ABSTRACTS

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PHYSIOLOGY OF MOVEMENT CONTROL

Brain stem control of eye movements

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Here we review the essential brain stem circuitry generating saccades. In addition we develop a conceptual scheme for understanding how saccade speed is determined, and how saccadic oscillations (flutter and opsoclonus) are both prevented when fixation is required, and released in pathological circumstances. We introduce new ideas about how the ion channel kinetics of the membranes of brain stem burst neurons (which generate saccades) determine saccade properties with potential therapeutic implications. We illustrate these principles with videos of patients with various disorders of saccade speed, accuracy and stability.

3-D brainstem mapping

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For an innovative approach to MR-based *in vivo* brain stem mapping, we prospectively recruited 265 patients with signs and symptoms suspective of acute brain stem ischemia. All patients underwent standardized MR-imaging. For statistical analysis individual MRI lesions were normalized according to brain stem outlines and anatomical landmarks and imported in a three-dimensional voxel-based anatomical model based on data from several topometric and stereotactic atlases. Based on this mapping model several functional/anatomical correlation analyses were performed.

Firstly, we report a correlation analysis on the somatopic order of the corticospinal tract. In 41 patients with motor hemiparesis, we found the greatest level of significance between the pontomesencephalic junction and the mid pons. Lesion location was significantly more dorsal in patients with hemiparesis affecting more proximal muscles and was significantly more ventral in patients with predominantly distal limb paresis. Comparison of magnetic resonance lesion from patients with paresis predominantly affecting arm or leg did not show significant topographical differences. We conclude that a topographical arm/leg distribution of corticospinal fibers is abruptly broken down as the descending corticospinal tract traverses the pons. Corticospinal fibers, however, follow a somatotopical order in the pons with fibers controlling proximal muscles being located close to the reticular formation in the dorsal pontine base, and thus more dorsal than the fibers controlling further distal muscle groups.

Secondly, we report on a correlation analysis in 49 patients with acute hemiataxia. According to the mapping analysis, ataxia following brainstem infarction may reflect three different pathophysiological mechanisms. Ipsilateral hemiataxia was due to dorsolateral medullary infarctions that resulted in a lesion of the dorsal spinocerebellar tract and the inferior cerebellar peduncle conveying afferent information. Pontine lesions caused contralateral and not bilateral ataxia presumably due to major damage to the descending cortico-pontine projections and pontine base nuclei, while already crossed ponto-cerebellar fibres were not completely interrupted. Finally, bilateral ataxia probably reflected a lesion of the dentate-rubro-thalamic tract and thus represented damage of cerebellar outflow on a central, rostral pontomesencephalic level.

Changes in motor cortex and spinal excitability following pedunculopontine nucleus stimulation in humans

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Objective: The PPN is a brainstem nucleus involved in motor control and locomotion and has emerged as a promising new target for DBS in Parkinson's disease (PD). In order to increase our understanding of the physiology of this structure in conscious human subjects, we studied the effects of PPN stimulation on motor cortex and spinal excitability in planted patients with PD.

Methods: Four PD patients implanted in PPN were studied with the DBS electrode externalized. EMG was recorded from first dorsal interosseous muscle, motor cortex TMS was applied to elicit a 1 mV motor evoked potential (MEP), unconditioned and with prior single stimuli to PPN at interstimulus intervals (ISI) of 2,4,6,8 and 10 ms. H-reflexes were recorded from soleus and flexor carpi radialis with single stimuli and continuous PPN stimulation at 25 Hz. In one patient we recorded scalp evoked EEG potentials during 0.2 Hz PPN stimulation.

Results: Single PPN stimuli inhibited the MEP from the ipsilateral motor cortex by an average of 37% ± 9 maximal for ISI = 4-6 ms. No inhibition was observed of MEP evoked from the contralateral hemisphere. Single PPN stimuli did not alter H-reflex amplitude. However, continuous stimulation at 25 Hz produced a progressive increase in H-reflex amplitude over minutes (average 67% ± 21) and which outlasted PPN stimulation by several minutes. Finally, PPN stimulation produced a cortical evoked potential with an early negative waveform (onset latency 4.6 ms, peak 8 ms, amplitude 0.61 μV) and a later larger positive waveform (onset latency 33 ms, peak 47ms, amplitude 2.2 μV) over the central scalp.

Conclusions: Single PPN stimuli result in ipsilateral motor cortex inhibition and an evoked potential at a similar short latency. These effects may be due to antidromic stimulation of cortico-PPN fibres or activation of adjacent medial lemniscus or cerebellar fibres. The progressive facilitation of H-reflexes during and after 25 Hz PPN stimulation suggests short-term plasticity within descending reticulospinal control of spinal excitability.

Brain stem control of gait and balance

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Normal gait and balance require a delicate balance between many different interacting neuronal systems, located at different “hierarchical levels” in the nervous system. Virtually all levels of the nervous system are required for normal gait and balance. The case is clear for the “lowest” levels (the peripheral nervous system and also the spinal cord, where “pattern generators” are situated that can generate rhythmic stepping movements). The evidence is also accumulating for involvement of the “highest” levels of the nervous system. Indeed, the traditional view that walking and equilibrium are “automatic” motor tasks that require little, if any, higher mental functions is increasingly challenged. In my presentation, I will address the possible contributions of the brain stem, which can be seen as an “intermediate” level where presumably important regulations of both gait and balance are governed. Insights into the role of brain stem structures have been obtained from e.g. focal lesion studies in animals and human patients with specific lesions, for example involving the pedunculopontine nucleus. Other supporting evidence comes from specific manipulations of brain stem functions, e.g. vestibular stimulation techniques. Much is expected from new neuroimaging approaches, using techniques such as functional magnetic resonance imaging to identify patterns of brain activity while persons imagine to stand, walk or run while lying in the scanner.

Contribution of subcortical motor tracts to voluntary movements

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Preparation for a voluntary ballistic movement involves enhancement of excitability in subcortical motor tracts. This occurs in both, simple reaction time (SRT) and in some forms of choice reaction time (CRT). However, little is known about the characteristics of that preparation and, specifically for how long the excitability enhancement takes place and how much voluntary control do we have of it. We used the effects induced by a startling auditory stimulus (SAS) on reaction time (the StartReact effect) as a probe for assessing motor preparation of subcortical tracts. Subjects were asked to make a ballistic wrist extension movement to the presentation of a visual imperative signal (IS). A SAS was applied at random in 25% of trials either at negative intervals (between -50 and –500 ms) or positive intervals (from 0 to 120 ms) with respect to IS. SAS was also applied in a condition of no preparation (control trials). We measured reaction time as the latency of the first burst of EMG activity in the agonist muscle and the magnitude of the startle reaction as the area of the EMG burst recorded from the sternocleidomastoid muscle. SAS induced reaction time shortening in negative and positive intervals, from a mean of -421 ms (SD= -71 ms) until a mean of 44 ms (SD=10 ms) for SRT, and from a mean of -138 ms (SD= 63 ms) to a mean of 52 ms (SD= 18 ms) for CRT. The startle reaction was enhanced with respect to control trials, irrespectively of the interval at which the SAS was applied. These results indicate that preparation of subcortical motor pathways occurs before the execution of ballistic movements. This involves a steady enhancement of the excitability in pathways responsible for the startle reaction. These findings contrast with the reported progressive increase of cortical excitability beginning at about 80 ms before onset of EMG activity. Therefore, preparation for execution of a ballistic movement consists on an increase in excitability of subcortical motor pathways that is kept steady for about 500 ms for SRT and 200 ms for CRT. This can lead to movement execution after increasing cortical excitability or with an appropriate external trigger.

Dysarthria due to ischemic brainstem lesions

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Background: Dysarthria is a frequent symptom of cerebral ischemia. The frequency, localisation and speech characteristics of ischemic brainstem infarcts leading to dysarthria are investigated in a prospective patient series.
Methods: In a prospective study we included 106 consecutive patients with sudden onset of dysarthria due to a single, not space-occupying cerebral infarction confirmed by MRI. Out of these, in the last 64 consecutive patients we investigated the auditory perceptual features using standardized speech samples stored on a digital tape recorder within 72 hours after stroke onset. Speech samples were assessed off-line independently by two experienced speech-language therapists which were unaware of the clinical and neuroradiological findings.
Results: Out of 106 patients, dysarthria was due to a ventral brainstem infarction in 28.3% patients (midbrain: 0.9%, pontomesencephal: 1.9%, pons: 23.8%, pontomedullar: 1.9%). In 10.4% a combined brainstem and cerebellar infarction was responsible for dysarthria. Left-sided lesions were more oftenly (80.0%) found than right-sided infarctions (16.7%). Bilateral infarctions were present in 3.3% of the patients. Additionally, left-sided brainstem lesions were associated with a more severe impairment of speech, articulation and prosody than right-sided lesions (ANOVA, $p<0.001$). Clinically, in patients with pure brainstem infarctions (n=30) dysarthria was most oftenly associated with pyramidal tract signs (facial paresis: n=18, upper limb paresis:n=24, lower limb paresis: n=19), ataxia of stance and gait: n=14, limb ataxia: n=6, hemihypesthesia:n=8, while other typical brainstem signs were only rarely found (nystagmus:n=4, INO:n=2, horner-syndrome: n=2, dysphagia:n=2).
Conclusions: The underlying cause of ischemic dysarthria was a brainstem lesion in only 28.3% of patients. We found that dysarthria was most commonly due to a ventral pontine infarction. The lesion localisation explains the frequent association of dysarthria with pyramidal tract signs and ataxia which is due to a lesion of the cerebro-ponto-cerebellar tract fibres. Left sided lesions were more oftenly responsible for dysarthria and showed a more severe dysarthria and more severely affected articulatory and phonatory abnormalities as compared with the right side, supporting the assumption of a left hemispheric dominance for articulation.

The effect of prepulse stimulation on the post-inhibition EMG rebound following the cutaneous silent period

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Objective: The cutaneous silent period (CSP) is a spinal inhibitory reflex mediated by A-delta fibers. The post-inhibition excitatory electromyographic activity following the CSP ("EMG rebound") has been attributed to resynchronization of motoneurons, but has also been suggested to contain startle reflex activity (SR). The SR is a defence response which is generated following an unexpected intense stimulus in structures located in the caudal brainstem. One important physiological SR characteristic is its suppression by a preceding weak stimulus – a phenomenon called prepulse inhibition (PPI). Our aim was to study whether PPI would diminish the "EMG rebound", thereby providing evidence of startle-like activity contained within the post-inhibition excitatory EMG activity following the CSP. **Methods**: Ten healthy subjects (mean age: 32.7 ± 6.2 years) underwent CSP testing in two conditions, with and without prepulse (PP), "CSP-only" and "CSP-PP". Rectified surface EMG recordings were obtained from right orbicularis oculi (OOc), sternocleidomastoid (SCM), and dominant thenar muscles during thumb abduction with 25% of maximum force. CSPs (number of trials, n = 15) were elicited by ipsilateral noxious digit II (D2) stimulation with 25 times sensory threshold intensity (25ST) every 5 to 15 seconds, randomly preceded by PP stimulation with 2ST (n = 15) applied to ipsilateral digit III (D3). Target muscle activation was continuously monitored with a force transducer. Additional recordings were obtained of the SR following 25ST stimulation to D2 at rest ("SR-only") (n = 7), and following 2ST stimulation to D3 at rest ("PP-only") (n = 3) at random intervals. We measured CSP onset and end latency, CSP duration; mean EMG amplitude during a 100 ms epoch preceding PP, during the CSP, and during a 100 ms epoch following the CSP ("EMG rebound"); and area-under-the curve in OOc and SCM, in single traces which were averaged post-hoc. **Results**: The area of EMG responses in OOc and SCM was significantly larger in the conditions "SR-only" and "CSP-only" in comparison to "PP-only" and "CSP-PP". Group average CSP onset and end latency, CSP duration, and the magnitude of EMG suppression were not influenced by PPI. EMG area during the "EMG rebound" was significantly smaller in "CSP-PP" vs. "CSP-only" ($p = 0.02$). **Conclusion**: Inhibition of the "EMG rebound" by PP stimulation supports the hypothesis that the post-inhibition excitatory EMG activity following the CSP contains SR activity.

