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Abstract

A conference was held in Magdeburg, Germany on March 4–6 where experts discussed current research in neurotraumatology and neuropsychological rehabilitation. A total of about 60 research projects of a nationwide program project funded by the German Ministry of Education and Research (BMBF) were presented in conjunction with projects from the BMBF-initiative program "Neuropathology" of the Otto-v.-Guericke University of Magdeburg and the Graduate Program in Neuroscience which were funded by the German Research Society (DFG) and the State of Sachsen-Anhalt. The scientific program ranges from molecular, cell biological, anatomical, physiological and behavioral analyses of secondary cell death, regeneration and plasticity to clinical outcome studies and epidemiological evaluations. As such, the conference provides a broad overview of German neuroscience in the areas of neurotrauma, rehabilitation and brain plasticity. The abstracts are part of a special issue of *Restorative Neurology and Neuroscience* on "Neurotrauma and Neuropsychological Rehabilitation" which was published on the occasion of the conference.

Quality vs quantity of neuronal regeneration after axotomy and microsurgical nerve suture

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The speed of regeneration velocity and the amount of axonal reinnervation after axotomy can rather easily be increased. For that purpose the effect of Calcium-entry-blockers (nimodipine) [1], the predegeneration of nerves [2] or the application of nerve growth factors (CT-1, NT-1, NT-4) have been proved. Higher speed of reinnervation, however, does not lead to better quality of reinnervation. The bad functional outcome (autoparalytic syndrome) after axotomy and surgical repair is correlated to 3 histomorphologic findings: 1) Resprouting axons do not reach their original targets. Due to this *first order of misdirection* of reinnervation somatotopy is lost. 2) As *second order of misdirection* sprouting axons branch at the site of the nerve suture: One axon permanently innervates two or more muscles, causing incorrigible autoparalysis. 3) *Hyperinnervation* [3] of reinnervated muscles may cause additional problems in functional adaptation after regeneration.

The plasticity of central pathways and cognitive processing is able to correct these structural disturbances only in part.

References

[1] Angelov, D.N., Neiss, W.F., Streppel, M., Andermahr, J., Mader, K. and Stennert, E. Nimodipine accelerates axonal resprouting after facial nerve suture. *J. Neurosci*. **16** (1996) 1041–1048.

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0922-6028/99/$8.00

[2] Guntinas-Lichius, O., Angelov, D.N., Stennert, E. and Neiss, W.F. Delayed hypoglossal-facial nerve suture after predegeneration of the peripheral nerve stump improves the innervation of mimetic musculature by hypoglossal neurons. *J. Comp. Neurol.* **387** (1997) 234–242.
[3] Angelov, D.N., Gunkel, A., Stennert, E. and Neiss, W.F. Recovery of original nerve supply after hypoglossal-facial anastomosis causes permanent motoric hyperinnervation of the whiskerpad muscles in the rat. *J. Comp. Neurol.* **338** (1993) 214–224.

Longterm outcome after traumatic brain injury (TBI) in childhood: neuropsychological sequelae, academic performance, psychosocial and emotional adjustment.

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Current data about survivors of childhood TBI are only beginning to show a comprehensive picture of the long-term course of cognitive and social development of this group, but typically follow-up intervals tend to be relatively short. Our study [1] is concerned with the situation of this group in late adolescence or early adulthood.

Subjects (age 16 to 23 years at follow-up) undergo a comprehensive neuropsychological test battery, a neurological examination and a semi-structured interview. Questionnaires answered by subjects and their parents include the German versions of the Child Behavior Checklist and the Youth Self Inventory (CBCL, YSR; Arbeitsgruppe Deutsche Child Behavior Checklist, 1993) for evaluation of long-term emotional adaptation and social integration.

For 94 patients, after a mean time-interval of 9 (±3) years post trauma, IQ group mean is "low-average" (VIQ: 92, PIQ: 88), ranging from very poor to excellent individual scores. Subgroups with different kinds of persisting neuropsychological deficits can be identified. Early age at injury results in lower levels of intellectual functioning and scholastic placement. Preliminary analysis (n = 55) of CBCL and YSR data reveals a substantially higher level of perceived attention impairment and social problems for our subjects, compared to published data from a recent epidemiological study (PAK-KID study, Döpfner et al., 1977), whereas there was no difference in respect to physical complaints and aggressive behavior. Parental evaluation was consistently more favourable than self report.

Reference

[1] "Verbund Neurotrauma Kiel / Projekt IV: *Evaluation of neurological rehabilitation and course of cognitive development in children and adolescents with secondarily acquired brain damage*" FKZ 01 KO 9512

Allograft-Inflammatory-Factor-1 is not upregulated in microglial cells in the early phase after human traumatic brain injury

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Intracellular calcium has been shown to function as a second messenger and to be associated with activation of different cell types including microglia. In a previous study we reported a delayed expression of MRP8 (S100A8), a member of the calcium-binding S-100-protein family, in microglial cells after human traumatic brain injury (TBI). This issue raised the question whether other calcium-binding proteins associated with activation are expressed in an similar time course. We therefore examined immunohistochemically the expression of allograft-inflammatory-factor (AIF-1, identical to mrf-1), a 17 kD-peptide which is constitutive expressed in human microglia and has been associated with microglial activation in experimental animal models and in human cerebral infarctions. Paraffin-embedded brain tissue from 24 patients after TBI (survival times: few minutes to 6 months) was investigated for microglial AIF-1-expression and compared with 20 normal control cases. Detection of AIF-1 in normal controls confirmed the constitutive expression of this peptide in a subset of microglia. After TBI the density of immunoreactive microglia and the intensity of the AIF-1-expression did not markedly increase within the first week. In contrast early upregulation of AIF-1 has been reported in ischemic brain lesions. We conclude that the previous described delayed MRP8-expression and the lack of AIF-1 upregulation in microglia after TBI is in contrast to ischemic brain lesions and possibly reflects different activation of microglia.

Astroglial and microglial response to mechanical trauma in the infant rat brain

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Mechanical trauma to the parietal cortex of infant rats causes a local acute excitotoxic lesion and disseminated lesions, which occur in a delayed fashion and are morphologically apoptotic in nature. Apoptotic neuronal death is detectable by TUNEL staining at 6 hrs, peaks at 16–24 hrs, declines significantly by 48 hrs and has run its course by 5 days after trauma. It affects the frontoparietal and cingulate/retrosplenial cortices, thalamic nuclei, caudate, dentate gyrus and subiculum and is associated with profound elevations of CPP-32 like activity, upregulation of c-jun and downregulation of bcl-2 expression. Here we studied the response of micro- and astroglia within areas that display apoptotic cell death following trauma to the 7-day-old rat brain using GFAP (astroglia) and lectin-HRP (activated microglia) immunohistochemistry. Activation of microglia occured mainly around the area of acute excitotoxic injury in the parietal cortex and within white matter tracts, which were mechanically disrupted by the injury. Within the areas that suffered apoptotic cell death,

minimal microglia activation was detectable starting at 18 hrs after trauma. Increased numbers of astroglial cells appeared in areas suffering apoptotic deletion, starting at 12 hrs and peaking at 48 hrs after trauma. Apoptotic neurodegeneration is not associated with profound activation of microglia. Activation of astroglial cells appears to parallel severity of apoptotic neurodegeneration, possibly indicating that astroglia are actively involved in elimination of apoptotic cells.

Neurobehavioral early effects of occupational exposure to organic solvents mixtures

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To define proper and sensitive indicators of neurologic early effects after occupational exposition by organic solvents mixtures of car painters psychometric/-pathologic methods were used.

