aspiration in moderately and severely disabled multiple sclerosis patients. It is not known if the breathing pattern during swallowing is disturbed in multiple sclerosis.
METHODS The study participants included 42 healthy subjects, median age 47 yr and 20 patients with multiple sclerosis, presenting with a median EDSS of 5.75 (median age 48 yr). A 2-channel computer assisted system (Bioimpulser DYS10/A, Haynl Electronics Comp., Schönebeck, Germany) was used to obtain concurrent respiratory and submental surface electromyography signals. Subjects were seated in an upright position and asked to swallow boluses of 5, 10 and 25 ml water and 5 ml applesauce presented in random order. Eight swallows of each bolus volume and viscosity were recorded. For each swallow, (1) the latency between the onset of swallowing and swallowing apnea (SA); (2) the duration of each SA; (3) the pattern of breathing before and after each SA was evaluated.
RESULTS In healthy subjects and patients a total of 1.984 swallows were performed. The latencies between the onset of swallowing and SA did not differ significantly between controls and patients. However, in the patient group SA duration was significantly prolonged ($p < 0.0001$) at all bolus volumes and viscosities (5 ml: 0.73 ± 0.19 sec vs 0.82 ± 0.31 sec; 10 ml: 0.76 ± 0.19 sec vs 0.89 ± 0.40 sec; 15 ml: 0.75 ± 0.20 sec vs 0.90 ± 0 .38 sec, applesauce: 0.76 ± 0.21 sec vs 0.88 ± 0.41 sec). Expiration/inspiration before SA occurred in healthy subjects in 87.3% / 12.7% and in patients in 89.4% / 10.6% (n.s.). Expiration / inspiration after SA occurred in healthy subjects in 98.9% / 1.1% and in patients in 93.0% / 7.0% ($p < 0.0001$). The difference was highly significant at all bolus volumes and viscosities.
CONCLUSION Our study confirmed that the great majority of swallowing apneas in healthy subjects are followed by expiration. However, in multiple sclerosis patients the SA is followed by inspiration more frequently than expected which might increase the risk of aspiration or laryngeal penetration. Furthermore the duration of swallowing apnea is significantly increased. Our findings indicate a disturbed temporal coordination between respiration and swallowing in moderately to severe disabled multiple sclerosis patients most probable due to pontomedullary lesions.

Supported by MAIFOR (University of Mainz).

P3 OCULO-JAW SYNKINESIA IN PARKINSON'S DISEASE AND MSA-P. NEUROPHYSIOLOGICAL FINDINGS

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**Unitat de Neurofisiología, Centre Hospitalari Althaia, Manresa, Barcelona, Spain*
***Servei de Neurologia, Hospital Clinic, Barcelona, Spain*