Sound-evoked p11/n15 and p16/n21 responses in human masseter muscles originate respectively in activation of vestibular and cochlear receptors

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Objectives: To determine which end organ in the inner ear is the source of the p11/n15 and p16/n21 responses evoked by loud click stimulation in masseter muscle EMG of healthy subjects.
Methods: Following neuro-otological assessment, subjects were divided into: normals (n=9); patients with selective cochlear deafness (n=5); patients with unilateral selective vestibular failure (n=1); patients with mixed disorder (n=5). Masseter responses to clicks (70-100dB NHL, 0.1ms, 3Hz) were investigated in actively contracting muscle.
Results: In normals, 100dB clicks induced bilaterally, in the unrectified mean EMG (unrEMG), a clear p11 wave, but the n15 wave was hardly visible. The p11 wave was absent after 70dB clicks, while a p16 wave appeared. The p11 and p16 waves differed significantly in onset and peak latency, with an average peak latency difference of 4.7±1.2 ms. Rectified mean EMG (rectEMG) showed, at all intensities, an inhibitory deflection corresponding to the p16/n21 wave in the unrEMG. The p11 waves were not significantly different in deaf patients and normals. However, while the n15 wave was always readily detected in the deaf, p16/n21 waves, and their corresponding inhibition in the rectEMG, were absent. The vestibular patient exhibited bilaterally clear p11 waves only when 100dB clicks were delivered bilaterally or to the unaffected ear. Stimulation of the affected ear induced only p16/n21 waves. Mixed patients showed neither waveform when clicks were delivered to the ear with both vestibular and cochlear lesion.
Conclusions: Vestibular and cochlear receptors are responsible respectively for click-induced p11/n15 and p16/n21 waves in active masseter.

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PAIN

Laboratory investigations in trigeminal neuralgia

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Trigeminal neuralgia (TN) may be classified as *classical* TN (with no apparent cause other than vascular compression) and *symptomatic* TN (pain indistinguishable from that of *classical* TN but caused by a demonstrable structural lesion other than vascular compression). TN is a rare disease and secondary TN accounts only for about 1%–2% of cases. Even though vascular compression remains the most studied and supported hypothesis for *classical* TN, several factors may contribute to its development.

Indirect evidence that vascular compression may not be the only cause is that microvascular decompression often fails to provide complete and persistent pain relief.

In patients with *classical* TN, trigeminal reflex testing yields normal responses or, occasionally, mild reflex abnormalities. Conversely, in patients with symptomatic TN, trigeminal reflex testing constantly discloses abnormal responses. Posterior fossa tumours producing mechanical damage to the proximal portion of the trigeminal root, or a demyelinating plaque affecting the intrapontine presynaptic primary afferents near the root entry zone in patients with multiple sclerosis, typically lead to abnormalities of all responses. The short-latency, oligosynaptic reflexes (R1, SP1 and JJ) are more sensitive than the long-latency, polysynaptic reflexes (R2 and SP2) in detecting abnormalities in symptomatic TN. In patients with TN who have undergone trigeminal reflex testing, LEPs can often provide useful complementary diagnostic information. Patients with symptomatic TN and about 50% of those with classical TN have abnormal LEPs. Hence LEPs may indicate trigeminal dysfunction also in patients with normal trigeminal reflexes and no evidence of structural lesions involving the trigeminal system. Possibly because LEPs are mediated by a small number of afferents, they are diagnostically more sensitive than trigeminal reflex testing.

Spinothalamic nociceptive pathways

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The spinothalamic tract (STT) is one of the ascending somatosensory pathways passing through the brainstem. It mediates pain and temperature sensations from skin and deep tissues in the trunk and limbs. Dorsolateral brainstem infarctions mostly affect both the STT and the spinal trigeminal tract and nucleus (STTN), the function of which is assessed by the R2 component of the blink reflex. In some cases, STT and STTN may be affected differentially by small lesions. Therefore, it is useful to have a technique for STT functional assessment available in the clinical neurophysiological workup of patients with brainstem lesions.
STT functions can be assessed by laser-evoked potentials (LEPs). By varying the diameter of the laser beam, peripheral Aδ- and C-fibers can be activated preferentially. LEPs are sensitive to document spinal and brainstem lesions and the efficacy of their treatment.
Cells of origin of the STT are located in superficial (lamina I) and deep dorsal horn (lamina V). There is an old and still ongoing controversy on the relative contributions of these two populations to sensation and to the input into various somatosensory thalamic nuclei that project to different cortical regions.
Recent studies on conduction velocity in the human STT have suggested that the following components may be differentiated:
1) A fast nociceptive and a slow thermoreceptive pathway, both to midcingulate and parasylvian cortex.
2) A very fast pathway to primary somatosensory cortex possibly dominated by lamina V input and less fast pathway to parasylvian and midcingulate cortex, possibly dominated by lamina I input.
This presentation will outline the structure of the spinothalamic tract system, its clinical assessment by laser-evoked potentials, and several case examples.

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Long-term depression of orofacial somatosensory processing

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Long-term depression (LTD) describes sustained decrease of synaptic strength as a model for learning and memory in the nervous system. LTD of trigeminal pain processing recently has been demonstrated by noxious electrical low-frequency stimulation (LFS) of cutaneous afferents. Current studies address LFS parameters and spatial organization of LTD in the trigeminal system.

Electrical test and conditioning (LFS) stimulations were performed by a concentric electrode with a small central cathode and a large ring anode. Electrical test stimulation series consist of 10 to 15 pulses. Stimulus intensity was adjusted to multiples of pain threshold (I_P). Volunteers rated pain perception according to a verbal rating scale (0 to 100). Electromyographical blink reflex (BR) recordings of ipsilateral R2i and contralateral R2c were conducted from both orbicularis oculi muscles.

Stimulus parameters

In 29 healthy volunteers and 120 experiments the influence of various LFS parameters on LTD of pain processing was addressed. LFS with various frequencies (0.5, 1, 2 Hz; 1200 pulses, $4\times I_P$) and number of pulses (300, 600, 1200 pulses; 1 Hz, $4\times I_P$) showed significant LTD of pain perception without statistical group differences. Variation of LFS stimulus intensity with fixed frequency (1 Hz) and number of pulses (1200) resulted in significant LTD effects with $2\times I_P$ and $4\times I_P$ but not with $1\times I_P$. Double application of identical LFS (1 Hz, 1200 pulses, $4\times I_P$) with an interval of 40 min significantly increased level of LTD.

Spatial organization of trigeminal LTD

Ten healthy volunteers participated in three experiments each. BR was elicited by unilateral supraorbital nerve (V1) test stimulation. LFS (1 Hz, 1200 pulses, $3\times I_P$) was applied ipsilaterally or contralaterally in relation to electrical test stimulation. No LFS was performed under control condition. Ipsilateral and contralateral LFS evoked LTD of both R2i and R2c. In contrast to bilateral effects of LFS on BR, exclusively ipsilateral LFS induced LTD on pain perception as compared to control and contralateral LFS. Remote LFS of the right hand dorsum did not induce any decrease of BR and pain perception.

In 10 healthy volunteers the effect of LFS (1 Hz, 1200 pulses, $4\times I_P$) applied to supraorbital (V1), infraorbital (V2), or mental (V3) nerve areas on the V1 evoked BR was addressed. Electrical test stimulation and LFS were applied to the same side of the face. V1 LFS induced LTD of pain

perception and bilateral R2 as compared to all other conditions. V2 and V3 LFS remained without any statistical effect in comparison to control.
Noxious LFS with 1 Hz, 1200 pulses, and an intensity of at least double I_P seems to induce LFS reliably. LTD of electrically evoked pain in V1 needs strictly homotopic LFS. LTD of V1 evoked BR is subject to bilateral V1 LFS. Effects on BR by bilateral V1 LFS prove heterosynaptic mechanisms of LTD. Divergent influence of LFS on pain perception and BR strongly indicates different neural networks at least for R2c that probably involves reflex interneurons but no projection neurons. Further studies will address spatial organization on V2 and V3 levels and interference of different afferent pathways in order to develop a comprehensive concept of synaptic plasticity in the trigeminal system.

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Blink reflexes in orofacial pain conditions

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Examination of the trigemino-facial human blink reflex (BR) can be useful in the diagnosis of lesions along the afferent, central, or efferent pathways of the reflex (Jääskeläinen, 2004a,b; Jääskeläinen et al., 2005). The reflex can be elicited by laser, electrical or mechanical stimulation of skin innervated by branches of the trigeminal nerve (V) (Kimura, 1989; Ellrich et al., 1997), for example over the supra- or infra-orbital foramina or the mental foramen. The V afferent fibers project via the V ganglion to the V brain stem complex, consisting of the V main sensory nucleus and the V spinal tract nucleus (Svensson and Sessle, 2004).
The BR response consists of three components, an early ipsilateral component, R1, and two bilateral components, R2 and R3 (Kimura, 1989; Ellrich and Hopf, 1996). The R2 interneurons are situated in the medullary spinal tract nucleus, where they project to facial motorneurons controlling the orbicularis oculi muscles (Ellrich, 2000) and this component has been used for examinations of the functions of the V nociceptive pathways (e.g. Jääskeläinen et al., 1999; Katsarava et al., 2002; Baad-Hansen et al., 2005; Baad-Hansen et al., 2006; Peddireddy et al., 2005).
In migraine patients, the R2 of the BR is facilitated during attacks, whereas acute sinusitis pain in otherwise healthy persons does not change BR excitability, possibly indicating a dysfunction of endogenous pain inhibitory systems occurs during migraine attacks (Katsarava et al., 2002). In patients with tension type headache (TTH), R2 responses are reduced compared with healthy controls (Peddireddy et al. in preparation). In patients with the chronic orofacial pain condition, atypical facial pain, the BR is abnormal in a large proportion of patients (Jääskeläinen et al., 1999) and in the related condition, atypical odontalgia, the R2 is delayed and decreased compared with healthy subjects (Baad-Hansen et al., 2006). This suggests abnormal processing of trigeminal nociceptive information in these clinical orofacial pain conditions. New data will be presented on BR in patients with temporomandibular disorders (TMD) (Abrahamsen et al., ongoing study).
Also experimental pain modulates the R2 response in patients and controls, probably through activation of endogenous pain inhibitory systems (Baad-Hansen et al., 2006; Peddireddy et al., 2005; Ellrich and Treede, 1998; Drummond, 2003). Both remote painful stimuli and trigeminal stimuli,

for example application of capsaicin on the gingiva, can cause inhibition of R2 responses.
In conclusion, the R2 component of the BR is abnormal in patients with orofacial pain conditions with different underlying pain mechanisms and therefore, this technique can not be used to distinguish between conditions. This needs to be kept in mind when the data are interpreted.