Forty five male clinically healthy volunteers (36.2 ± 10.1 years old, for 15 years exposed by organic solvents mixtures below the German limit) were compared with 48 male matched controls (40.8 ± 12.3 years old) without occupational exposition to neurotoxins. The test battery included a psychological screening. Thereby paper-pencil-tests were appropriated (MWT-B, KAI, HAWIE and d2-Test). Two PC-oriented psychometric systems were applied: COMBITEST-system and Swedish Performance Evaluation System SPES. These were used to test split attention, reaction time (simple, and multi-choice), and short-term memory. A complaint/ grievance profile was raised through the psychologic-neurologic questionnaire PNF by Seeber.

The car painters and the controls showed an identical level of the premorbid intelligence measured by the MWT-B-test (IQ = 100.3 ± 10.0 and 104.1 ± 13.8; $p > 0,05$). Fluid intelligence detected by KAI-test did not differ between the exposed subjects and the controls (IQ = 111.6 ± 11.8 and 113.0 ± 13.1; $p > 0,05$). The occupationally exposed men performed the following tests worse the controls: HAWIE (general knowledge; $p = 0.003$), d2-test (concentration-power value; $p = 0.026$), split attention (number of errors; $p = 0.042$, error time; $p = 0.020$). The both groups did not differ at all other mentioned tests. The exposed and the controls did not differ in PNF (neurological symptoms, drive, excitability, and specific symptoms).

Psychometric and psychopathologic performance indicate first signs of a neurotoxic degeneration after long-standing occupational exposition to organic solvents mixtures below the German limit (MAK-values), a combination with other clinical methods including physiological parameters improves the early diagnostics.

Mechanisms of functional recovery: investigations of target-reaching and food-taking in the cat

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A remarkable potential for functional recovery after lesions within the CNS is found in animal experiments. It is essential to understand the contribution of the different mechanisms, that might be involved. Size and location of the lesion will define the systems involved. The severity of the deficits, but also the ability to recover depend upon the amount of parallel processing in these systems and whether specific information is lost or only reduced in amplitude after the lesion. Furthermore, it is of importance whether the same or equivalent function was or can be achieved by several different systems. It is probable that this requires the induction of neuroplasticity. Whether plastic changes occur at a structural or at a synaptic level at the site of the lesion or at remote sides is still unclear.

We have addressed these questions in cats having received a surgical lesion of the dorso-lateral funiculus in C5 interrupting the descending input of cortico- and/or rubrospinal tracts onto the forelimb segments. In the target-reaching and food-taking task functional (by inspection of the behaviour) and kinematic (by three-dimensional X-ray cinematography) performance were quantified.

Long-term outcome could be either functionally and kinematicly complete, functionally complete with kinematic strategy shift or with permanent kinematic deficits depending on the tracts that were interrupted.

Cytokine-mediated regulation of antigen presenting molecules MHC1, MHC2 and B7-2 in the axotomized mouse facial motor nucleus

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The presentation of antigen is a key element in the development of the immune response which is mediated by association of antigen to major nistocompatibility complex glycoproteins (MHC1, MHC2) and expression of immunoaccessory molecules (B7, ICAM-1). Although the brain is an immunopriviledged site, recent evidence has suggested an immune surveillance for the injured mouse neural tissue (Raivich et al., *J. Neurosci.* **18** (1998) 5804). In the current study we therefore examined the regulation of the MHC1, MHC2 and B7-2 molecules in the axotomized mouse facial motor nucleus.

The normal facial nucleus showed rare MHC2+ perivascular macrophages but no immunoreactivity for MHC1 and B7-2. Transection of the facial nerve led to a strong and selective upregulation of MHC1 and B7-2 on the microglia in the affected nucleus, beginning at day 2 and reaching a max-

imum 14 days after axotomy. MHC2 was selective for perivascular macrophages. Expression of MHC1 and B7-2 was particularly strong on phagocytotic microglia, showing close temporal correlation with delayed neuronal cell death, phagocytosis of the neural debris and the induction of mRNA for TNFa, IL1b und IFNg. Transgenic deletion of IL6 or IL1 receptor type I did not affect the microglial expression of MHC1 or B7-2. Similar absence of effect was also seen in animals with severe combined immunodeficiency (scid), that lack T- und B-cells. However, a combined deletion of TNF receptors 1 and 2 (TNFR1&2-KO) led to a massive decrease in the expression of microglial MHC1 and B7-2 and to a striking absence of phagocytotic microglial nodules.

In summary, neural injury leads to the induction of MHC1 and B7-2 on activated, phagocytotic microglia. The impaired induction of these molecules, up to now, only in the TNFR1&2-deficient mice underlines the central role of TNF in the immune activation of the injured nervous system.

Preliminary epidemiological insights into a "black box": prehospital care of brain injured patients in Cologne

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Epidemiological data on the prehospital care of traumatic brain injury in Germany are scarce. Most clinical studies start collecting data beginning in the emergency room in average one hour after the accident. The prehospital care often remains a "black box".

We conducted an epidemiological study identifying 530 patients with severe brain trauma ($GCS \leq 8$ or $AIS_{Head} \geq 3$) out of 90.000 prehospital emergencies in Cologne from 1990 until 1996. Their prehospital and hospital charts were reviewed for defined variables. Univariate statistical analysis was performed.

Most severe brain injuries occurred in the afternoon between 3 and 6 pm. The average age of the population was 39 years, the average GCS was 6.8 and the average TS was 8.3 points. 39 % had a cerebral contusion and 11 % experienced an epidural hematoma, 23 % subdural hematoma, 3 % an intracerebral hematoma and 39 % had a cerebral contusion. Cerebral contusion and epidural hematoma had a lower hospital mortality of 20 % compared to subdural or intracerebral hematoma with a mortality rate of 43 %.

Severely brain injured patients are in a bad physiological condition already at the site of the accident. Unconsciousness as well as severe impairment of circulatory and respiratory functions are a challenge for prehospital care providers. The quality of prehospital care under these conditions may have a profound influence on the severity of secondary brain damage.

First clinical data of the tailored laminectomy for neuromodulator implantation

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Introduction and objectives: Neuromodulation of sacral roots provides an alternative mode of therapy for patients with urge incontinence or detrusor hypocontractility. We present our first followup data on sacral (S3) nerve stimulation in patients with a new surgical approach for sacral neuromodulator implantation. Sacral laminectomy and bilateral electrode placement led to distinct improvement of stimulation, positioning and dislocation. To minimize the surgical trauma we developed the tailored laminectomy for bilateral neuromodulator electrode implantation.

Materials and methods: 6 Patients with urge incontinence and 2 patients with a hypocontractile detrusor were treated in the following technique: After a 10 cm longitudinal skin incision, the spinous processes of S2 and S3 were exposed. Instead of a complete 2-level laminectomy, we performed an upside-down U-shaped laminectomy of S2 and S3 utilizing a high-speed ball drill. Thus, the spinous process of S3 remained in place and only the S2 process was partially removed. An electrode fixation hole was drilled at the edge of the laminectomy window and the wire was fixed with non-absorbable suture material.

Results: The average surgery time was 144 minutes. Complications: A seroma near the impulse generator. Patients with urge incontinence (followup 9 months): The number of leakages decreased from 7.2 to 0/day and functional bladder capacity increased from 298 to 352 ml. Patients with a hypocontractile detrusor (followup 8.5 months): Detrusor pressure increased from 12 cm H_2O to 38 cm H_2O. The post-voiding residual decreased from 350 to 38 ml.

Conclusion: Sacral tailored laminectomy is a fast, minimal invasive and successful technique for neuromodulator implantation.