BACKGROUND Limbs motor synkinesias in PD patients and normal subjects have been reported elsewhere in the medical literature. However, to our knowledge oculo-Jaw synkinesia (OJS) is a novel observation in PD patients and normal subjects. We can find other well defined facial muscle conjugated synkinesia in other communication but none of them talk about this curious conjugated movement which consist in the ipsilateral deviation of the jaw when the subject direct the gaze to this side. We have observed that the OJS is easily observed in some normal subjects and PD patients for this reason we decided to carry out a protocol to determine the clinical and electrophysiological characteristics of OJS in normal subjects, PD patients and multi system atrophy parkinsonian type.
PATIENTS AND METHODS We recruited ten consecutives (10) PD patients, five (5) of them dyskinetic and five (5) with no dyskinesias. Aged from 57 to 72 yo, mean disease onset 5.6 years, H-Y scale: three (3) of them (stage I), Two (2) of them (stage II) and five (5) stages III and IV. five (5) MSA-p (Quinn criteria, Probability MSA-P) patients aged from 55 to 64 yo. Mean disease onset 3.5 years who did not need help for activities of daily living and ten normal subjects with similar demographics characteristics. Two neurologists evaluated all the patients and subjects separately previous unification of criteria. The OJS was described in a scale where 0 = non, 1 = doubt, 2 = Mild, 3 = moderate, 4= exaggerated. A close facial video-film was realised to every patient and subjects, we recorded both orbicularis oculis and both masseter muscles with surface electrodes in the normal subjects and place an accelerometer to determine the chin direction.
RESULTS All of normal subjects n = 10 (100%) showed the OJS for both independent examiners, three (3) of them stage 2 in the OJS scale, four (4) stage 3 and three (3) stage four. PD patients showed three (3) of them stage 0 (30%), two (2) of them stage 1 (20%), three (3) of them stage 2 and two stage 4 of the OJS scale (Stages 2 and 4 = 50%). no MSA-p patients showed a clear OJS, three (3) of them stage 0 and two (2) stage 1.
CONCLUSION OJS is a novel facial synkinesia easily to determine in the physical examination and with surface electromiography in normal subjects. It was observed in 50% of PD patients, exaggerated in the dyskinetic ones and was not observed or doubtly observed in the physical examination in 50% of them maybe for anatomical facial characteristics of this patients and it was not observed in none MSA-p patients. We don't know what these findings mean probably the OJS could be present in normal subject and PD patients and could be abolished from the very beginning in MSA-p which could be an interesting differential finding between PD and MSA-p patients. We are awarded about the necessity to confirm these electrophysiological finding in PD and MSA-p patients in a larger group.

P4 UNILATERAL MASSETER REFLEX ABNORMALITIES WITH MEDULLARY LESIONS INVOLVING THE IPSILATERAL SPINAL NUCLEUS OF THE TRIGEMINAL NERVE

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BACKGROUND Experimental data indicate a suprasegmental influence on the masseter reflex (MassR), which is mediated via the 5th nerve spinal nucleus (5thSpN). To the best of our knowledge, corresponding data in humans are still lacking.

PATIENTS AND METHODS We retrospectively analysed the files of 258 consecutive patients with clinical signs and symptoms of acute ischemia in the vertebrobasilar territory for unilateral infarctions caudal to the levels of the motor and main sensory nucleus of the 5th nerve. Biplane T2- and echo planar-diffusion weighted magnetic resonance imaging with slice orientation parallel and perpendicular to slices of a stereotactic anatomical atlas were done in all patients. Individual slices were normalized and the lesions were projected into the corresponding slices of the anatomical atlas.

RESULTS We identified 39 patients with unilateral infarctions caudal to the level of the 5th nerve motor and main sensory nucleus. Six of these patients had an abnormal delay of the MassR on the side of the infarction. In all patients, the infarction involved the region of the 5thSpN.

CONCLUSIONS Our findings indicate, that medullary brainstem lesions involving the 5thSpN may cause ipsilesional MassR abnormalities. We attribute this finding to an impaired excitation (or disfascilitation) of masseter motoneurons, as there is experimental evidence for an excitatory projecting from the amygdaloid nucleus via the 5thSpN to trigeminal motoneurons, which may be interrupted at the level of the 5thSpN.

P5 ELECTROPHYSIOLOGIC STUDY OF THE MOTOR-MOTOR REFLEX RESPONSES IN HEMIFACIAL SPASM

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Diagnosis of HFS is usually based on clinical features. However, in certain patients differential diagnosis with other abnormal facial movements may be difficult. In these cases, electrophysiological methods may be used to help in the diagnosis. The electrophysiological characteristics of HFS are: 1) Spontaneous repetitive discharges appearing simultaneously in different hemifacial muscles. 2) Postdischarges following direct or reflex responses. 3) Cross transmission of antidromic impulses between different facial nerve branches. 4) Enhanced blink reflex R1-like responses appearing in facial muscles other than orbicularis oculi and 5) Increased latency of the R1 blink reflex response on the affected side.

Following supraorbital (frontalis) nerve stimulation, early R1-like responses on ipsilateral orbicularis oris muscle may be seen in HFS patients due to the ephaptic transmission of impulses between facial nerve motor axons. Displacing the stimulation point from supraorbital to zygomatic position always caused a progressive shortening of the early response latency, implying a shorter distance between stimulation and recording points.