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The trigemino facial inhibitory reflex: physiology, recording technique and topodiagnostic use

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Objective: To describe some physiopathological aspects and a standardized technique for the clinical use of the trigemino-facial inhibitory reflex (TFIR) and its abnormalities in patients with brainstem lesions.
Methods: In 20 healthy subjects aged 20-60 years the TFIR was recorded bilaterally with concentric needle electrodes from the depressor anguli oris (DAO) muscle during voluntary activation of the muscle. The insertion point was a spot localized approximately 1 cm upwards and then 1 cm laterally from the mandible margin starting on a vertical line intersecting the modiolus. The mentalis nerve was stimulated via surface electrodes. The recovery cycle was studied at interstimulus intervals (ISIs) of 200, 350 and 500 ms. Conditioning of facial nerve F-waves in the DAO muscle by trigeminal stimuli on the mental nerve was investigated. Finally the TFIR was recorded in patients with lateral medullary lesions.
Results: Upper normal limits (mean + 3 SD)of latency of the ipsilateral and contralateral TFIR were of 65 ms. The recovery was 65 % at the ISI of 200 ms and 100% at 500 ms. The frequency of facial nerve F-waves was uninfluenced by conditioning stimuli. In patients we observed abnormalities consisting in ipsilateral or bilateral absence of the TFIR for ipsilesional stimuli, while contralesional stimuli always elicited a normal TFIR.
Conclusions: We describe a standardized technique and normal values for TFIR recording. The reflex is extremely robust showing recovery at short ISIs. Its central pathway includes the lateral medulla oblongata, analogously to the R2 component of the blink reflex.

The role of the brain stem in central sensitisation in humans

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The abnormal processing of somatosensory inputs in the central nervous system (also called central sensitization) is the mechanism accounting for the enhanced pain sensitivity in the skin surrounding tissue injury (secondary hyperalgesia). Secondary hyperalgesia shares clinical characteristics with neurogenic hyperalgesia in patients with neuropathic pain. This lecture will describe the evidence obtained from two human functional MRI studies for a central role of the brainstem in this state of central sensitisation. (1) The patterns of brain activation found in previous metabolic neuroimaging studies of experimental hyperalgesia relates not only to the process of central sensitisation, but also to the unavoidable increase in pain perception that occurs during mechanical stimulation of the hyperalgesic area, thus making impossible to dissect brain areas specifically involved in central sensitisation. By producing a state of experimental central sensitisation in normal volunteers (using the intraepidermal injection of the vanilloid capsaicin), and by applying a graded mechanical stimulation of A-delta fibers we were able to compare the functional MRI brain responses during nociceptive stimulation that was perceived as being of equal intensity in both normal and centrally-sensitised state. We showed that the only brain region significantly more active during central sensitisation – independently of the differences in intensity of perception – was the brainstem. (2) Using functional MRI in normal volunteers, we also studied the pharmacological modulation of brain activity in response to nociceptive mechanical stimulation of normal skin and capsaicin-induced secondary hyperalgesia (an experimental model of neuropathic pain). The administration of a single oral dose gabapentin, a drug effective in treating neuropathic pain states, produced a significant reduction of the activation in the brainstem, only during central sensitisation. This significant interaction between the presence of central sensitisation and the drug administration supports the concept that the brainstem plays a crucial role in central sensitisation, and that gabapentin is effective in relieving the symptoms of secondary hyperalgesia through a modulatory action at brainstem level.

Bilateral brainstem activation by noxious thermal stimulation in the face

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Objectives: Afferent input from craniofacial nociceptors bilaterally projects to the spinal trigeminal nucleus (STN) in rodents. Contralateral sensory deficits in Wallenberg´s lateral medullary syndrome suggest bilateral sensory processing in human brainstem as well.
Methods: Nociceptive processing in the brainstem was investigated by functional magnetic resonance imaging (fMRI) in 18 healthy volunteers (21 to 31 years). Noxious heat stimuli (39, 43, 46°C) were applied by a Peltier type thermode to the left forehead (V1) and the left mental region (V3). Analysis of fMRI data was performed with SPM2 and BrainVoyager. Thereafter, a region-of-interest approach was applied to select activation in STN.
Results: Noxious heat evoked significant bilateral activation in STN ($p<0.01$). Contralateral activation was more frequent during stimulation of V1 than of V3 region. Level of brainstem activation increased with temperature. Whereas activation by V1 stimulation was located in caudal STN, V3 stimulation induced activity in more rostral parts of STN.
Conclusions: FMRI data in man suggest bilateral brainstem activation during painful heat in the face. Contralateral brainstem activity seems to be more pronounced by V1 stimulation as compared to V3. These results indicate similar nociceptive processing in man and rodents and may explain clinical findings.

Saturday, 13th October

IMAGING

High-resolution functional and structural imaging of the brain stem and spinal cord

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Until recently it has been difficult to obtain reliable objective information from normal subjects and patients regarding their subjective pain experience. Relating specific neurophysiological markers to perceptual changes induced by pharmacological agents and identifying their site of action within the human nervous system has been a major goal for drug discovery. With the advent of functional neuroimaging methods, such as functional magnetic resonance imaging (FMRI), positron emission tomography (PET) and electroencephalography (EEG), we and others have been able to show robust and reproducible activation in response to nociceptive stimuli within the human brain and spinal cord. This activation can be related to what the subject describes and issues such as how anxiety, attention, distraction and anticipation alter pain perception can be better understood an a neuroanatomical level.

We have performed several experiments that have specifically isolated areas of brainstem and cortex that are central to the processes of expecting pain, being anxious about pain and altering your attention to pain (1-4). Furthermore, the central relevance of descending brainstem modulatory pathways in the generation and maintenance of chronic pain states is increasingly recognised (5) and advances in our ability to image, from a structural and functional perspective, this challenging area have been made in recent years (6,7). Many studies are now relating these basic science findings to clinical pain disorders (8,9). Furthermore, there have been recent advances in our ability to image functional activation in the human spinal cord (10). This talk will enable the audience to appreciate the value of functional imaging methods to directly examine pain in human subjects and patients, in addition to an investigation of drug effects targeted for pain alleviation.

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Brain stem and cerebellar activation during optokinetic stimulation

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Earlier fMRI studies during horizontal optokinetic nystagmus (OKN) showed bilateral activations of a cortical network in the primary visual cortex, motion-sensitive areas in the temporo-occipital cortex as well as in cortical eye fields [1, 2]. From animal studies it is known that certain brainstem nuclei and cerebellar areas are involved in the processing of ocular motor answers. The aim of this fMRI study was to identify and differentiate brain stem and cerebellar areas involved in the generation of horizontal (hOKN) and vertical OKN (vOKN) in humans [3]. In nine healthy volunteers the protocol included 320 volumes each of 40 slices of a T2*-weighted EPI sequence in alternating blocks of ten images at rest (looking at stationary target) and ten during either small-field hOKN or vOKN (no self-motion perception). During hOKN and vOKN activations were found in the pretectum and posterior thalamus bilaterally. In addition, during hOKN activations were located in the dorsal medullary and pontine brain stem, whereas during vOKN they were found in the paramedian ponto-mesencephalic brain stem. Under both stimulation conditions cerebellar activations were located in the superior/inferior semilunar, simple, and quadrangular lobules, flocculus, as well as in the pyramis (VIIa), declive (VI), and folium (VII) of vermis.
This study shows activations in the brain stem identically located for both stimulation directions, which can be attributed to the nuclei of the optic tract (NOT) and accessory optic system (AOS) situated in the transition zone between the posterior thalamus and the midbrain. These neuronal substrates are known to be responsible for the execution of OKN. For hOKN, additional areas can be attributed to the dorsal pontine nuclei, the PPRF, and probably perihypoglossal area. For vOKN, additional areas could be attributed to ocular motor nuclei (III) and the rostral interstitial nucleus of MLF (riMLF). The latter might reflect the involvement of the saccadic system in fast phases. These results are discussed in comparison to the activation pattern during vestibular stimulation by vestibular evoked myogenic potentials.

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Functional imaging in migraine

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Regarding the pathophysiology of the migraine attack, the early functional imaging work using PET demonstrated a consistent increase in rCBF in the rostral brainstem which persisted, even after sumatriptan had induced complete relief from headache, nausea, phonophobia and photophobia (1). This increase was not seen outside the attack and has been confirmed in a single case study, which further refined the activation to the dorsal rostral pons (2). Dysfunction of the regulation of brainstem nuclei involved in anti-nociception, extra- and intra-cerebral vascular control and sensory-gating provides a far reaching explanation for many of the facets of migraine. The importance of the brainstem for the genesis of migraine is further underlined by reports of non-headache patients who developed migraine-like episodes after stereotactic placement of electrodes in the PAG for treatment of chronic pain (3, 4). Certainly, brainstem activation per se has been reported in many pain conditions other than migraine, including tonic cold stimulation (5), laser induced pain (6), painful touch produced by a stylus (7) and even experiencing empathy in case someone else suffers pain (8). However, the brainstem activation in almost all these studies appears to be caudal extension of periaqueductal grey activation rather than a discrete area of pontine activation.

Recently, Goadsby and co-workers have reinforced the view that migraine is a subcortical disorder with significant brainstem involvement by investigating five patients during a spontaneous migraine attack using $H_2{}^{15}O$-labelled PET and providing evidence for dorsal pontine activation in migraine (9). Furthermore, the same group defined the laterality of brainstem activation using $H_2{}^{15}O$-labelled PET in 24 patients during nitroglycerine- induced migraine attacks. They demonstrated ipsilateral activation in the dorsal pons in strictly unilateral migraine attacks whereas a bilateral activation was found in patients suffering from bilateral headaches (10). Also recently, eight patients with chronic migraine (> 15 days per month of attacks of migraine without aura) (11), who had shown a marked beneficial response to implanted bilateral suboccipital stimulators, were studied using PET. Comparing stimulation (improved headache) with no stimulation (headache) demonstrated significant changes in rCBF in the dorsal rostral pons, anterior cingulate cortex (ACC) and cuneus, correlated to pain scores (12). The localization and persistence of activity during stimulation was exactly consistent with the dorsal pontine region activated in episodic migraine and suggests a crucial role for this structure in the pathophysiology of chronic migraine.

A recent brief abstract reported the findings in a PET study in seven migraineurs (13). The patients were imaged under three conditions: within six hours after a spontaneous migraine attack onset; after headache relief by subcutaneous sumatriptan 6 mg; and during an attack-free interval. The authors reported significant activations not only in the midbrain and pons but also the hypothalamus, which persisted after headache relief by sumatriptan. Specific hypothalamic activation has been reported in the trigeminal autonomic cephalgias (14-16) but has hitherto not been observed in migraine. A major limitation of this study is that it did not have a control group and is, therefore, potentially confounded by order- and

session-effects. This issue is crucial since brain activation in other pain states, such as hypothalamic activation with cardiac pain (17), has subsequently been shown to be due to an order effect when an appropriate control group was included (18).