Hippocampal cell damage after a contusion trauma in the brain of rats

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A contusion model described by Bernert and Turski, 1995 was used to investigate neurotraumatic changes in the hippocampus of rats. During narcosis with pentobarbital a 10 g weight from a height of 17 cm was guided onto a footplate resting upon the surface of the dura (4.5 mm diameter; 1.5 mm posterior and 2.5 mm lateral to the bregma of the right hemisphere). One, two and seven days after the trauma the number of neurons were quantitatively assessed after staining of coronal sections with cresyl violet. Cortical areas located immediately below the impact site were characterized

by a pronounced cell loss through all cortical layers. One day after trauma the number of pyramidal cells of the CA3 region in the ipsilateral hippocampus was reduced by 57 % in comparison to the contralateral hemisphere and to the corresponding areas of control rats. Cell loss was less pronounced in the CA1 and CA2 regions and not detectable in the CA4 area. Two days after the trauma the cell loss increased in the CA1, CA2 and CA3 regions and became also visible in the CA4 area. Surprisingly, the loss of pyramidal cells was less pronounced seven than two days post trauma in all hippocampal regions indicating a neurogenesis of these cells in the hippocampus. In this model of neurotrauma the effect of cortistatin-14 (CST-14) was investigated. CST-14 is a neuropeptide which binds to somatostatin receptors, shows neuroprotective effects in rats after kainic acid treatment and reduced the infarct size after middle cerebral artery occlusion. When injected intraventricularly 10 min before or 30 min after the trauma, a small dose of CST-14 (1 nmol) failed to affect focus size in the cortex or the cell loss in the hippocampus. The possibility that higher doses of CST-14 or other subtype specific somatostatin peptides have protective effects against the contusion trauma is presently investigated.

Discrimination training to intracortical electrical stimulation in Mongolian gerbils

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Research into cortical prostheses has been ongoing for several decades. So far, the focus in animal and human experimentation has been on visual cortical prostheses, but an auditory cortical prosthesis could potentially be a useful alternative for that part of the deaf population whose deafness is of central origin and thus cannot benefit from a cochlear implant. We have been conducting research on the principal feasibility of such an auditory cortical prosthesis, and have previously demonstrated that in an animal model, electrical stimulation in the middle layers of the auditory cortex reliably leads to cortical activation and can be used as a cue in avoidance learning (Breindl & Scheich, Assoc. Res. Otolaryngol. Abs. #662, 1999). However, any useful cortical stimulation will have to be not only detectable, but different forms of stimulation will have to lead to distinct perceptions. We thus conducted discrimination training using pulse rate-modulated stimuli.

Young adult mongolian gerbils were deafened with an intracochlear injection of neomycin and implanted with stimulating electrodes in the primary auditory cortex. After recovery from surgery, animals were trained in a shuttle-box to discriminate upward-modulated pulse trains of 10-1000 pulses per second (pps) from downward-modulated pulse trains of 1000–10 pps. When assessed with χ^2 and time-series analysis, some but not all individual animals showed significant discrimination between the two stimuli. Group discrimination was significant on days 4, 7, 8, and 10 of the 10-day training. This demonstrates that in electrical stimulation of the auditory cortex, modulation of the interpulse interval rate leads to specific sensations, and can in principle be used to convey information.

Spontaneous tissue repair processes following experimental spinal cord injury in the rat

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Recently, it has been demonstrated that axonal regrowth into the lesion following experimental spinal cord injury is more extensive and more organised than had previously been appreciated. Longitudinally orientated regrowth of of intrinsic CNS axons was associated with a “framework” of Schwann cells which formed within the lesion site. We have investigated the involvement of the cell adhesion molecules L 1 and PSA-NCAM in this spontaneous process of attempted tissue repair. Furthermore, we have investigated the possible role of neovascularisation in determining the remarkable degree of orientation displayed by the Schwann cells and axons within the lesion site. Double immunofluorescence demonstrated that L 1 was widely associated with the numerous neurofilament-positive nerve fibres within the lesion, however, there was very little evidence of PSA-NCAM expression associated with these axons. The vascular response to spinal cord injuv was rapid. Within 2 days, fine processes of migrating vascular endothelia could be observed entering the lesion. There was no clear spatial correlation between the newly formed vascular bed and Schwann cells within the injuyry site. This suggests that other, as yet poorly defined mechanisms, are responsible for influencing the orientation of thc regenerating L 1-positive axons within experimental spinal cord lesions. This work was supported by grants from the BMBF and the European Community (BIOMED.2).

Frequency analysis of EEG activity during electrical stimulation of sacral roots

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Introduction and objectives: Numerous neurological disorders are combined with impaired or lost bladder sensibility. It is difficult to objectively assess the afferent pathways from the bladder if patients experience no sensation. The aim of this study was to develop a method that enables, in an easy way, a statement whether the afferent pathways are intact or not.

Material and methods: In 4 male anesthetized foxhound dogs, EEG activity was recorded before (3 minutes), during (2 mintes) and after (3 minutes) continuous electrical stimulation of the sacral roots S2 (rectangular, biphasic impulse,

20 Hz, 100 µs pulse width, 1 mA amplitude). The frequencies of EEG activity were analysed by fast Fourier transformation of the time domain signal.

Results: Before stimulation, maximal intensity was observed in a frequency band between 1 and 3 Hz. During stimulation, the intensity between 1 and 3 Hz was clearly reduced and the intensity of frequencies around 4 Hz and 8 Hz was clearly higher. After stimulation, maximal frequency intensity returned to a range between 1 and 3 Hz comparable to the EEG activity before stimulation.

Conclusions: We conclude that the function of afferent pathways can be assessed by analysis of EEG activity. Further studies must be carried out by analysis of changes in EEG activity following bladder distension. If these results are reproducible in human investigations, this analysis may be an easy alternative or supplemental method for the evaluation of these pathways in patients with impaired bladder sensibility.

The role of selective bladder afference stimulation in cerebral evoked potentials

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Introduction and objectives: Previous studies in evoked potential recording by stimulation of the afferent pathways from the bladder by bladder distension showed latencies of the maximal response between 3.3 and 6.2 seconds. The aim of this study was to specify these long latencies by evoked potential recording electrical stimulation.

Material and methods: In 6 male anesthetized foxhound dogs, cerebral evoked potentials were recorded by electrical stimulation of the sacral roots S2/S3 with rectangular pulses (activation of all fibers) and quasitrapezoidal pulses (selective C-fiber resp. Aδ-fiber activation) before and after deafferentation of the sacral roots that were not stimulated. Evoked potentials were also recorded by direct electrical stimulation of the bladder. 4000 ms after the stimulus was investigated.

Results: Stimulation with rectangular pulses resulted in maximum cerebral responses within approx. 800 ms after stimulation. Smaller responses were observed up to 3500 ms after stimulation. Quasitrapezoidal pulses showed clearly reduced responses within 800 ms compared with rectangular impulses, whereas the cerebral response after 800 ms was clearer or almost unchanged. Direct stimulation of the bladder wall resulted in a maximal cerebral response between 2500 and 3500 ms after stimulation.

Conclusions: Selective stimulation of afferent pathways from the bladder (bladder wall, C-fibers or Aδ-fibers) seems to be important for the evaluation of bladder afferences by evoked potential recording due to reduction of artefacts from large myelinated fibers. Furthermore, it seems to be essential to record the late responses up to 4000 ms after the stimulus.