We studied 12 patients with confirmed clinical diagnosis of HFS (average of 6.4 years). We also studied 10 patients with blepharospasm and 10 normal subjects as a control group.

Reflex responses were recorded from the orbicularis oculi and oris muscles. Then, these same responses were elicited after displacing laterally the stimulating electrode over the facial nerve trunk from supraorbital to zygomatic areas and the changes in latency induced by this maneuver recorded. Mean latency and amplitude of the early blink reflex R1 responses were not statistically different between the two sides in 10 of the 12 HFS patients, in all blepharospasm patients, and in all normal subjects. Early blink reflex R1 responses in orbicularis oris are never seen in our normal subjects and in the blepharospasm patients. In contrast, HFS patients had early blink reflex R1-like responses in orbicularis oris following supraorbital nerve stimulation. Displacing the stimulation point from supraorbital to zygomatic positions caused in all cases progressive shortening of the early response latency, implying a shorter distance between stimulation and recording points. This demonstrates the motor-motor character of the reflex response. Frequently, this early response was the steady first component of a burst of abnormal muscle activity of variable morphology that was intermingled with the late components of the blink reflex. This abnormal activity was coincident in time with the visible muscular twitch of the HFS.

This method permits differentiation of the ephaptic responses of HFS from diffused R1 responses of the blink reflex, which can appear in other muscles of the face apart form the orbicularis oculi.

P6 HEMIFACIAL SPASM AND POSTERIOR AURICULAR MUSCLE

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PURPOSE Hemifacial spasm (HFS) is characterized by involuntary movements of the muscles innervated by facial nerve limited to one side of the face. The orbicularis oculi and perioral muscles are involved most frequently, however all facial innervated muscles may contribute. Posterior auricular muscle (PAM) is a rudimentary muscle which is located behind the pinna and together with anterior and superior auricular muscle groups allows for movement of the pinna. Based upon the complaint of a sensation of retroauricular twitching and tinnitus with each spasm in a few patients, we aimed to investigate to which extent PAM was affected and whether it contributed to the reflex activity in HFS patients.

METHODS 12 HFS patients, one of whom had bilateral involvement, with symptom duration of 6 months - 20 years were included. Spasm activities were recorded from orbicularis oculi, orbicularis oris and posterior auricular muscles by surface electrodes. With the electrodes placed on the above mentioned muscles, electrically elicited blink reflex and auditory blink reflex responses were studied in 12 patients (5 male, 7 female). The results were compared with those of 9 healthy subjects (3 male, 6 female).

RESULTS Spasm activity of PAM was recorded synchronously with the other facial muscles on the symptomatic side in 12 patients. Electrically elicited blink reflex response latencies were normal in patients. Auditory elicited blink reflex response latencies were found to be 44.3 ± 13.1 msecs and 45.2 ± 11.9 msecs on the spasm and unaffected sides, respectively. Reflex response latencies of the same stimulus were found to be shorter in the control group (33.3 ± 14.1 msecs on the right side, 35 ± 14.9 msecs on the left side). Following supraorbital stimulation, lateral spread of reflexes to orbicularis oris and posterior auricular muscles were recorded in all patients. Reflex latencies of orbicularis oris muscle elicited by auditory stimulation were found to be longer than those elicited by electrical stimulation in the patient group. When auditory stimuli were applied, 6 of 12 patients and 5 of 9 healthy subjects elicited a delayed reflex contraction in PAM. Reflex latencies of posterior auricular muscle elicited following supraorbital stimulation ranged between 45 and 81 msecs on the right side, 31 and 81 msecs on the left in the control group. They were between 30 and 65 msecs in HFS group on the spasm side. Auditory elicited reflex response latencies of control and patient groups in PAM ranged between 43 - 84 msecs and 33 - 58 msecs, respectively.