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Functional brainstem infarction studies: previous results and new ways of lesion coregistration

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In comparison to lesion studies in the cerebral hemispheres, which were the first tool to map functional anatomy, similar investigations of brainstem lesions are rare. A reason may be that in spite of the fact that lesions affect densely packed nuclei and tracts, patients with isolated brain stem infarctions usually have a good prognosis as compared to supratentorial stroke, and post-mortem examinations are rare.
Eight years ago, we prospectively collected neurological, electrophysiological, and imaging data from over 200 patients with acute brainstem infarctions. Using diffusion weighted and high-resolution T2 weighted MR imaging, lesions were outlined, transferred to an anatomical atlas (Schaltenbrand & Wahren), and correlated with the functional deficit. We thus got information about somatotopic organization of the corticospinal tract and sympathetic pathways in the brainstem, about affection of body lateropulsion, induction of chronic facial pain and masseter reflex anomalies in medullary infarcts, about topography of the R1 and R2 components of the blink reflex and other brainstem reflex circuits etc.
Nowadays, new diffusion tensor imaging (DTI) evaluation methods allow direct demonstration of major brainstem tracts, and some errors resulting from the MRI-atlas transformation of lesions may be eliminated. Results of our previous functional brainstem infarction study are summarized and first results of the co-registration of brainstem infarctions into colour-coded reference DTI templates are given.

Saccular activations in the brainstem and the cerebellum (fMRI)

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The aim of this fMRI study was to determine whether vestibular evoked myogenic potentials (VEMP) which are a routine diagnostic instrument for sacculus function for the past years can activate areas other than the vestibular nuclei in the brainstem and the cerebellum in humans. If so could one also demonstrate a dominant saccular input from either ear?
Therefore, the differential effects of unilateral VEMP stimulation on activation of the brainstem and cerebellum were studied in 18 volunteers in a clinical 1.5 T scanner. Each volunteer underwent three randomised sessions: 1. One with a 95 dB 500 Hz VEMP tone burst signal. 2. One control session with a similar sub threshold 65 dB 500 Hz tone burst signal. 3. The third control trial consisted of a 95 dB white noise signal. Random effects statistical analysis was done with SPM2 ($p < 0.005$, uncorrected).
Unilateral saccular stimulation from the right ear gave activations only in the right dentate nucleus and the nodulus. These could not be seen after stimulation of the left ear. But the VEMP stimulation from either side resulted in a significant deactivation of the declive and culmen bilaterally. In a paired t-test right side vs left side, which excluded the auditory effects, significant activations were found in the right dentate nucleus, the nodulus, the right inferior semilunar lobule and the inferior vermis.
This is the first demonstration of otolith activations in humans in the brainstem and cerebellum by means of fMRI. We found a dominance for the saccular input from the right ear. Monaural otolith stimulation from the right side in right-handers caused significant activation in the nodulus and right dentate nucleus and simultaneous deactivations of the culmen and declive.

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Functional imaging in automatic movements

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In learning a motor skill, there are several phases of ability. There is initial learning, consolidation, refinement and then automaticity. At the automatic stage, the movement can be done well without thinking much about it. Experimentally, automaticity is reached when a second task done at the same time does not lead to deterioration in the learned task. Colloquially, people sometimes think about automatic movements as functioning at brain stem level. Evidence for changes of cortical activity with automaticity has been obtained using functional magnetic resonance imaging (Wu, Kansaku & Hallett 2004). Normal subjects were asked to practice some self-initiated, self-paced, memorized sequential finger movements with different complexity until they could perform the tasks automatically. The secondary task was a letter-counting task where subjects were asked to identify the number of times a target letter from the letter sequences was seen. The data showed that both before and after automaticity was achieved, sequential movements activated similar brain regions. However, there was less activity in bilateral cerebellum, presupplementary motor area, cingulate cortex, left caudate nucleus, premotor cortex, parietal cortex, and prefrontal cortex during the automatic stage. More recent results show that these regions are more strongly connected at this stage. There is no evidence for increased brain stem activity with automaticity. Older subjects have more difficulty with automaticity than do younger subjects and they deactivate less (Wu & Hallett 2005). Patients with Parkinson Disease have even more difficulty and they deactivate less than the older subjects (Wu & Hallett 2005).

Are signs of ocular tilt reaction in cerebellar lesions mediated by the dentate nucleus?

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Objective: A sensitive clinical sign of a vestibular tone imbalance in the roll plane is the ocular tilt reaction (OTR), a combination of head and perceptual tilts, vertical divergence of the eyes (skew deviation, SD) and ocular torsion (OT) in the same direction. While these signs are regularly seen in patients with acute unilateral brainstem lesions affecting central vestibular pathways, only a few case studies are available on its occurrence in patients with cerebellar lesions.[1, 2, 3] Thus, the question arises whether contra- and/or ipsiversive tilts of the perceived vertical and the other signs of OTR, such as SD and OT can be found in pure cerebellar lesions and if so, which cerebellar structures may be involved. **Methods:** We used lesion mapping technique in MRI and CT in a total of 36 patients with acute circumscribed cerebellar strokes all showing a significant tilt of the perceived subjective visual vertical (SVV). Twenty-seven patients had a contraversive tilt of the SVV; they were compared to 9 patients with ipsiversive tilts of the SVV. Both groups were comparable with respect to age, acuteness of lesion, size of lesion, and the occurrence of additional central ocular motor symptoms such as OT and SD. In an additional analysis we further compared the lesions of the two subgroups with contra- and ipsiversive OT and SD. **Result:** MRI/CT lesion mapping revealed that in patients showing contraversive signs of OTR in general and contraversive SVV tilts in particular the dentate nucleus was the commonly damaged structure. Ipsiversive signs of OTR were associated with lesions of the biventer lobule, the middle cerebellar peduncle, the tonsil, and the inferior semilunar lobule. **Conclusion:** Our data give evidence that OTR is a common sign in patients with pure unilateral cerebellar lesions. Therefore, OTR can not only indicate acute unilateral brainstem, thalamic or peripheral vestibular lesions but also cerebellar lesions. Furthermore, these data suggest that the dentate nucleus is the critical anatomical structure within the cerebellum belonging to a network involved in the perception of verticality. A lesion of the dentate nucleus causes tilts of the SVV in the contraversive direction, i.e., a vestibular tone imbalance to the contralateral side, whereas cerebellar lesions excluding the dentate nucleus induced a tone imbalance to the ipsilesional side.

Saturday, 13th October

“MEET THE EXPERT”

Brainstem-derived tremor: diagnosis and treatment

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Despite considerable efforts the origin of tremor is still unknown. The reason for this may be that such a dynamic movement disorder is unlikely to be generated within a single nucleus or structure. It is much more plausible that neuronal circuits are causing the abnormal rhythmicity. Good examples for such neuronal networks can be demonstrated in slice experiments of rat brains. The transfer of such models into the pathophysiological models of human tremors remains plausible but still speculative.
So far we are not really able to describe the location where tremors start but we know that almost all tremors must have a considerable brainstem contribution because lesions in the brainstem can either cause tremors, they can abolish tremors or they can modulate tremors. Such modulations are well-described for essential tremor, Parkinsonian tremor, cerebellar tremor, orthostatic tremor and palatal tremor. This explains the selection of tremors for this presentation. Some new developments for the understanding of cerebellar tremor and another new drug trial is available. Treatments for Parkinsonian tremor are also improving. Important new developments have taken place for essential tremor. New concepts are available with respect to its causes and some new drugs are available.

Clinical usefulness of brain stem reflexes

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Brain stem reflexes can be elicited and recorded with routine EMG equipment. Not all these reflexes are useful in clinical neurology. But those that are early (R1) and late (R2) blink reflex, early (SP1) and late (SP2) masseter inhibitory reflex, and jaw jerk (JJ) exhibit distinct patterns of abnormality that have clinical diagnostic and localizing value in various diseases. A schematic summary of abnormality patterns is provided in the Table.

Lesion/Disease	Abnormal responses to ipsilateral stimulation	Abnormal responses to contralateral stimulation
1.Facial neuropathy	R1 and d-R2	c-R2
2.Focal trigeminal neuropathy (distal)	either R1 or SP1 or JJ (R2 or SP2)	Normal
3.Focal trigeminal neuropathy (retrogasserian and root entry zone)	R1 and SP1 and JJ (R2 and SP2)	Normal
4.Sensory polyneuropathy	R1 and SP1 and JJ (R2 and SP2)	R1 and SP1 and JJ (R2 and SP2)
5.Sensory-motor polyneuropathy	All abnormal	All abnormal
6.Ganglionopathy	R1 and SP1 (R2 and SP2)	R1 and SP1 (R2 and SP2)
7.Dorsal midbrain lesion	JJ	Normal
8.Dorsal pontine lesion	All can be abnormal according to lesion site	Normal
9.Midline medullary lesion	c-R2 and c-SP2	c-R2 and c-SP2
10.Lateral medullary lesion	d- and c-R2 d- and c-SP2	Normal
11.Suprasegmental (pyramidal)	Normal	d- and c-R2 (d- and c-SP2)
12.Suprasegmental (extrapyramidal)	Enhanced excitability of R2 and SP2	Enhanced excitability of R2 and SP2

Clinical findings with brain stem microinfarcts

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This presentation reviews the literature on clinical signs of small brain stem infarcts. There is a significant number of individual patients with cranial nerve palsies as the only clinical sign of MRI- and, less frequently, CT-documented small brain stem infarcts. Such microinfarcts most commonly involve the 3rd and 6th nerves and, less frequently, the 4th, 5th, 7th, and 8th nerves. The clinical significance of such infarcts may be underestimated if the diagnosis is based solely on MRI-documented lesions. Abnormal electrophysiologic findings indicating brain stem lesions may be independent of MRI-documented morphological lesions. Small pontine and mesencephalic infarctions are probably the main cause of non-traumatic cranial nerve palsies in the middle-aged and elderly population. Isolated internuclear ophthalmoplgia is another sign of small brain stem infarcts and seems to occur as frequent as 3rd and 6th nerve palsies. Other clinical manifestations of brain stem microinfarcts are rare and include isolated voluntary facial paresis, isolated total tongue paralysis, central paroxysmal positional vertigo, upbeat nystagmus, and sudden deafness with vertigo.

Management of basilar artery occlusion

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Acute basilar artery occlusion is mainly caused by two different mechanisms: basilar embolism with sudden onset of severe clinical symptoms like loss of consciousness, tetraparesis and loss of brain stem reflexes, and basilar atherothrombosis with warning symtoms like dizziness and double vision for hours to days before the arteriosclerotic stenosis is finally occluded by an in-situ thrombosis. Untreated basilar artery occlusion results in death in 80- 90% of all patients, the surviving patients suffer from severe disability and often a locked-in-syndrome is seen. The first successful treatment option was intraarterial thrombolysis using urokinase or rt-PA inaugurated by Zeumer and colleagues in 1982. Nowadays, mainly three different treatment options are available: intraarterial thrombolysis, intravenous thrombolysis, and new mechanical devices for recanalization. No large randomized trials for this life threatening disease are availabe. Also, no comparative trials between the different treatment options have been performed. Mainly based on clinical case reports, case series or small trials the now available evidence for the management of acute basilar occlusion can be summarized: intravenous thrombolysis according to the NINDS-rt-PA protocol (0,9 mg rt-PA per kg body weight within an hour given intravenously, 10% as bolus, only within the first three hours after symptom onset) seems to be as effective as intraarterial thrombolysis. Intravenous thrombolysis for basilar occlusion should be used when intraarterial thrombolysis is not available or needs to much time to be used. Intraarterial thrombolysis is a clear treatment option for centers with experienced neuroradiological teams. The advantage of higher recanalizations rates compared to intravenous thrombolysis is reduced by a longer periprocedural time needed to place the catheter and inject the thrombolytics. Some centers use bridging strategies with quick start of intravenous thrombolysis and subsequent intraarterial approach to avoid any loss of time. Mechanical devices (various models are in use like retrievers, laser devices or stents) and sucction of a thrombus into a catheter allow rapid and complete recanalization. According to the development in myocardial infarction, new and better devices will probably be the future in recanalization of basilar artery occlusion.
Beside the recanalization, regular intensive care or stroke unit treatment is additionally used in these patients. An new internet based registry (BASICS) is installed at www.strokecenter.org/trials and should be used to collect all the different cases and increase the database on this severe disease. The requested study to compare intravenous and intraarterial thrombolysis or thrombolysis with mechanical devices is not available for years, even not planned yet.