Implantable spinal cord cooling thermode for the treatment of pathological reflexes

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Lesions of the spinal cord are often accompanied by overactivity in the reflex pathways caudal to the lesion. A frequent sequel is reflex incontinence of the urinary bladder. At present, there is no satisfactory surgical or drug treatment of this urinary bladder hyperreflexia which often leads to irreversible damage of the bladder and kidney.

With the newly developed device a completely novel concept of treatment is introduced, namely the interruption of spinal reflex pathways by local cooling of the spinal cord. The implantable system consists of a thermoelectric spinal cord cooling thermode and a regulatory unit which contains the power supply of the thermode and the electronics for automatic control of the implant's performance.

For the treatment of urinary bladder hyperreflexia following spinal cord injury, the thermode is placed on the sacral spinal cord segments. The local cooling of the dorsal portion of the cord blocks reversibly the signal transmission between the overactive sensory nerve fibres from the bladder and the motor nerve cells that elicit the reflex contractions of the bladder. As at the used temperature of 18 °C only the dorsal portions of the spinal cord are blocked, the motoneurones in the ventral cord that supply the external urethral sphincter are unaffected. The result of the cooling treatment is a completely relaxed urinary bladder with a contracted sphincter, i.e. the formerly incontinent bladder becomes continent.

The device is presently employed successfully in animal experiments. For the treatment of patients with reflex incontinence the device is planned to be implanted under the skin and operated by an extracorporal transmitter via magnetic induction.

Reactive sprouting of central primary afferent C-fibre terminals following spinal cord transection

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The enzyme thiamine monophosphatase (TMP) is exclusively found in non-peptidergic small dorsal root ganglion neurones and can serve as a selective marker for a subset of primary afferent C-fibres. Using TMP-histochemistry we investigated the role of afferent C-fibres in the reorganization of spinal pathways following spinal cord transection (SCT).

Experiments were conducted on 6 adult rats 6 weeks after complete midthoracic (T7–T9) SCT. Sections of the spinal cord segments T6 and L1-S1 were processed for TMP and inspected light- and electronmicroscopically. The area of stained neuropil in the dorsal horn was quantitatively analy-

sed and the results compared to control rats with intact neuraxis.

In control rats TMP-positive terminals were restricted to lamina IIi of the dorsal horn and the lateral collateral pathway projecting to the sacral parasympathetic nucleus (SPN). In SCI rats TMP-positive fibers extended into lamina IIo, III and spread over a wider area in the region of the SPN. In both groups, TMP reaction product was exclusively found in unmyelinated (C-) fibres and scallopped synaptic terminals.

The expansion of TMP-positive neuropil suggests sprouting of C-fibres into spinal regions that are normally occupied by A-fibre terminals and which process input from pelvic viscera. Most TMP-positive C-fibres are assumed to originate in cutaneous receptors. Therefore, the results may provide an anatomical basis for the emergence of cutaneo-visceral excitatory reflexes in paraplegic humans and animals, such as reflex micturition by tapping of the abdominal wall or stimulation of the perigenital skin.

Recovery after locally applied high dose radiotherapy

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Purpose: To identify longitudinal effects of stereotactically guided conformal radiotherapy on brain functioning in adults with tumors adjacent to brain tissue.

Methods and materials: 14 patients with tumors adjacent to brain tissue were evaluated with neuropsychological measure of working memory, attention, psycho-motor function, long-time memory, with psychopathological tests and with MRI brain scans following surgery/biopsy prior to radiation, 3, 9 and 21 months postcompletion radiation. Data were analysed with repeated measurement analysis in combination with factor analysis.

Results: No patient showed tumor progress or radiation induced necrosis in MRI brain scans in postradiation measurement. Significant correlations were found between baseline and test 3 months postcompletion radiation in all mainfactors (n = 14). Reduction of significant correlations were found from baseline to 9 months (n = 13). Adverse effects on cognitive functioning were not to evaluate after 21 months postcompletion radiation (n = 7).

Discussion: Results show an early-delayed effect of stereotactically guided conformal radiotherapy in healthy brain tissue. Recovery were found over time after high dose irradiation concentrated to the target volume. Early-delayed postirradiation cognitive dysfunction might be influenced by microvascular damage. Further investigations in this prospective study will clear the nature of the process.

Processing of conversational and discourse information in patients with traumatic brain injury

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Patients with closed head trauma may often present problems of producing or comprehending language or of participating in conversations, although they are not aphasic in the sense of standardized aphasia assessment batteries. Most prominent in their communicative behavior is (1) a reduced ability of processing textual structures, e.g. the coherence of a piece of text, (2) disturbances at the level of conversational interactions (e.g. turn-taking-behavior), or (3) problems of comprehending the *pragmatic* aspects of language use [2,5]. These deficits, which are usually attributed to a cognitive rather than a linguistic impairment, are known to be of outmost clinical relevance, particularly as a predictor of rehabilitation outcome [1]. Experimental and parametric approaches in the assessment of non-aphasic, traumatic language disorders are still lacking.

We present two experiments which we developped to investigate traumatic patients' abilities of monitoring conversationally relevant information in *spoken* language. Experiment 1 was focussed on the processing of prosodic information used to guide the turn-taking-behavior in conversation. The experimental setting resembled a dual-task-situation in that a processing of both the textual content and the regulative intonation of short conversational interactions was required. The experiment used a reaction time paradigm to assess the advantage of natural over "gated" conversations in the detection of turns [4]. First results have shown that normal subjects, in fact, were able to utilize this advantage. Moreover, we identified brain-imjured subjects who failed to show any prosodically motivated RT-differences in the detection of turns.

Experiment 2 centered on the monitoring of changes in discourse topic. The task required subjects to respond to violations of textual coherence and cohesion in spoken discourse. It was considered to imply high attentional demands in addition to linguistic and inferential processing requirements. Our first data have demonstrated a severe failure of patients with dysexecutive disturbances to detect abrupt changes in discourse topic, whereas aphasic subjects showed-up with problems in the detection of errors concerning "small" cohesive elements.

References

[1] Chapman, S.B., Levin, H.S. and Culhane, K.A. Language impairment in closed head injury. In: Kirshner, H.S. (ed.) Handbook of Neurological Speech and Language Disorders. Dekker, New York. 1995, 387–414.
[2] Coelheo, C.A. Discourse production following traumatic brain injury: a critical review of recent literature. Aphasiology **9** (1995) 409–429.
[3] Glindemann, R. and von Cramon, Y. Kommunikationsstörungen bei Patienten mit Frontalhirnläsionen. *Sprache, Stimme, Gehör* **19** (1995) 1–7.

[4] Grosjean, F. and Hirt, S. Using prosody to predict the end of sentences in English and French: Normal and brain-damaged subjects. *Language and Cognitive Processes* **11** (1996) 107–134.
[5] Mentis, M. and Prutting, C.A. Analysis of topic as illustrated in a head-injured and a normal adult. *Journal of Speech and Hearing Research* **34** (1991) 583–595.

Nitric oxide produced by the inducible nitric oxide synthase is an important mediator after brain injury

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After brain trauma inflammation develops with an upregulation of inducible NO-synthetase (iNOS) and large amounts of NO are released into the surrounding tissue.

Four groups of male Wistar rats received a cold lesion on the exposed dura over the parieto-temporal cortex: Group 1: 1 h before and 7.5 h after 60 sec lesion therapy with aminoguanidine (AG). Group 2: as group 1, but sham therapy with sterile saline. Group 3: as group 1, but a less servere lesion for only 6 sec. Group 4: as group 3, but sham therapy with sterile saline. After 24 h brains were removed and 1 mm (group 1 and 2) or 0.75 mm (group 3 and 4) slices were cut with a vibratome followed by 2,3,5-triphenyltetrazolium-chloride staining and morphometric analysis. AG 10 mg/kg was disolved with sterile saline for intraperitoneal injection.