CONCLUSIONS PAM, innervated by facial nerve, may be of value for understanding the facial nerve related disorders owing to its proximal localization. These patients presenting with retroauricular symptoms and showing spasm activity in their PAMs can be thought as a candidate for botulinic toxin treatment scheme.

P7 THE DIAGNOSTIC VALUE OF THE TRIGEMINO-CERVICAL REFLEX

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In 1898 Sherrington for the first time reported an inhibitory effect of trigeminal stimulation on neck muscles in the cat. We have recently described trigemino-cervical reflexes in humans showing that trigemino-cervical reflexes can be recorded from sternocleidomastoid muscle after stimulation of the infraorbital branch of the trigeminal nerve.
To evaluate the diagnostic contribution of trigemino-cervical reflexes in humans, we recorded the trigemino-cervical reflex in patients with MR evidence of brain-stem involvement. We also compared the responses obtained in patients with brainstem lesions with the responses recorded in patients with a supratentorial lesion in order to evaluate the effects of lesion outside the brainstem on the reflex. Abnormalities of the trigemino-cervical reflex were evident in most of the patients with a brainstem lesion and were more pronounced in patients with lesions of the medulla. Patients with a supratentorial lesion had normal reflexes, therefore supratentorial lesions seem to have no effect on the trigemino-cervical reflex. These findings suggest that the trigemino-cervical reflex may help in disclosing and localizing brainstem lesions.

P8 DISSOCIATION BETWEEN UPPER AND LOWER FACIAL MUSCLE RESPONSES TO MEDIAN NERVE STIMULATION IN PATIENTS WITH MESENCEPHALIC LESIONS

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PURPOSE OF THE STUDY Median nerve stimulation can induce facial responses in orbicularis oculi (OO) and mentonian muscles (MM) in healthy subjects and in patients with enhanced palmomental reflex. The pathways mediating these responses are unknown. However, some integration at the level of the brainstem is possible for at least the response of the OO, since this response is absent in patients with progressive supranuclear palsy (PSP).
METHODS We examined whether vascular lesions in upper or lower brainstem interfere with the production of those responses. In 3 patients with residual mesencephalic vascular lesions, and in 4 patients with long standing Wallenberg's syndrome, we recorded the EMG activity of the OO and MM with pairs of surface electrodes. Electrical stimuli were delivered to the median nerve at the wrist using an intensity able to induce a supramaximal compound action potential in the thenar muscle. We also obtained the blink reflex responses to electrical supraorbital nerve stimulation, and the jaw jerk to mandibular taps.
RESULTS In the three patients with mesencephalic lesions, the OO response was bilaterally absent while the MM response was present. Conversely, in all 4 patients with the Wallenberg's syndrome, the responses were present in both, the OO and MM muscles. Blink reflex latencies were normal in all patients with mesencephalic lesions and showed a delay or absence of the R2 and R2c in patients with Wallenberg's syndrome. The jaw jerk was unilaterally absent in one patient with mesencephalic lesions, whereas it was normal in all patients with Wallenberg's syndrome.
CONCLUSION The dissociation between OO and MM responses indicates that both responses are conveyed through different pathways. The generation of the OO response to median nerve stimulation requires the integrity of upper brainstem structures and could be considered helpful in the neurophysiological assessment of patients with mesencephalic lesions.