Basilar and vestibular migraine

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Vestibular migraine is a recognized medical entity in most dizziness units. It accounts for approximately 10 % of these “dizzy” patients and is the most common cause of spontaneous episodic vestibular vertigo. In about one third of the patients it is not associated with headache. Vestibular migraine is characterized by an extremely varied manifestation; its attacks last from seconds to days; it can occur at any time in life; and its diagnosis is difficult, especially since it must be differentiated from Menière’s disease, vestibular paroxysmia, and transient ischemic attacks. During the attack pathological spontaneous or positional nystagmus and postural imbalance are found in 70 – 90 %; during the attack-free interval less severe ocular motor signs are found in about 60 %.
The talk delineates the clinical features of vestibular migraine and distinguishes it from motion sickness-like symptoms and nonvestibular dizziness in migraine. Finally, the case is made for including the term “vestibular migraine” in the International Headache Classification as a subcategory of migraine which is distinct from “basilar-type migraine” and “benign paroxysmal vertigo of childhood”.

Saturday, 13th October

POSTERS

P01
Auditory and electrically evoked brain stem reflexes in hemifacial spasm and postparalytic facial syndrome

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Objective: We aimed to investigate the characteristics of the auditory blink reflex (ABR) and the posterior auricular muscle response (PAMR) in patients with hemifacial spasm (HFS) and postparalytic facial syndrome (PFS).
Methods: Spasm activities and responses to supraorbital and auditory stimuli were recorded using surface electrodes from orbicularis oculi (O.oc), posterior auricular (PAM), and mentalis muscles of 27 HFS patients and 18 PFS patients. The results were compared to those of 23 healthy subjects.
Results: Supraorbital stimulation elicited early and late responses from the O.oc in all three groups. All HFS and PFS patients had responses in the lower facial muscles and PAM on the symptomatic side with latencies closer to R1 and R2. We did not observe early responses in the O.oc or the other facial nerve innervated muscles associated with early response of PAM. A late reflex response from PAM was obtained in 11 (40.7%) HFS patients and 10 (62.5%) PFS patients.
Conclusions: ABR spread in a manner similar to that of supraorbital BR. Of note, PAMR did not spread to any other muscles. However, based on the literature, they may share the same pathway. The difference in the pattern elicited by sound may be due to characteristics of the PAMR nucleus.

P02

Sound and vibration evoked vestibular potentials in the active masseter muscles of normal subjects

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Background: Beside the cochlea, intense air conducted sound activates saccular afferents and bone conducted sound (vibration) activates additional utricular afferents.
Objectives: To compare the waveforms and frequency tuning properties of vestibulomasseteric responses to sound and vibration using air and bone conducted pure tones (AT and BT).
Methods: Rectified and unrectified masseter EMG was recorded from 7 volunteers in response to intense monaural tones of 500Hz, 8ms (AT: 120dB SPL; BT: 136dB FL). To separately assess cochlear responses, low intensity (90dB SPL) AT were also used in 5 subjects. Reflex tuning properties were examined between 250-5000 Hz.
Results: Both AT and BT evoked masseteric potentials of similar waveform, consisting of two partially overlapping positive waves (p1 and p2) followed by a single negative peak n1 at 24.47±2.87ms. The mean p1 and p2 peak latencies (13.57±1.06ms and 17.6±1.66ms, respectively) were significantly separated in time ($p<0.0001$). Corresponding with the p2, a negative peak was recorded on the rectified EMG of all subjects. At a low stimulus intensity, only a single positive peak occurred, at latencies similar to p2, accompanied by a corresponding negativity on the rectified trace Only the p1 wave demonstrated tuning properties, with maximal amplitudes at 500 or 1000Hz . Only a p2 response occurred in response to 5000Hz stimuli.
Conclusions: AT and BT evoke vestibular dependent masseteric responses, which may prove useful in testing saccular and utricular function. Each possesses an early vestibular and later cochlear positivity. The use of BT enables examination of subjects with conductive hearing loss.

P03
Saccadic eye movement abnormalities in children with type 3 Gaucher disease are indicative for brainstem reticular formation pathology.

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Objective: To evaluate the saccadic eye movement abnormalities in children with type 3 Gaucher disease including a monozygotic twin and two infants.
Background: In type 3 Gaucher disease neurological involvement includes abnormalities of saccadic eye movements. They may consist of saccadic dysmetria, decreased saccadic velocity, gaze evoked nystagmus, gaze paresis and oculomotor apraxia (OMA).
Methods: Seven children with type 3 Gaucher disease based on genotype and phenotype have been investigated, including a boy (21 months), three siblings (a boy of 4 months; a sister of 10 years, and a sister of 14 years) another boy (11 years) and two sisters from a monozygotic twin (16 years). Eye movements were recorded with an accurate double magnetic induction method. Saccades were tested including saccades (pro-saccade paradigm) and smooth pursuit. Peak saccade velocity (main sequence) and saccadic gain were calculated. In addition, video recordings were performed to evaluate OMA.
Results: Oculomotor abnormalities ranged from a complete ophthalmoplegia to dysmetric saccades. Slowing of saccades was found in six out of the seven patients. Five out seven patients showed OMA. Interestingly, unlike her sister one of girl the monozygotic twin did not show any eye movement abnormality. Smooth pursuit was normal except for the patient with complete ophthalmoplegia.
Conclusions: All observed eye movement abnormalities in the patient group with type 3 Gaucher disease are indicative for brainstem pathology. Particularly, the neural circuitry consisting of burst neurons and pause cells in the reticular formation is malfunctioning. Phenotype varied, even between monozygotic twins.

P04
Intermuscular Coherence and Eye Movement Studies in Two Sisters with Orthostatic Tremor

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Objectives: Orthostatic tremor is usually sporadic and is characterized by a 16 Hz tremor in the legs during stance that is bilaterally coherent (1;2). We investigated the origin of orthostatic tremor in two sisters with coherence analysis and performed eye movement recordings (3;4).
Methods: In two sisters with tremor, aged 66 and 71, we performed polymyography of proximal and distal muscles of the arms and legs during isometric muscle contractions when lying down, sitting, and standing with the hands leaning on the back of a chair. In one patient coherence was computed between all possible muscle pairs for the different conditions. Eye movements (spontaneous movements, smooth pursuit, saccades) were recorded with the double magnetic induction method.
Results: Polymography showed bursts of 14 Hz in all muscles during stance and leaning diminishing during other conditions in both patients. Coherence reached values up to 0.8 (1 is maximal coherence) around 14 Hz with supraharmonics, for all muscle pairs during stance and leaning. Eye movement recordings showed spontaneous downbeat nystagmus, saccadic hypometria, and decreased peak saccadic velocity.
Discussion: In this familial form of orthostatic tremor, polymyography and coherence studies point to a 14 Hz central generator. Eye movement abnormalities suggest functional changes in both the brainstem and cerebellum. Abnormal eye movements have, as far as we know, not been reported previously in orthostatic tremor patients. Further studies must elucidate whether these abnormalities are associated with idiopathic orthostatic tremor or are specific for this rare familial form.

P05

Startle reactions to somatosensory inputs. Different response pattern to stimuli of upper and lower limbs.

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Objectives: To define the characteristics of startle reactions induced by somatosensory inputs from upper and lower limbs in naive healthy subjects.
Methods: Patients scheduled for electromyography who had normal neurological examination and had an exaggerated reaction to the first electrical stimuli applied for nerve conduction studies were recruited for the study. We characterized the startle response pattern by recording the EMG activity from orbicularis oculi (OOc) and sternocleidomastoid (SCM) muscles to electrical stimuli of median nerve at the wrist, and posterior tibial nerve at the ankle. We measured the latency of the earliest response and the distribution of EMG bursts.
Results: Stimuli applied to median nerve induced a patterned reaction, with the OOc activated first (two bursts; the first at 63.6 +/- 6.8 ms and the second at 93.7 +/- 8.8 ms), followed by the SCM at 88.2 +/- 7.6 ms. In contrast, the first OOc burst was absent to stimuli applied to the posterior tibial nerve and the earliest response was that of the SCM at 108.8 +/- 10.3 ms.
Conclusions: The pattern of somatosensory startle is different with stimuli applied to lower or upper limbs. The first OOc burst to median nerve stimuli is compatible with a somatosensory blink reflex, which may be absent or delayed to inputs from lower limbs. The prominence of SCM responses to lower limb stimuli could also suggest a more caudal processing of afferent inputs from lower than from upper limb or acceleration of SCM response as part of a defensive reaction.

P06
Holmes Tremor of the head caused by a left midbrain astrocytoma

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Objectives: To investigate eye and head movements in patients with midbrain lesions.
Methods: A 59 year old male patient with a known left midbrain astrocytoma gradually developed rest and intention tremor of the right hand (Holmes tremor), but no visible head tremor. The patient was instructed to follow a laser point in the dark, first with the eyes only (head fixed on a chin rest), then with eyes while the head was free to move and finally by pointing with a laser mounted on the forehead. Eye and head movements were measured using 3D search coils.
Results: When the patient had to keep his head still in darkness, he developed a 4.5 Hz vertical-torsional head tremor. No head tremor was observed when the patient followed the target with the eyes during the head-free paradigm. However, when he had to point to the target with the head laser, the patient developed a predominantly vertical tremor of the same 4.5 Hz frequency, the amplitude of which depended on head position.
Conclusions: To our knowledge, this is the first clinical description of a patient with a known Holmes tremor exhibiting head intention tremor. Holmes tremor is usually developed after a combined nigrostriatal and rubrocerebellar pathway lesion. In this patient, the head tremor was only obvious when the head task was dissociated from the eye task, thus indicating that the head is controlled through different pathways depending on its function either as end-effector (laser task and chin rest) or as an intermediate segment (gaze movements).