24 h after the 60 sec. lesion a 60.3 ± 18.1 (mean ± SD) mm^3 lesion developed, while after the 6 sec cold injury a much smaller lesion with 16.8 (2.6 mm^3 developed in the vehicle treated groups 2 and 4, respectively. After treatment with AG the attenuation in the 60 sec group was not significant but in the 6 sec group a significant protection of 22 % versus vehicle treatment was found.

NO from iNOS is a harmful mediator after brain trauma because blocking the enzyme reduces lesion size in less severe cold injury. In more severe injury the benefit of inhibiting iNOS is dramatically reduced since other mediator systems achieve more relevance.

Spatial behaviour in healthy and brain-impaired infants

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In order to investigate the development of spatial functions in infants and babies we had to adapt the Kiel Locomotor maze. The infants aged 13–15, 19–21 and 25–27 months play a “cuckoo-game” in which they have to find and remember working bells to ring for the cuckoo during acquisition. The 8 and 9–10 month old babies are exposed to an experimental setup analogous to the Acredolo-paradigm. The babies are trained to expect the cuckoo at one of two locations to either side from a fixed starting position. In order to assess spatial orientation strategies we changed the response requirements and maze configuration during testing for all age-groups. Results infants: No significant differences between the age-groups were found during acquisition. During testing nearly all infants showed a cue-strategy. Results babies: The 8 month-olds needed more time to reach the criterion than the older babies did. Testing revealed that a developmental change in spatial behaviour seems to take place between 8 and 10 months. While half of the 8 month-olds were still bound to egocentric orientation, most of the 9–10 month-olds showed an active search behaviour which can be interpreted as a transition from an egocentric to a nonegocentric strategy and some babies of this group already showed an object centered orientation. Preliminary observation of very-preterm neonates and infants after hypoplastic left heart syndrome are reported.

Combined sacral anterior and dorsal root stimulation for electrically induced micturition in the dog

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Introduction and objectives: In contrast to humans the physiological canine voiding pattern, is characterized by alternating rapid relaxations and contractions of the somatic urethral sphincter in the distal urethra at a frequency of 1–2 Hz. Since this pattern is abolished by deep anesthesia or dorsal rhizotomy, it is probably triggered by afferent impulses from the distal urethra when fluid is entering this area. Aim of our study was to investigate the effect of combined afferent and efferent stimulation on micturition in the dog, when choosing an afferent stimulation pattern, imitating the physiological canine voiding pattern.

Methods: In four female mongrel dogs the intradural left dorsal S2 nerve root was stimulated for 10 sec with biphasic 500 µsec quasitrapezoidal pulses using 20 Hz bursts of 1 sec on and off periods. While the afferent stimulation was still going on, the bilateral S1 and S2 sacral anterior roots were continuously stimulated for 10 sec with biphasic 500 µsec quasitrapezoidal pulses at 20 Hz and a current amplitude giving maximum block of somatic urethral sphincter activity. Afferent stimulation was stopped 10 sec after turning off the anterior root stimulation. For comparison isolated stimulation of the same sacral anterior roots for 10 sec was performed, using either continuous 20 Hz trains of 500 µsec quasitrapezoidal pulses or 100 µsec conventional rectangular pulses (1 mA).

Results: While sufficient voiding could be achieved only after complete sacral deafferentation when only the anterior sacral roots were stimulated with quasitrapezoidal pulses, combined afferent and efferent stimulation resulted in the most effective micturition even without performing any dor-

sal rhizotomy. Statistically there was no difference between the urodynamic parameters obtained during isolated efferent stimulation with quasitrapezoidal pulses after deafferentation and combined afferent and efferent stimulation without sacral deafferentation. With isolated continuous sacral anterior root stimulation using conventional narrow rectangular pulses no micturition, or evacuation of minimal amounts of fluid could be achieved, no matter whether a complete sacral deafferentation was performed or not.

Conclusions: In spite of many unanswered questions (efficacy after spinalization, evocation of pain and autonomic dysreflexia etc.) this is a very interesting observation, since in sacral root stimulation for bladder evacuation afferent impulses have been predominantly seen as undesirable. Further investigations are planned in order to determine whether natural afferent impulses can be suppressed during the storage phase, allowing low pressure storage of urine, while using afferent stimulation in combination with selective anterior root stimulation for improved bladder evacuation.

Sacral Neuromodulation: Long-term results of 55 patients with incontinence and voiding dysfunction

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Introduction and objectives: Sacral neuromodulation has now become a more widely used treatment modality for lower urinary tract dysfunction. Aim of this study was to determine the clinical responserates of percutaneous sacral nerve test stimulation and permanent sacral foramen implants and to investigate the long term clinical efficacy and safety of permanent sacral foramen implants.

Patients and methods: Since May 1990 percutaneous sacral nerve test stimulation was performed in 184 patients with incontinence or severe voiding dysfunction. In all patients conventional treatment modalities had been unsuccessful. If symptoms, quantified by a voiding chart, improved at least 50 % during the test stimulation period, unilateral implantation of a S3 foramen electrode (Pisces Quad Lead, Medtronic Inc., U.S.A.) and a battery powered pulse generator (Itrel II, Medtronic Inc., USA) was performed. 55 patients (49 women and 6 men, mean age 49,0, range 24 to 77 years) out of 184 initially screened (29,9 %), received a permanent implant. The mean follow up was 44,3 months, range 1 to 89 months. 21 patients suffered from idiopathic motor urge incontinence and 28 from urinary retention due to severe detrusor sphincter dyssynergia. Additionally 5 patients with sensory urge incontinence and one patient with stress/urge incontinence were implanted.

Results: Symptomatic improvement by more than 50 % during the entire follow up period could be achieved in 16 of the 21 patients with motor urge incontinence (76,2 %). 6 of the 21 patients were clinically cured (28,6 %). 22 of the 28 patients with urinary retention (78,6 %) improved by more than 50 %. 18 of these 28 patients (64,3 %) voided without residual. 3 of the 5 patients with sensory urge incontinence improved by more than 50 %. The individual with mixed incontinence did not respond to the treatment. Complications requiring surgical revisions occured in 14 of the 55 implanted patients (25,5 %). They included infections in 5 cases (9,1 %), lead migrations in 2 cases (3,6 %), pain at the site of the implanted pulse generator in 3 cases (5,6 %) and a lead fracture, an electrode insulation defect, a skin erosion at the site of the pulse generator and a polyurethane allergy in 1 case (1,8 %) respectively. The initially high reoperation rate (1990–1995: 29,7 %) could be significantly reduced by hardware modifications and by gaining more experience (1996–1998: 16,6 %).

Conclusions: Only 29,9 % of all patients screened percutaneously improved significantly during the stimulation test period. This low rate is at least partially caused by an inappropriate position of the test lead. Permanent implants offer a sustained clinical effect. In patients with urge incontinence it should be considered in those refusing temporary techniques or in those requiring too much effort to achieve a sustained clinical effect. In patients with urinary retention the decision for a chronic implant is easier because of the lack of effective therapeutic alternatives.