P9 CLINICAL AND ELECTROPHYSIOLOGICAL STUDIES IN MOEBIUS SYNDROME

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OBJECTIVE Moebius syndrome is a congenital disorder, characterised by complete or partial bilateral VII nerve palsy, variably associated with other cranial nerve palsies. The purpose of the present study was to investigate the facial muscles and the excitatory and inhibitory trigemino-facial reflexes by EMG and neurophysiological techniques in patients with Moebius syndrome.
METHODS we examined 17 patients, 10 females and 7 males, aged 6 - 47 years. The neurophysiological assessment consisted of: a) blink reflex (BR); b) M response of the facial nerve; c) inhibitory trigemino-facial reflexes in perioral muscles; d) concentric needle EMG of facial muscles; e) Jaw reflex and masseteric silent period.
RESULTS The BR was absent bilaterally in 8 and unilaterally in 7 patients. The reflex responses when present had normal latencies. R2-like responses were present in perioral muscles in most patients. The inhibitory trigemino-facial reflex was present in spared perioral muscles (depressor anguli oris and/or levator labii superioris) in 9 out of 11 cases, with normal latency and duration. No spontaneous activity was evident on needle EMG examination of facial muscles. In 10 patients we observed marked neurogenic changes of motor units (MUs); in 2 patients MUs had low amplitude and short duration, mainly with simple form and poor voluntary recruitment. Tongue muscles were weak and hypotrophic in 8 cases (bilaterally in 4 and unilaterally in 4). Masticatory muscles were clinically and electrophysiologically affected in 1 case only.
CONCLUSION In Moebius syndrome several sites of abnormalities have been suggested at various levels, from brainstem nuclei to the cranial musculature. In our cases the facial muscles were clinically affected with partial sparing mainly of the lower facial muscles. The EMG abnormalities were heterogeneous suggesting variable pathogenetic mechanisms. The absence in all patients of spontaneous activity on needle EMG seems to confirm the non-evolutive features of the disease. Excitatory and inhibitory trigemino-facial reflexes were normal in surviving muscles, with some hyperexcitability of the blink reflex.

P10 DIFFERENCES BETWEEN THE EFFECTS OF ELECTRICAL AND MECHANICAL STIMULI ON PAIN PERCEPTION AND LASER EVOKED POTENTIALS

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Interference between afferent volleys of different sensory modalities is the basis of some treatments of pain. Transcutaneous electrical nerve stimulation (TENS) uses high frequency low intensity electrical stimuli to diminish the pain sensation. Laser stimuli is capable of inducing controlled pain stimulation. Therefore, we have investigated the effects of electrical and mechanical stimuli on the pain sensation induced by a laser stimulus. Also, we have examined the possible correlate between pain sensation and late evoked potentials induced by laser stimuli conditioned by the preceding stimuli of other sensory modality. The study was done in 4 healthy volunteers, aged 28 to 53 years of age. They were lying relaxed in a bed with surface recording electrodes in Cz with reference to both ears. Pain stimuli were laser CO2 stimuli (15 watts intensity; 10.6 μm wavelength; 8 ms stimulus duration; 6.25 mm2 skin area) directed to the dorsum of the hand. Laser stimuli were applied either alone (control condition) or together with an electrical stimulus to the 3rd finger (test electrical condition) or a mechanical tap to the first dorsal interosseous space (test mechanical condition). The laser-induced pain sensation was measured with a visual analogic scale (VAS) ranging from 0 (no pain) to 10 (intolerable pain). The amplitude of the laser evoked potential was measured peak to peak. The electrical stimulus was incapable of modifying the subjective perception of pinprick induced by the laser (mean of 3.8 in control condition and 3.6 in test electrical condition). However, the mechanical stimulus reduced the pain sensation significantly (mean of 3.6 in control condition and of 2.7 in test mechanical condition). Similarly, the amplitude of the laser evoked potentials reduced significantly in test mechanical condition in comparison to test electrical condition (t-test, $p < 0.01$). The results of our study suggest a different effect of different sensory modalities on pain perception and laser evoked potentials. The interference of pain sensation induced by mechanical stimulus in comparison to the electrical stimulus may be due to a longer lasting and more disperse volley reaching spinal cord, brainstem and cerebral sites of sensorimotor integration.