P07

Localized brainstem dysfunction in patients with Parkinson´s disease and central pain

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Introduction: There is increasing evidence that brainstem structures participate in modulation of pain inputs. The sudomotor skin response (SSR) is considered an index of autonomic function that reflects the integration of pain inputs on autonomic centers at brainstem level.
Objective: Analize the SSR in patients with primary central pain (PCP). For that we carried out a study of patients with Parkinson's disease (PD) who complained of pain not attributed to other causes.
Methods: We performed a psychophysical and neurophysiological study in 9 PD-PCP patients, 9 PD patients without pain (PD-NoP) and 9 healthy control subjects. We performed quantitative sensory testing with thermal probes, and recorded laser-evoked cortical potentials (LEPs) and laser-induced sudomotor skin responses (l-SSR) to repetitive stimuli in both OFF and ON conditions.
Results: In OFF condition, PD-PCP patients had lower heat pain and laser pinprick thresholds, higher LEP amplitudes, and reduced habituation of the l-SSR in comparison to PD-NoP patients and control subjects. Abnormalities were more marked in the most affected side. In ON condition, psychophysical and neurophysiological differences disappeared or were significantly attenuated.
Conclusion: Our findings indicate that probably there is a dysfunction in dopamine-dependent centers at brainstem level regulating both autonomic function and inhibitory modulation of pain inputs in PD-PCP patients. A degeneration of the periaqueductal grey matter zone would provide an explanation for such findings because of the dopaminergic activity in some of its neurons and its anatomical proximity to substantia nigra.

P08
Pathophysiology of pain in postherpetic neuralgia. A clinical and neurophysiological study

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We aimed at investigating the pathophysiology of neuropathic pain in postherpetic neuralgia (PHN) by performing clinical and neurophysiological examination in patients with ophthalmic PHN.

In 33 patients with ophthalmic PHN we investigated sensory disturbances such as hypoesthesia, paresthesia, itching and pain, whose intensity was assessed with an 11-point verbal rating scale. In all patients we recorded the blink reflex, (mediated by Aβ fibres), and laser evoked potentials (LEPs) related to Aδ- and C-fibres activation. We also sought possible correlations between neurophysiological data and sensory disturbances.

All neurophysiological responses were significantly abnormal after stimulation of the affected side compared to the normal side ($P < 0.001$). The different qualities of pain correlated with different neurophysiological abnormalities ($P < 0.05$).

In patients with ophthalmic PHN, stimulation of the affected side yielded markedly altered neurophysiological responses, thus demonstrating a severe impairment of all sets of fibres. The neurophysiological – clinical correlations indicate that different types of pain show positive correlation with abnormalities of different sub-set of afferents, thus suggesting that qualitatively different types of PHN pain may involve different mechanisms.

P09
Trigeminal neuralgia in patients with multiple sclerosis. Quantitative MRI-neurophysiological correlations with a voxel-based 3D brainstem model

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Trigeminal neuralgia (TN) is often associated to multiple sclerosis (MS). Some investigators proposed a neurovascular conflict as the real cause. Furthermore it is still debated whether a central mechanism is involved in TN. In a multi-centre study, we collected 80 consecutive MS patients who presented with sensory disturbances in the trigeminal territory. Besides standard investigations for MS, all patients underwent pain assessment, trigeminal reflex testing, and dedicated MRI scans focussed on the brainstem. The MRI scans were imported and normalised into a 5268-voxel 3D brainstem model that allows statistical analysis. Patients were divided into two groups: those with TN and those with any other kind of trigeminal sensory disturbance, including hypestethesia, paresthesia, dysesthesia, allodynia, and constant pain. The onset age of both MS and of trigeminal symptoms were significantly higher in the TN group than in the non-TN group. The frequency histogram of onset age showed a bimodal distribution in the TN-group, with the second peak in the age range of classical TN. Some patients (of either group) had a normal brainstem MRI and some had a neurovascular contact with the trigeminal root. 3D brainstem analysis showed one area of very high probability of lesion ($P < 0.0001$) centred in the ventrolateral pons between the trigeminal root entry zone and the trigeminal nuclei in the TN group. In the non-TN group, the lesions were more scattered, with the highest probability ($P < 0.001$) in a region still in the pons, but more caudal, medial, and dorsal, which involved the subnucleus oralis of the spinal trigeminal complex.
We conclude that the most likely cause of TN is a pontine plaque rather than a neurovascular contact, but some patients do have a neurovascular contact and may suffer from a double-crush mechanism. Although the lesion is intra-axial, it is still the presynpatic terminals of primary afferents that generate the paroxysmal pain of TN. Because patients with infarction in the same area never present with trigeminal neuralgia, demyelination must be another necessary condition. The other kinds of sensory disturbances, including constant pain, may arise from damage to various parts of the brainstem trigeminal pathways, but the second-order neurons of the spinal trigeminal complex are most often involved.

P10
Trigeminal sensory changes following gamma knife radiosurgery

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Objectives: Gamma knife is a treatment modality for small acoustic neuromas and skull base meningiomas located close to trigeminal nerve. This study investigated early sensory dysfunctions of trigeminal nerve following gamma knife radiosurgery via Quantitative Sensory Testing (QST).
Methods: Thirteen patients (10 male, 3 female; 39 to 77 years; 6 meningiomas, 7 acoustic neuromas) were treated with doses of 13 to 65 Gy (trigeminal nerve: 2-26 Gy). Pre- and postoperatively (within 24 hours), thermal detection and pain thresholds, mechanical detection threshold, wind-up ratio, mechanical pain threshold and sensitivity, allodynia, vibration detection and pressure pain thresholds were bilaterally (control, test area) tested in infraorbital or mental nerve innervation areas.
Results: Patients did not report any spontaneous sensory dysfunctions. Pathological QST results were diagnosed in 8 patients. Four patients presented warm and cold hypoesthesia within 24 hours after radiosurgery. Three patients had hypoesthesia only to cold and one patient only to warmth. In control areas, thresholds remained unaffected. Cold perception thresholds negatively correlated with radiation doses (Pearson, $r=0.7$, $p<0.01$).
Conclusions: Radiosurgery is associated with thermal sensory changes occurring within 24 hours in a dose-dependent manner. Thermal sensory dysfunctions seem to be early side effects of gamma knife treatment. Further QST measurement will address possible long-term effects on sensory function.

P11

Impact of emotional stress on pain perception in an experimental pain model

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Background: Former studies examining the influence of emotional stress on pain perception in patients have come to different results. Depending on the group of patients under investigation and on the modus of stress induction, pain increasing and decreasing effects have been described. Our current study presents an experimental model which further characterizes the effect of a emotional stress task on pain perception in a tonic electrically evoked pain model. For this purpose, we used the Colour-Word interference task (CWT) by Stroop, for which we were able to show that it activates the sympathetic nervous system in a stable, reproducible way.
Methods: After reaching of constant pain ratings, CWT was presented to 15 healthy subjects in an interferent and a congruent (colour and word representing the same) version. The presentation was performed in a balanced order. For registration of a sympathetic response induced by the stress task, we recorded sympathetic parameters (i.e. cardio-vascular parameters, emotional sweating).
Results: Pain perception was directly after performance of interferent CWT significantly lower than before (3.1 vs 3.9 cm VAS; $p < 0.01$), whereas the congruent version did not lead to a significant reduction of pain.
Considering activation of the sympathetic parameters, the interferent version resulted in a significantly stronger increase of systolic blood pressure (9 vs. 4 mmHg; $p < 0.05$), of heart rate (4 vs. 2/min; $p < 0.01$), and of emotional sweating (AUC of cumulative sweat production: 17 vs. 8 V*s; $p < 0.05$) than the congruent CWT.
Conclusion: Our results show that the Colour-Word interference task causes a reduction of pain in a tonic electrically evoked pain model in healthy subjects. The mechanisms involved will be subject for further investigation.

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P12
Cortical representation of experiemental trigeminal pain in humans

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Using fMRI, brain activation was compared when pain was applied to a trigeminal region or a limb. 8 healthy volunteers participated in a training session, where autonomic reflexes and rating were recorded, and in an fMRI session. The stimuli were electrical tooth pulp stimulation of the left upper incisor (TPS) and repetitive impact stimuli to the dorsal side of the left middle phalanx (FS). Stimulus intensities were adjusted to get pain ratings of 60% or 30% on a visual analogue scale (VAS). In the first experiment FS (60% VAS) and TPS (60% VAS) were compared, in the second experiment weak (30% VAS) and strong TPS (60% VAS).
Strong TPS lead to clear changes in the autonomic reflexes (vasoconstriction, increase in blood pressure).
In the first experiment the contralateral S1 cortex was activated during FS, whereas TPS lead to bilateral activation of S1. The S2 and insular region were bilaterally activated by both stimuli. In S2 the center of gravity of the activation during FS was more medial/posterior compared to TPS. The anterior and medial parts of the insular cortex were activated stronger by TPS. In the anterior cingulate gyrus, FS induced a stronger activation of the posterior part. Differential activations were also found in motor and frontal areas.
The second experiment indicated that activation induced by strong TPS is in most cases identical with the areas activated by TPS in the first experiment. Only in the medial frontal and right superior frontal gyri an inverse relationship between pain intensity and BOLD contrast was found.
It is concluded that the cortical network activated by TPS is in some respects different from that of FS – in the somatotopically organized regions as well as in the medial pain projection system.

P13

Compensation processes for central vestibular dysfunction in patients with acute medullary infarctions (FDG-PET study)

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Earlier functional imaging studies in healthy volunteers during vestibular stimulation and in patients with acute peripheral vestibular neuritis found a reciprocal inhibitory interaction between the vestibular and visual systems. Aim of this fluorodeoxyglucose (FDG)-PET study was to define areas involved in processing and compensating central vestibular dysfunction caused by acute infarction of the lateral medulla.

Twelve patients (10 m, 2 f; mean age 68.3 years) with unilateral ischemic infarction in the medulla oblongata (6 right, 7 left) affecting the vestibular nucleus and causing signs of acute vestibular dysfunction were examined twice by FDG-PET (A) in the acute phase and (B) seven of them 6 months after recovery. Single subject and group subtraction analysis were performed and patient data were compared with a data set of 12 age-matched controls.

In the acute phase (contrast PET A vs. B) differences were disclosed mainly in the medulla and cerebellar peduncle contralateral to the infarction and in both cerebellar hemispheres. The inverse contrast (PET B vs. A) revealed bilateral signal changes (i.e., deactivations) in the visual cortex (BA 17-19), including the motion-sensitive area MT/V5 (BA 19/37) and secondary visual areas (BA 19/39) as well as temporo-parietal areas (GTm/s, LPi, BA 39/40).

Interestingly, in the acute stage no relevant activations were found at cortical level but the signal decreases were seen within the visual cortex bilaterally. Instead, activations were located in the cerebellum and contralateral brainstem which leads to the suggestion that compensatory processes take place in cerebellar loops rather than in cortical areas.

P14
Impaired balance with brain stem infarcts

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Objective: Patients with brain stem infarcts report a variety of symptoms to describe impaired balance. We analysed patients with unilateral brain stem infarcts for different forms of impaired balance and the site of the lesions.
Methods: We analysed 151 prospective patients with acute, MRI-documented unilateral brain stem infarcts for the occurrence of impaired balance. Complaints of the patients were classified as follows:

- "Rotational Vertigo": a perception of a rotation of the patient or the environment
- "Swaying": a perception of to-and-fro or fore-and-after sway
- "Dizziness": complaints such as unsteadiness, light-headedness, giddiness, "as if "drunken", "walking on a swaying deck", "walking on clouds".