Pro- and anti-inflammation after multiple trauma – an analysis of plasma levels on the time course and type of injury

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Introduction: Different pro- and anti-inflammatory mediators are involved in the restoration of the disturbed physiological balance after accidental-trauma. For the outcome of the traumatized patient it is very important to gain an inflammatory mediator-homeostasis as fast as possible. If the inflammatory potential predominates, SIRS is a consequence, if the anti-inflammatory mediators predominate immunosuppression with septic complications may follow. Interleukin (IL)-10 is known as the predominant anti-inflammatory cytokine, released into liquor and plasma after polytrauma, which counterregulates inflammatory cytokine-productions. IL-13, not found in the brain, is also known to have anti-inflammatory physiological functions. *In vitro*-experiments have shown that IL-13 incubation of isolated monocytes reduce the LPS-induced synthesis of tumor-necrosis-factor (TNF)-α, IL-1β, IL-6 and IL-8. Soluble tumor necrosis factor receptors (sTNFr) p55 and p75 may also participate in

anti-inflammation by inactivating excessive circulating TNF-levels. Till now it is unknown, if there is any correlation between the anti-inflammatory mediators after trauma.

Methods: Blood was taken from 93 polytraumatized patients from day 1 to 10, 14, 21 and 28. During the first three days additional samples were taken every 6 hours. Patients, who participated in this study were divided into 3 subgroups: Patients with an isolated severe head trauma (SHT; Grp. I), patients with SHT and additional polytraumatic injuries (Grp. II) and patients with polytraumatic injuries without SHT (Grp. III). After preparation of the plasma the IL-6, IL-10, IL-13 and sTNFr-levels were determined by ELISA-technique. The injury severity was defined by the abbreviated injury score (AIS). The correlation between the different plasma cytokines after accidental-trauma was calculated using the correlation-coefficient by Spearman.

Results: Pro-inflammatory IL-6 elevations during the first 24 hours of accidental-trauma were closely accompanied by increased anti-inflammatory IL-10 and sTNFr ñlevels, which both declined rapidly during the next 3 days if there were no further clinical complications. A strong correlation between IL-10 and IL-6 levels with a correlation-coefficient of $r = 0.66$ ($p < 0{,}005$) was determined. There was a smaller but clear cut correlation of anti-inflammatory IL-10 to sTNFr (IL-10/ sTNFr p55 = 0,379; IL-10/ sTNFr p75 = 0,214; $p < 0{,}005$). Additionally the IL-6, IL-10 and sTNFr plasma-levels of patients with an isolated SHT were lower than in polytraumatized patients with or without SHT. Anti-inflammatory IL-13 plasma-levels were not elevated in comparison to healthy donors either after accidental- or surgical-trauma. Interestingly no correlation between the anti-inflammatory parameters IL-10 and IL-13 became evident ($r = 0.046$; $p = 0.88$).

Conclusions: IL-6, IL-10 and sTNFr are valuable tools to describe the clinical situation of the traumatized patient, which corresponds to the severity and type of injury. IL-13 does not add any further systemic anti-inflammatory potential to the patients homeostasis. We assume that IL-13 is either produced in very low amounts or is only produced locally. Monitoring of IL-6 and IL-10 in combination with anti-inflammatory soluble TNF-receptors may help to get a better understanding of the patients clinical situation. In this context monitoring of these parameters may help in decision making (timing, type) for secondary surgical interventions (e.g. osteosynthesis). This is subject of our further investigations.

A novel role of connective tissue growth factor in brain repair processes?

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Connective tissue growth factor (CTGF) is a 38 kD cysteine-rich protein expressed by fibroblasts and endothelial cells. CTGF is strongly mitogenic for fibroblasts and a potent inducer of extracellular matrix (ECM) synthesis by these cells. CTGF is overexpressed in a variety of fibrotic diseases and during wound healing. However, a role of CTGF in brain injury has not been demonstrated yet. Here, we used unilateral intraventricular application of kainate in mice to produce a severe lesion in the CA3 region of the ipsilateral hippocampus. Interestingly, this lesion was accompanied by a strong upregulation of CTGF mRNA and protein expression as shown by RNAse protection assay and immunohistochemistry, respectively, with higher expression levels in the ipsilateral hippocampus compared to the contralateral side. We next investigated the effect of the potent neuroprotective factor bFGF on CTGF expression. Upon co-injection of bFGF and kainate a strong enhancement of CTGF mRNA expression was observed. To determine a possible correlation between CTGF expression and ECM production, we compared the temporal and spatial expression pattern of CTGF with that of fibronectin and collagen I. Both matrix molecules were present at high levels in the ipsilateral hippocampus as early as one day after kainate lesion and a strong staining with both antibodies was still seen at day 14 after injury. These data provide the first evidence for CTGF expression after CNS injury and suggest a role of neuroprotective factors in the regulation of CTGF expression. Furthermore, our data indicate that increased levels of CTGF might contribute to glial scar formation.

New aspects in the gait rehabilitation of hemiparetic subjects after traumatic brain injury and stroke

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A first gait analysis study investigated the immediate effects of a therapeutic facilitation of the gait of hemiparetic subjects as compared to when walking without and with a cane. The results showed that the subjects walked faster, with a longer stride, more symmetric, and with a longer single stance period of the affected lower limb during the therapeutic intervention. At the same time, the therapists were able to facilitate the activity of several weight-bearing muscles because of a promotion of hip extension and adequate loading of the affected lower limb. In conclusion, the study confirmed therapists' intention of training a more dynamic and more balanced gait with facilitation of relevant weight-bearing muscles. An after-effect, however, could not be demonstrated.

A second project compared the gait outcome of two groups ($n = 24$) of non-ambulatory chronic hemiparetic subjects. The first group received the treadmill training alone over a period of three weeks while the second group additionally received physiotherapy focused on gait training. The gait ability of the second group scored higher at the end of

treatment, the differences, however, waned six months later. The study thus showed that more therapy effected better immediate effects but that differences got less after demission.

A third project is on the development of a computer-assisted gait trainer enabling non-ambulatory subjects to train a gait-like movement supported by a servo-controlled machine. First results show that hemiparetic subjects actually can train a gait-like movement with comparable activation of weight-bearing muscles without over stressing therapists.

Neural plasticity in the auditory system of the gerbil (Meriones unguiculatus) after early binaural deprivation followed by Cochlear Implant -rehabilitation

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Problems arising during the habilitation of prelingually deafened children using Cochlear implants (CI) deal with technical aspects and the effects of long-term stimulation of the developing auditory system. The success of habilitation is correlated with the onset of deafness and the begin of rehabilitation. We carried out systematic investigation of these questions in animal experiments using the gerbil (*Meriones unguiculatus*), a well-etasblished animal model in hearing research.

Deafness was induced on the 14th **d**ay **a**fter **b**irth (DAB), i.e. before the late natural onset of hearing (16th DAB), by a single intracochlear application of an ototoxic aminioglycoside antibiotic (neomycine sulfate). Animals were provided with specific one-channel CI on the 30th DAB. To simulate the relevance of speech in humans social sounds of gerbil uttered during mother-child communication were recorded, frequency transformed, combined with noise signals and stored on **d**igital **a**udio **t**ape (DAT). During the stimulation period this signal was transmitted from DAT to the speech processor (CLARION® Advanced Bionics) and to the freely moving gerbil for 2 h every day (35.–90. DAB). For investigation of the maturation of the auditory system, click-evoked eABR (electrically evoked auditory brainstem response) were registrated with needle electrodes (vertex / mastoid) from the 35th to the 90th DAB. There were 4 groups examined: normal hearing animals (NORM, n = 24), binaural deafened – implanted and **not stimulated** (VO30, n = 7), binaural deafened – implanted and **early stimulated** (VK30, n = 7) and binaural deafend – implanted and **late stimulated** (VK60, n = 3). Finally the cochleae were investigated with scanning electron microscopy (SEM) and the *Nucleus cochlearis* were compared histologically.