P11 PREPULSE MODULATION OF THE STARTLE REACTION DURING PREPARATION FOR MOVEMENT EXECUTION

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A relatively weak sensory signal inhibits the startle reaction when applied at about 100 ms before the stimulus, a phenomenon known as prepulse inhibition. In the experiments presented here we aimed at investigating whether prepulse inhibition was still effective during preparation for execution of a ballistic movement. The combination between a startle and the voluntary commands causes two facilitory effects: An enhancement of the startle response, and a shortening of the reaction time. Therefore, we considered that the effects of prepulse inhibition during motor preparation, if apparent, they could consist in a decrease of the size of the startle response, a reduction in the startle-induced shortening of the reaction time, or both. Eight healthy volunteers were presented with different combinations of stimuli in the context of a visual simple reaction time task. Low intensity electrical shocks to the middle finger were used as somatosensory prepulse stimuli (Prep), and loud auditory stimuli were used as startling stimuli (Start). We recorded the EMG activity of orbicularis oculi and sternocleidomastoid muscles to assess the startle response, and of the wrist extensor muscles to assess the reaction time. Subjects were asked to react to the visual stimulus (React), by pressing a button with their right hand. They were warned that the visual cue could actually be presented on its own or associated with any possible combination of Prep and Start, but we emphasized that they were required to react only to the visual cue. Prep, presented 100 ms before Start, caused a significant decrease of, or completely abolished, the startle response. Start, presented together with React, caused a significant shortening of reaction time, and a persistent startle response. When Prep preceded the combination Start-React, the startle response was suppressed, but the startle-induced reaction time shortening was unchanged, with respect to StartReact trials without Prep. Our results indicate that prepulse inhibition does not act on the startle-induced reaction time shortening that takes place during motor preparation for a ballistic reaction. The method used here demonstrates that the startle reaction and the startle-induced reaction time shortening are two different effects of a startling acoustic stimulus due, probably, to partially different physiological mechanisms.

P12 ACTIVITY INDUCED IN THE ORBICULARIS OCULI MUSCLES BY DEEP BRAIN STIMULATION IN PATIENTS WITH PARKINSON'S DISEASE

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A blink reflex can be induced in humans by stimuli of various sensory modalities. The most constant response recorded in the orbicularis oculi (OOc) by surface EMG electrodes is a long latency (at about 40 ms) bilateral response known as the R2. Electrical stimulation of the supraorbital nerve induces also a shorter latency ipsilateral R1 (at about 10 ms). We have had the opportunity to examine the activity induced in the orbicularis oculi by an electrical stimulus delivered with the electrode inserted in the subthalamic nucleus (STN) for deep brain stimulation (DBS) treatment in 4 patients with Parkinson's disease. Single unilateral DBS induced several responses. A short latency (3.1 ± 0.2 ms) small amplitude smooth response was recorded in the ipsilateral OOc. The response was more likely obtained when the stimulus was delivered using the lead of the electrode tip as the cathode. A bilateral short latency response was recorded at a latency of 8.7 ± 1.2 ms, with higher amplitude in the side contralateral to the stimulation. Occasionally, this response was only apparent in the contralateral OOc. Another bilateral response was recorded at a latency of 38.6 ± 4.5 ms, compatible with the R2 response, which size was similar in both sides. Using the DBS as a prepulse for the classical supraorbital nerve electrically induced blink reflex caused the R2 response to inhibit at interstimulus intervals of 5 to 20 ms. The data obtained in these patients suggest the following comments. The small ipsilateral short latency response could be due to recording of volume-conducted activity from extraocular muscles. The short latency response, which was larger in the contralateral side was probably due to activation of the cortico-nuclear tract, since its latency is comparable to that of the motor evoked potentials obtained with transcranial magnetic stimulation. The long latency bilateral response is probably due to activation of circuits impinging on the reticular formation, with projections to bilateral facial nuclei. The effects of DBS as prepulses for the supraorbital nerve electrically induced blink reflex may be attributed to activation of circuits responsible for prepulse inhibition. The pedunculopontine tegmental nucleus (PPTgN) is considered to be an important part of this circuit, and there are projections from the STN to the PPTgN that could have been activated by DBS. More neurophysiological studies are required to fully comprehend the effects of DBS on many different circuits involving the capsula internal and the upper brainstem.