Results: In general, impaired balance was more common with medullary/ponto-medullary infarcts than with pontine and mesencephalic lesions (40 of 49 patients vs. 55 of 102 patients; χ^2: 10.894, $p < 0.001$). This difference was also seen for rotational vertigo (12 of 49 patients vs. 8 of 102 patients; χ^2: 7.982, $p < 0.005$), but not for swaying (8 of 49 patients vs. 10 of 102 patients; χ^2: 1.341, $p < 0.25$), or dizziness (20 of 49 patients vs. 37 of 102 patients; χ^2: 0.291, $p < 0.6$). The infarcts of patients with impaired balance occurred significantly more often in the region of the intrapontine 8th nerve.
Conclusions: Impaired balance with brain stem lesions, especially rotational vertigo, is more common with medullary and ponto-medullary infarcts. This may be attributed to lesions of the vestibular system involving in particular the intrapontine segment of the vestibular nerve.

P15

Exaggerated auditory startle responses in patients with spinal cord injury

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Objective: Central nervous system reorganization after the lesion may be the cause of changes in functions of the motor tract in patients with spinal cord injury (SCI) as in the auditory startle response (ASR), in which increasing response has been reported. We hypothesized that if the increased ASRs in patients with incomplete SCI is due to a kind of compensatory mechanism, those changes would be related with the severity and/or the localization of the lesion.

Methods: We examined the changes in the characteristics of the ASR in twenty-nine SCI patients and fourteen age-matched healthy volunteers. Fourteen patients had incomplete and fifteen complete SCI. Ten patients had cervical and 19 thoracolumbar SCI. ASRs were elicited by five auditory stimuli with a 5 minute interstimulus interval applied binaurally in a sitting position. Surface electromyographic recordings were obtained from orbicularis oculi (OOc), sternocleidomastoid (SCM), biceps brachii (BB), and tibialis anterior (TA) muscles.

Results: ASR probability was higher and area was larger in SCM and BB in patients than in controls. ASR latency was significantly shorter in SCM and BB in patients with cervical than thoracolumbar injury ($p<0.02$), but there were no statistically significant differences between complete and incomplete SCI ($p>0.1$). Time since onset correlated significantly with ASR area in OOc, SCM and BB ($p<0.05$).

Conclusion: The capability of the adult central nervous system to reorganize its circuits over time in order to functionally recover is probably the key for exaggerated ASRs in patients with SCI.

P16
Rare case of a skull-base meningioma

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Objectives: Most commonly, skull-base meningiomas are diagnosed randomly, in the context of a non- specific symptomatology. We will describe a similar case of a patient with an extended skull-base meningioma.
Methods: A 44-year old female patient presented with a five month history of non-specific headaches, progressive visual blur and left-sided pulsies of the face with ipsilateral deformity. She undertook neurophysiological (24-hour electroencephalogram, Brainstem Auditory Evoked Potentials-BAEPs) and neuro-radiological control. The MRI gave evidence for a diffusely expanded skull-base meningioma. The tumor, originating from the parasellar region, was suppressing the left optical nerve and fundum, causing optical neuropathy and exopthalmos. It also invaded the pterygoid muscles and the seventh cranial nerve, resulting to the hemifacial asymmetry.
Results: The meningioma had expanded along the medial and lateral sphenoid wing, reaching also the region behind the optical chiasma, Thus, it could not be exerted. This wide tumor extension, made it non susceptible to surgical treatment and the patient was submitted to radiotherapy.
Conclusion: The skull-base meningioma is not as rare as it used to be considered. Its frequency was underestimated due to its poor or silent symptomatology for a long period. It is needless to say that even the minor symptoms should be immediately evaluated with a detailed neurophysiologic and radiological control. In that way, early diagnosis will permit effective surgical removal of the tumors.

P17
Pathological yawning in brainstem stroke

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Introduction: Yawning is a phylogenetically ancient behaviour, the physiological role of which is still not fully understood. It is hypothesized that the neural substrate of yawning includes a "yawning centre" in the lower brainstem. We report on 5 patients who showed excessive pathological yawning associated with brainstem stroke.
Case reports: All patients presented with excessively frequent yawning and gait ataxia as first symptom. Additional signs and symptoms that were present in only some patients included hemiparesis, vertigo, nystagmus and dysmetria, according to the extension of the lesion. Yawning was perceived as compulsive, irresistible, inappropriate and not associated with drowsiness or boredom. It occurred in all patients in frequent bouts of at least 3 consecutive yawning acts. Excessive yawning was the first symptom of stroke in all patients and it disappeared from a few hours to a few days after the onset. Imbalance of stance and gait persisted for weeks. MRI showed acute or subacute ischemic lesions involving invariably a paramedian region in the upper pons and ponto-mesencephalic junction. Lesions were lateralized in all cases, but the side was not consistent throughout all patients.
Discussion: The exact mechanism of excessive yawning following focal brainstem lesions is not clear. Possibly it is the expression of the liberation of a putative yawning centre from supranuclear control. Pathological yawning can be an early sign of brainstem infarction. In our patients a syndrome consisting of excessive yawning and gait ataxia is associated with lesions of the paramedian upper pons and ponto-mesencephalic junction.

P18

Auditory evoked brain stem reflexes in peripheral facial paresis

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Introduction and objectives: Blink reflex (BR) may be obtained by different modalities. The constriction of orbicularis oculi muscle in response to auditory stimulation is a part of the startle reflex. Posterior auricular muscle (PAM) response (PAMR) may be elicited by PAM which is innerveted by facial nerve with auditory stimuli. Peripheral facial paresis (PFP) is a ideal model to study the changes in these reflexes.
Subjects and methods: We included 51 patients aged between 15-75 with PFP and 25 healthy volunteers to our study. Duration of disease at the time of evaluation was between 5 days and 5 months. EnoG, electrically and auditory evoked BR responses and PMAR were studied. The patients and their reflex responses were evaluated according to the level of severity of paresis by using the House-Brackmann scale (HBS).
Results and conclusion: Trigeminal and auditory BR latencies and number of evoked PAMR was similar between the asymptomatic sites of PFP patients and control group. On the symptomatic site PMAR could not be elicited in 21 of 31 responsive PFP patients. R1 could not be elicited in 25 patients on the symptomatic site, R2 in 20 and ABR in 31. All the decrease in responses on the symptomatic site was correlative with the increase in HBS.
We concluded that ABR is a sensitive reflex response as BR. PAMR is a useful brain stem reflex, although it sometimes could not be elicited.

P19

Nonlinear analysis of dynamic changes in brain spirography. Results in patients with ischemic stroke

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Objectives: Respiration rhythm during ischemic stroke characterizing complicated structure of dynamics changes. We purpose the comparative dynamics study of this changes in patients in different clinical state. A nonlinear data analysis for investigating properties of human respiration rhythms was applied.
Methods: Brain Spirography (BSG) as a new method of experimental clinical breath research is based on detecting system coupled with pressure sensors. Signals from the sensors through the digitals converter are transferred to the computer for analyzing. The clinimetric scale for stroke patients based on NHISS and GCS scale are compare with the results of nonlinear analysis of breath dynamics changes. We collect the data from 55 patients with first-ever supratentorial ischaemic stroke and investigate a changes of breath dynamics. Dynamics was calculate using Return Map Plot (RMP) and Fractal Dimension (FD) for 3 times per day during 5 days of hospitalization. The results of dynamics changes was presented for different patients as a comparative study of clinical state of the patients.
Results: The parametrical dynamics structure was built for stroke patient as a comparison between FD value and RMP visualization. Numerical value of breath rhythms for different clinical state are proposed as a supplementation for clinimetric scale. Fractal Dimension was estimate as a range from 1.6 to 2.1 (+/- 0.05) for critical parameters of breath dynamic for stroke patients.
Conclusions: Investigation of dynamics changes using nonlinear methods take a possibility for predictions of parametric changes of nonlinear dynamics structure in breath rhythms. This procedure help to achieve practically important data about the correlation between nonlinear dynamic changing and clinimetric data. Another way will be computer modeling work of human respiration based on numerical simulation such a system of dynamics parameters for comparative study.

P20
Botulinum toxin treatment has no influence on auditory startle reaction in primary blepharospasm

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Objective: Primary dystonia is associated with abnormal brainstem function. In a recently published study we examined the auditory startle reaction – a brainstem reflex elicited by an unexpected loud stimulus – in patients with primary blepharospasm (BSP). Compared to normal controls, we found disinhibition of startle circuits in cranial muscles of BSP patients with the exception of the orbicularis oculi muscle showing fewer and smaller auditory startle responses (ASRs). In order to distinguish whether smaller ASRs in orbicularis oculi in BSP patients result from previous treatment with botulinum toxin (BTX) or are related to BSP itself, we investigated ASRs in de-novo patients with primary BSP who had never received BTX. **Methods:** ASRs were studied in two de-novo patients with primary blepharospasm (mean age 50.5 years) following binaural high-intensity auditory stimuli. Reflex electromyographic activity was recorded simultaneously with surface electrodes bilaterally from masseter, orbicularis oculi, sternocleidomastoid, and biceps brachii muscles. Data were compared with those obtained in 13 patients with primary BSP (mean age 63.8 years), who were pre-treated with BTX (6.9 ± 4.2 years), and in 13 healthy controls (mean age 63.1 years). **Results:** ASR area ratios (orbicularis oculi / masseter) were similarly small in de-novo BSP patients (1.79 ± 0.87, mean ± SD) and in pre-treated BSP patients (1.57 ± 1.02), and were larger in normal controls (3.48 ± 1.06). ASR area ratios (orbicularis oculi / sternocleidomastoid) were even smaller in de-novo BSP patients (0.52 ± 0.15) compared to pre-treated patients (1.05 ± 0.81) and healthy controls (1.60 ± 0.95). In addition, median ASR probability of all muscles combined was equal in de-novo and pre-treated BSP patients (84.4%, respectively) and higher than in healthy controls (71.9%). **Conclusions:** These preliminary data suggest that smaller ASRs in orbicularis oculi muscle in BSP patients as compared to normal controls are associated with the disease itself – independent of prior BTX treatment. This finding, together with a higher ASR probability in both de-novo and pre-treated BSP patients as compared to normal controls, supports the notion that pathophysiological mechanisms affecting brainstem circuitry in BSP are different from those in cervical dystonia.

P21
The somatosensory blink reflex in Guillain-Barré polyneuritis, Miller-Fisher' syndrome and Bickerstaff's brainstem encephalitis.

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Background: Miller-Fisher syndrome (MFS) and Bickerstaff's brainstem encephalitis (BBE) share similar dysfunction of brainstem circuits. However, brainstem reflexes have been only scarcely studied in these entities. Miwa et al. (J Neurol Neurosurg Psychiatry 1995;58:95-99) reported enhancement of the somatosensory blink reflex (SBR) to median nerve electrical stimuli in MFS patients. We investigated the characteristics of the SBR in 5 BBE patients and compared the results with those of 5 patients with MFS.
Methods: Patients were seen within the first 72 hours after onset of symptoms, and the exams were repeated at 1 and 3 months in most of them. The SBR was recorded from both orbicularis oculi muscles to median nerve electrical stimuli. We also performed a conventional blink reflex study to trigeminal nerve stimulation (TBR).
Results:Four out of the 5 patients with BBE showed no SBR in the first exam while all 5 MFS patients had SBR present. Two MFS patients had enhanced amplitude and reduced habituation to repeated stimuli. The TBR was abnormal in all patients, exhibiting a variable delay of R1, delay of R2, or absent responses, with no differences between MFS and BBE.
Discussion: Here were clear cut differences between MFS and BBE in regard to the consistency of the SBR. Our results suggest that intra-axial disorders of the brainstem may present with abnormal sensorimotor integration of inputs from the median nerve while this is not the case with extra-axial lesions. The SBR is a neurophysiological tool with clinical applicability in disorders of the brainstem.