During maturation of normal hearing animals (NORM) latencies and interpeaklatencies (IPL) of the ABR decrease. As a consequence of acoustic deprivation, the IPL III-VI of group VO30 increase. Early electrostimulation (VK30) prevents this functional degeneration, whereas late provision with a CI (VK60) has no positive influence. The electrophysiological results correlate with morphological changes in the cochlea and the Nucleus cochlearis. The study shows, that the neural plasticity of the auditory system after early sensory deprivation is maximal in an early ontogenetic stage.

Monohydroxy fatty acids as lipid peroxidation products in rat brain mitochondria

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Degenerative diseases of the nervous system are associated with defects in energy metabolism accompanied by an elevated generation of reactive oxygen species ensuing oxidative damages of proteins, lipids and nucleic acids. A GC-MS method was developed to determine monohydroperoxy- and monohydroxy fatty acids as early and more specific markers of lipid peroxidation rather than TBARS, lipohydroperoxides and monofunctional aldehydes as 4-hydroxynonenal.

The monohydroxy fatty acids present in functionally intact mitochondria were 2-, 3-, 5-, 8+9, 11+12 and 15-HETE. After induction of an oxidative stress with iron/ascorbate especially 5-, 8-12 and 15-HETE increased with a TBARS like kinetics, whereas 2-HETE was characteristically enhanced during the induction phase of peroxidation. In mitochondria most hydroxy fatty acids are bound in phospholipids. Free hydroxy fatty acids exhibit much lower levels and remain nearly unchanged during peroxidation. Chiral phase analysis documents, that hydroxy fatty acids constitute a racemic mixture, indicating their formation mostly by autoxidation.

Influence of intracranial pressure on resolution of vasogenic brain edema following intracerebral hemorrhage

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Objective: Aim of the current study was to quantify resorption of vasogenic brain edema into the subarachnoid space and the ventricular system following intracerebral hemorrhage.

Method: An intracerebral hematoma was induced by injection of 500 µl of blood into the left frontal lobe of rabbits (n = 17) at a rate of 10 ml/h. Na^+-fluorescein (MW376) was administered as continuous intravenous infusion and Texas-Red-Albumin (MW67.000) as bolus, beginning after induction of the hematoma. To study clearance of these markers

by the ventricular system and the subarachnoid space, ventriculo-cisternal perfusion and superfusion of the exposed brain surface by a closed cranial window were employed. The ICP was maintained between 2-5 mmHg (low pressure group, n = 6), 9–12 mmHg (medium pressure group, n = 6) and 14–17 mmHg (high pressure group, n = 5) CSF and blood samples were collected every 30 min for 8 hrs and the concentration of the fluorescent markers in the effluates was measured by spectrophotometry.

Results: In all ICP groups Na^+-fluorescein started to accumulate at 60 min in the subarachnoid space, while at 90 min in the ventricular system. In contrast, clearance of Texas-Red-Albumin was not observed, neither into the ventricles nor the subarchnoid space. In the low pressure group Na^+-fluorescein (mean ± SEM) amounted up to 1.89 ± 1.05 µmol in the ventricular system as compared to 1.98 ± 1.31 µmol in the medium and 0.44 ± 0.25 µmol in the high pressure group. In the subarachnoid space the marker reached 2.52 ± 1.89 µmol under low pressure whereas 4.27 ± 2.76 µmol in the medium and 1.03 ± 0.67 µmol in the high pressure group.

Conclusion: Our preliminary data demonstrate that vasogenic edema fluid following intracerebral hematoma is drained into both CSF compartments, albeit with delay into the ventricular system. In all pressure groups resorption occurs earlier and to a higher extent into the subarachnoid space as compared to the ventricular system. Total edema resorption was found to be dependent on the intracranial pressure with the highest resorption at moderate intracranial pressures and the lowest resorption under high pressures.

Effects of αMβ2-integrin stimulation and deletion on the cellular reaction in mouse central nervous system

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The integrin αMβ2, also known as complement recept or type 3 (CR3), Mac-1 and CD11b/CD18, is a pluripotent receptor for cell-surface molecules (ICAM-1) and components of the coagulation and complement pathway. Although αMβ2 is already present on CNS microglia, it is strongly enhanced in almost all form so of brain pathology. Here, we studied the effects o f αMβ2 stimulation or genetic deletion on the cellular reaction in mouse CNS.

Intraperitoneal injection of αMβ2-specific monoclonal antibody 5C6 led to the entry of antibody in areas without blood-brain barrier, followed by diffusion into surrounding parenchyma and binding to the resident microglial cells. Clear influx was also observed in the cerebellum, dentate gyrus, submeningeal cerebral cortex and many 0.1–0.2 mm large round areas or “leaky spots” scattered throughout the brain, associated with an increase in microglial αMβ2 expression and cell number, reduced ramification, permeability to human serum album in and astrocyte GFAP- immunoreactivity. In contrast, deletion of the gene encoding the αM-subunit did not affect the cellular reaction in the axotomized mouse facial motornucleus, with a normal increase in the microglial cell number and activation markers, and astrocyte response which did not differ from wild type animals.

In summary, activation or deletion of the microglial αMβ2- integrin leads to two different sets of results. Antibody ligation of the αMβ2 induces cellular activation in the affected brain, but its deletion does not interfere with the normal neuroglial response in the axotomized facial nucleus. Despite the widespread induction of αMβ2, the current data suggest a more circumscribed and limited role, which is not operative in the indirect brain trauma models.

GAP-43, L1 and TAG-1 mRNA expression in rat retinal ganglion cells (RGCs) is influenced by BDNF, S-PBN and L-NAME after optic nerve lesion

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BDNF alone, the free radical scavenger S-PBN and the NO synthase inhibitor L-NAME in combination with BDNF increase the number of surviving RGCs after optic nerve lesion (Klöcker et al., *J. Neurosci*. **18** (1998) 1038–1046). Lesion-surviving and axon-regenerating RGCs synthesize GAP-43 and the cell adhesion molecule (CAM) L1, but downregulate the CAMs TAG-1 and SC-1 (Jung et al., 1997, *Mol. Cell. Neurosci*. **9** 116–131). Here, we investigated the influence of BDNF, S-PBN and L-NAME on GAP-43 and CAM mRNA expression in RGCs of lesioned and grafted rats. The effects of BDNF are: increase of GAP-43 and L1 mRNAs, de novo synthesis of TAG-1, but no change of SC-1 mRNA. The effects of S-PBN and L-NAME are: decrease of GAP-43, L1 mRNAs and no upregulation of TAG-1 and SC-1 mRNAs. Thus, although BDNF alone, S-PBN and L-NAME in combination with BDNF, improve cell survival, only BDNF promotes GAP-43 and CAMs mRNA expression. Still, BDNF does not increase the number of axon-regenerating RGCs. Supp. by the BMBF.

Trained discrimination of temporal patterns: cochlear implants in gerbils

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For rehabilitation of patients with cochlear implants a number of speech coding strategies have been tried. Practically all types currently in use transform spectral energy in separate frequency bands into amplitude modulations of constant rate pulse trains. While coarse spectral cues and temporal information about word and syllabic segmentation are preserved by these strategies, information about the rich

temporal fine structure of the complex wave forms of speech is largely lost.

In order to explore whether upward or downward interval modulation of pulse trains cause discriminable percepts, young adult mongolian gerbils were deafened by intracochlear injection of neomycine-sulfate and implanted with a set of cochlear stimulating electrodes. After recovery from surgery the animals were trained for six days in a shuttle-box to discriminate upward-modulated pulse trains from symmetrically downward-modulated pulse trains. When the modulation covered a range of 10 to 1000 pps pulse repetition rate, the animals showed significant (Wilcoxon Matched-Pairs Signed-Rank Test; $p = 0.05$) discrimination starting on the third day of training. When narrower ranges of repetition rate (e.g. 200 to 300 pps) were used, no significant discrimination was observed.