P13 TRIGEMINOCERVICAL REFLEX AND BLINK REFLEX IN MULTIPLE SCLEROSIS

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OBJECTIVE The aim of the present study was to determine the trigeminocervical reflex and blink reflex alterations in definite multiple sclerosis (MS) patients according to the criteria of Poser.
METHODS Trigeminocervical reflexes, recorded from semispinalis capitis muscle in the posterior neck were studied in 46 definite multiple sclerosis patients (mean age ± standard deviation) (32.54 ± 11.21) and 44 healthy volunteers (37.23 ± 12.39) in response to electrical stimulation of the supraorbital trigeminal nerve. The C3 latencies of trigeminocervical reflex were measured. Blink reflex responses were recorded using a surface electrode placed on the lower lateral aspect of the orbicularis oculi muscle with a reference electrode on the lateral surface of the nose and a ground electrode around the arm. Right and left supraorbital nerves were stimulated electrically with bipolar surface electrodes.
RESULTS In MS patients; C3 latency was 57.06 ± 19.3 ms ipsilaterally and 54.43 ± 17.2 ms contralaterally. In healthy volunteers; C3 latency was 47.75 ± 5.05 ms ipsilaterally and 47.03 ± 5.41 contralaterally. The difference between patients and healthy volunteers was significant ($p < 0.002$ for ipsilateral C3 latency and $p < 0.001$ for contralateral C3 latency. The results were evaluated statistically using unpaired Student t test and p less than 0.05 was considered significant.). In contrast, the R1, R2I and R2C blink reflex values did not differ significantly MS patients and normal controls ($p > 0.2$).
CONCLUSION The trigeminocervical reflex may help in disclosing and localising brainstem lesions. These findings suggest the difference of central pathways generating the trigeminocervical reflex and blink reflex.

P14 CLINICAL AND NEUROPHYSIOLOGICAL EVALUATION OF POSTHERPETIC NEURALGIA. PRELIMINARY RESULTS

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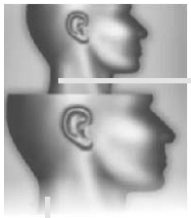
INTRODUCTION We aimed at gaining information on pathopysiology of postherpetic neuralgia (PHN) by performing clinical examination and recording blink reflexes and laser evoked potentials (LEPs) in patients with PHN. We present here the preliminary results of this study.

METHODS In 12 patients with supraorbital PHN we performed a standard clinical examination and investigated sensory disturbances such as hypoestesia, disesthesia, pruritus, and spontaneous and evoked pains. The intensity of sensory disturbances and pains was assessed with the Likert scale. In all patients we recorded the blink reflex, which is mediated by Ab fibers. Furthermore, using a Nd:YAP laser stimulator we recorded LEPs related to Ad and C fibers activation after supraorbital stimulation. We also sought possible correlations between neurophysiological measures and pain, age, and duration of disease.

RESULTS The laser perceptive threshold was higher and the LEP amplitude lower in the affected territories than on the contralateral side ($p < 0.02$). Two patients, with a pain intensity score £ 2, had no neurophysiological abnormalities. The correlation between pain intensity and LEP abnormalities approached statistical significance ($p = 0.08$). Regarding correlations with the type of pain, two patients with mechanical dynamic allodynia as their predominant pain complaint, and two patients with paroxysmal pain, had normal C-LEPs and only slightly abnormal Ad-LEPs and blink reflexes. Six patients with constant burning pain had all the responses abnormal (with the blink reflex less affected than LEPs).

CONCLUSIONS The finding that patients with constant burning pain as their main complaint had more severe abnormalities in all kinds of responses than patients with allodynia or paroxysmal pain suggests a deafferentation mechanism for the former type of pain. The complete sparing of C afferents found in patients with paroxysmal pain or allodynia suggests that other mechanisms (e.g. hyperexcitable nociceptors or fibres) should be responsible for these types of pain. The lack of significant correlations is probably due to the small number of patients; we are keeping on collecting more patients.



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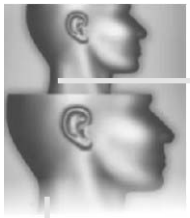

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