P22
Reinnervation activity in the unaffected facial nerve after complete unilateral peripheral facial palsy

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Introduction: Few weeks after complete peripheral facial palsy, small polyphasic 'reinnervation' motor unit action potentials (rMUAP) can be recorded from the orbicularis oris (OOr) of the paralyzed side. We have investigated timing and electrophysiological characteristics of such rMUAP.
Patients and methods: The study was performed in 25 patients with complete peripheral facial palsy of different causes (idiophatic, postoperative, postinfection and posttraumatic) 10 days after onset, and up to the beginning of ipsilateral reinnervation. The EMG activity was recorded with a concentric needle electrode implanted 1 cm lateral to oral comisure. We applied electrical stimuli to the unaffected facial nerve at different points along a line between tragus and midline lower lip. We measured response latency variability and conduction velocity in several segments.
Results: Responses to electrical stimuli of the unaffected facial nerve were found in all patients at 20-30 days after onset of facial palsy. Mean conduction velocity was 43.9 +/- 7.7 ms in the segment tragus-oral comisure, and 3.5 +/- 1.3 ms in the segment oral comisure-midline lip. Latency variability was 0.35 ms to facial nerve stimulation and 0.07 ms to oral comisure stimulation. The characteristics of the individual responses remained unchanged in subsequent examinations.
Conclusion: The rMUAP recorded in the paralyzed OOr are due to contralateral facial nerve reinnervation. Our results are compatible with muscle fiber propagation of impulses and not of axonal conduction across the midline. We suggest a short distance sprouting of axons innervating circular OOr muscle fibers through new motor endplates in the unaffected side.

P23
Large demyelinating lesion of the pons as a cause of a locked-in syndrome in multiple sclerosis

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Objective: To report a patient with multiple sclerosis (MS) and a locked-in syndrome due to a large demyelinating lesion of the pons.
Case report: Four months after an episode with diplopia and gait ataxia, a 33-year old woman developed bilateral internuclear ophthalmoplegia and left-sided hemiparesis, hemihypesthesia and hemihypalgesia. MRI documented multiple periventricular T2-hyperintense lesions and a large gadolinium-enhancing lesion in the right pons. High doses of intravenuous methylprednisolone were ineffective as were subsequent treatments with plasma exchange, intravenous cyclophosphamide, and intravenous immunglobulins. Within 6 weeks, she was quadriplegic and required mechanical ventilation. She had a loss of all horizontal but preserved vertical eye movements, which were used for communication. We started treatment with rituximab. She slowly improved over the next 2 years. At present, her EDSS is 5.0 and she lives an independent life. She is without another bout and without any new MRI-documented lesion.
Comment: A locked-in syndrome seems to be extremely rare with MS. We are aware of only 2 previously reported patients, who both died. We add a third surviving patient. Despite neurological deficits, this patient is able to lead an independent life. Rituximab may be considered as a treatment option when patients do not respond to standard treatments of MS.

P24
Classical brain stem syndromes: Myth or reality?

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Background: Especially in the 19th century, a wide variety of crossed brain stem syndromes has been described.. While hardly anything is known on the prevalence of these syndromes, definitions in the modern neurological literature are often inaccurate and inconsistent and it is debatable, if some of these syndromes do actually exist at all.

Methods: To assess the frequency of different classical alternating brain stem syndromes we prospectively assessed the symptomatology in 268 consecutive patients with acute brain stem infarction as documented on standardized MRI. For computer-based analysis, patients' signs and symptoms were entered into an ACCESS data base and were correlated to the symptoms as reported in the original historical publications.

Results: 10 of the 268 cases (3.7%) were matching the minimal clinical criteria of Wallenberg's syndrome. In all of these patients MRI revealed brain stem infarction affecting the lateral medulla oblongata. Two patients fulfilled the clinical criteria of Babinski-Nageotte and two the criteria of Raymond-Cestan syndrome. One patient showed all signs of Weber's syndrome. For none of the following classical brain stem syndromes a case matching the clinical criteria as reported in the original publications could be detected: syndromes of Avellis, Benedikt, Brissaud-Sicard, Cestan-Chenais, Dejerine-Spiller, Foville, Millard-Gubler, Nothnagel-Claude and Tapia.

Discussion: With the exception of Wallenberg's syndrome, none of the other historic descriptions of crossed brain stem syndromes seems to play a relevant role in clinical neurology. Wallenberg's syndrome is a clinical correlate of classical lateral medullary infarction, which is a frequent area of ischemia due to the vascular architecture of the brain stem. In modern neurology, other syndromes may serve as theoretical constructions only, which may illustrate possible neuroanatomical allocations in the human brain stem.

P25
Sensitivity of imaging and electrophysiological brainstem testing in the diagnosis of acute vertebrobasilar ischemia

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Background: The diagnosis of brain stem ischemia remains a difficult task due to still inadequate imaging techniques. We aimed to elucidate the sensitivity of different neuroimaging techniques and multimodal electrophysiological in patients with brain stem ischemia testing in the diagnosis of clinically suspected ischemic brainstem lesions.

Methods: We prospectively recruited 204 consecutive patients with acute signs and symptoms suspective of brain stem ischemia. Patients underwent CT-imaging and biplane EPI-T2 and EPI-DWI within 48 hours after onset of symptoms following a fixed protocol. Within 7 days multimodal electrophysiological brain stem testing was applied, including brain stem reflexes (jaw jerk, blink reflex, masseter inhibitory reflex), evoked potentials (AEPs, SSEPs with investigation of brain stem generated far field potentials, MEPs with investigation of orofacial and lingual projections) and electrooculography as well as the oculo-auricular phenomenon.

Results: Detection rate of brain stem ischemia as the best final diagnosis was 8% according to CT and 80% according to MRI. Detection rate of multimodal functional brain stem testing was 89.2%. When combining the results of DWI und functional testing, in 98% of all patients a brain stem lesion was verified. Multimodal electrophysiological testing was able to reveal a functional brain stem lesion even in 89% of the 38 patients with normal MRI. In general, four electrophysiological tests (jaw jerk, blink reflex, masseter inhibitory reflex, electrooculography) were sufficient to detect an appropriate number of pathologies (>80%).

Conclusion: DWI and electrophysiological testing are complementary tools in the diagnosis of vertebrobasilar ischemia. Electrophysiological testing may demonstrate an intra-axial pathology even in patients with normal imaging, which may influence further patient management. Sensitivity of the different electrophysiological tools does, however, differ substantially.

P26
Forehead-taps can evoke normal leg-muscle evoked postural reflexes in bilateral vestibulopathy

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Forehead taps applied with a reflex hammer can evoke short-latency muscular reflexes in activated neck muscles. This reflex is mediated by the vestibular organ, presumably the otoliths. Similar neck muscle reflexes can also be elicited by sound, vibration, and galvanic stimulation. We have previously described postural reflexes which can be elicited by gently tapping the forehead of a standing subject (Bötzel et al., Exp Brain Res 2001). It remained unclear whether these reflexes depend on the vestibular organ or on proprioception or both.
To clarify this point we applied forehead taps to a group of subjects with bilateral vestibular loss of different causes. In the standing patients, the surface EMG of leg muscles was recorded, amplified, rectified and then averaged with the impact of the hammer triggering the averager. The averaged and rectified traces of the leg muscle EMG showed normal tap-evoked postural responses in this group, when compared to an age-matched control group. In contrast, the vestibular dependent parts of the tap-evoked neck reflexes were absent or grossly reduced in the patients as well as the sound-evoked vestibular evoked neck muscle responses.
In conclusion, head taps can elicit muscular responses via proprioception as well as via vestibular receptors. Tap evoked leg muscle responses seem to rely purely on proprioceptive triggering whereas the early part of the tap evoked neck muscle response relies purely on vestibular receptors.

P27

Choice reaction times for human head rotations are shortened by startling acoustic stimuli, irrespective of stimulus direction

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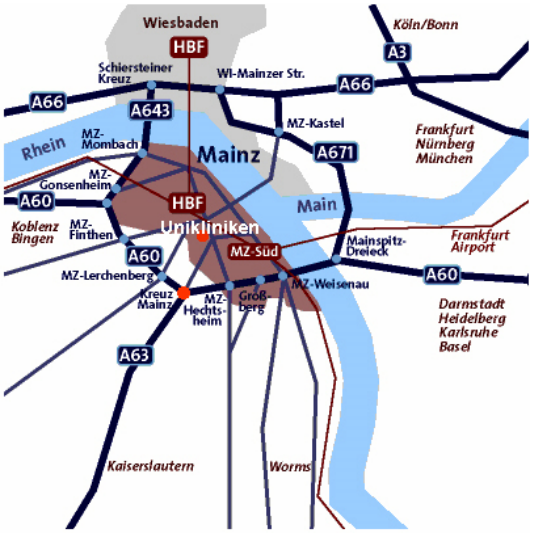
Background: Startle reflexes can accelerate simple voluntary reaction times (StartReact effect). To investigate the role of startle reflexes on more complex motor behaviour we formulated two questions:
(1) can auditory startle reflexes shorten choice reaction times?;
(2) is the StartReact effect differentially modulated when startling auditory stimuli are delivered ipsilaterally or contralaterally to an imperative "go" signal?
Methods: We instructed 16 healthy subjects to rotate their head as rapidly as possible to the left or to right in response to a guiding visual imperative stimulus (IS), in both a simple and choice reaction paradigm. Startling acoustic stimuli (113 dB) were delivered simultaneously with the IS (from either the same or opposite side) to induce the StartReact effect. We recorded kinematics of head rotations and electromyographic responses.
Results: The StartReact effect was present during choice reaction tasks (56 ms onset reduction; $p<0.001$). The presentation side of the startling stimulus (left/right) did not influence the effect in choice reaction tasks. We observed a directional effect in simple reaction tasks, but this likely occurred due to a flooring-effect of reaction times. Onsets of EMG responses in neck muscles were not influenced by the direction of the acoustic startling stimulus.
Conclusions: Startling acoustic stimuli decrease reaction times not only in simple but also in choice reaction time tasks, suggesting that startle reflexes can accelerate adequate human motor responses. The absence of a clear directional sensitivity of reaction times to startling acoustic stimuli suggests that the acceleration is not highly specific, but seems to provide a global preparatory effect upon which further tailored action can be undertaken more quickly.

CHAIRPERSON AND AUTHOR INDEX

TRAVEL INFORMATION

For approach by car please follow the map below. On “Autokreuz Mainz” follow the direction “Innenstadt”. Please follow the sign “Unikliniken” from there on.



Public transport

From Frankfurt International Airport trains (“S-Bahn, S8) run from the “Regionalbahnhof” every 30 min to Mainz Central Station, which is reached within 25 min. Transfer time from the airport by taxi is 25 minutes and costs are about €50.

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For travel within the city centre ticket s for a dense network of trams at busses can be purchased by the drivers. Taxis are of beige colour and have a sign on the top (“TAXI”). There are many taxi stops (main station, market place, university hospital etc.) scattered around the city centre. If you want to hail on in the street, just put your hand up when you see one approaching.