These data provide evidence that symmetrically upward and downward modulated pulse trains can be discriminated after training. However, the resolution of the percepts evoked by these stimuli appear to be limited and require further study. Since transients in speech marking the beginning transition between or the termination of phonemes are characterized by interval modulations of waveforms as one parameter in the temporal domain, it appears worthwhile to implement coding strategies that make use of interval modulated pulse trains to mimic such transients.

Significance of traumatic brain stem lesions for the outcome after severe brain injury

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Brain stem lesions after severe brain injuries (BI), not detectable on CCT because of bone artefacts, become visibible by Magnetic Resonance Imaging (MRI). The significance of brain stem lesions for the outcome is unknown. In this prospective study MRI was performed in 71 comatose patients within seven days (mean: 3.5 days) after BL Brain stem function was assessed by registration of somatosensory (SEP) and auditory evoked (AEP) potentials. Data were correlated to clinical parameters from intensive care treatment. Brain stem lesions were depicted in 70 % od the patients. Bilateral pontine lesions proved to be 100 % fatal, non-brain stem lesions had a mortality of 10 %. In singular cases circumstances allowed for a clear clinical distinction between primary and secondary brain stem lesions: In two clearly secondary brain stem lesion there were no traces of blood. Mean ICP levels of patients without brain stem lesions were simular to those with brain stem lesions. Predictive value for bilateral brain stem lesions was maximal for MRI and SEP, submaximal for AEP. It is concluded that brain stem lesions are more frequent in severe head injury than previously reported from studies based on neurophathological or CT data. Early MRI after head injury is of higher predictive value than CT. It is concluded that is was not mainly the increased ICP accounting for the high mortality of brain stem lesions, but the morphological lesions itsself.

Retinal glutamate receptor expression in response to optic nerve injury

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Previous work has shown that retinal ganglion cell death after optic nerve injury can be attenuated by the administration of NMDA receptor antagonists, suggesting that retinal excitotoxicity is involved in the degenerative response in the ganglion cell layer. We could recently show that after a partial optic nerve crush NMDA-R2 receptor subunits are downregulated and alternative splicing of the NMDA-R1 receptor is altered (Kreutz et al., *J. Neurosci*. **18** (1998) 8278). Significant changes in the regulation of AMPA receptor genes have been reported after brain ischemia and other neuronal disorders (Pellegrini-Giampietro et al., *TINS* **20** (1997) 464). We therefore sought to determine whether axonal injury of the optic nerve alters the expression of the AMPA receptors GluR1-4. We found that transcript levels of the GluR2 subunit are downregulated in the ganglion cell layer prior to retinal cell death (which occurs mainly between day 5 and 2 weeks post injury). This downregulation seems to preferentially occur in axotomized RGC and to a much lesser degree in RGC with an axon still in continuity to the superior colliculus. Thus, it is conceivable that after crush RGC will have a different response to glutamate and that degenerating RGC might have Ca^{2+}-permeable AMPA receptors. It remains to be prooven whether downregulation of GluR2 is part of a Ca^{2+}-dependent initiation of apoptotic cell death in response to axonal injury.

Kinematic analysis of reaching and grasping in healthy subjects and in children after traumatic brain injury

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Reaching and grasping movements of 54 healthy children (age 4–12 years) were studied by computerized motion analysis, using an optoelectronic system which recorded the positions of external markers attached to the wrist, thumb, and index finger of the dominant reaching hand. The experimental scene was scaled according to body proportions. The kinematic profiles showed a higher fluency of movement and a more stable coordination of hand transport and grip formation in older children. Movement duration, reaction time, and the number of acceleration-deceleration segments

(movement units) per reach declined with age. The younger children opened their hands relatively wider than the older ones, thus grasping with a higher safety margin.

Furthermore prehension movements were studied in 16 children (age 9.3 ± 2.6 years) after traumatic brain injury. The mean posttraumatic interval was 12 months. These patients showed a prolonged reaction time and an increased movement duration, compared to age-matched healthy control children. The quality of reaching and grasping could be documented by kinematic recordings. While the velocity of reaching was reduced, the patients opened their grip wider than control subjects. The averaged data showed no significant changes of this pattern after 8 weeks of rehabilitation, although improvements could be documented in individual cases.

Reorganization of the motor system after spinal cord lesion disappears with clinical improvement

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Introduction: In adults traumatic lesions of the central nervous system lead to changes in motor cortex excitability. At this point it is still unclear what the behavioral consequences of this form of motor reorganization are. Changes may be related to sequelae of the lesion or may represent compensatory changes reflecting recovery of function. To differentiate between these two mechanisms we performed follow-up studies in patients with spinal cord lesions [SCL].

Methods: At time 1 (T1) transcranial magnetic stimulation was performed in fifteen patients with spinal cord lesions and fifteen healthy adults. Motor evoked potentials (MEP) at rest and during voluntary activation were recorded from two unaffected target muscles proximal to the lesion (M.abd.poll.brevis [APB], M.biceps brachii [BIC]). Excitability (motor threshold [MT], facilitation effect [FE], maximal MEP-amplitude [MA], recruitment curves [RC]) and silent period [SP] were measured and correlated with localization and severity of the lesion. Six patients with improvement of clinical status were studied a second time after a mean interval of 12 weeks (T2).

Results: For APB, findings in patients and controls were not different. At rest, recordings in BIC were normal, except for a tendency towards lower MT ($p = 0.07$). However, during activation of BIC, patients showed a smaller FE ($p = 0.03$), lower MA ($p = 0.04$), smaller slope of RC ($p = 0.02$) and shorter SP ($p = 0.05$) compared to healthy subjects. Effects on FE, MA and RC-slope normalized with clinical improvement when studied at T2.

Conclusion: Our data suggest reorganization of the motor system in patients following SCI that disappears with clinical improvement. Motor reorganization after SCL, therefore, is more likely to be related to sequelae of the trauma than to represent compensatory changes reflecting recovery of function. The fact that changes were restricted to BIC in our patients may suggest that reorganization takes place at a cortical level, as BIC is represented closer to the disconnected area than APB.

Spatial behavior in healthy and brain-impaired preschoolers and school children

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We investigated spatial behavior in healthy and brain-injured children by using the Kiel Locomotor Maze, a maze for humans incorporating basic features of widely used animal paradigms. Children have to find and to remember defined locations in an experimental setup with completely controlled intra- and extra-maze cues until learning criterion is reached. Spatial strategies are assessed by altering the configuration of proximal and distal cues. The apparatus allows the assessment of spatial working memory, reference memory and of orientation strategies. 96 healthy children aged 3–12 years and 20 children with severe closed head injury (CHI) were investigated. All healthy children were able to learn the maze. Spatial strategies in healthy children revealed a developmental pattern.

3-, 4- and 5-year-olds were shown to use a “cue”-strategy, orienting towards proximal cues. 10- and 12-year-olds displayed a “place”-strategy, using distal cues for orientation. 7-year-olds were shown to be at an age of transition. CHI-children who had been in a coma for more than 14 days were not able to learn the maze. CHI-children who reached learning criterion were shown to be severely impaired with respect to orientation strategies. Assessment over a period of time showed that these impairments are partly reversible. It is concluded that spatial behavior develops successively and is differentially affected by CHI.

fMRI of Cortical Activation during Simple Motor Tasks in Patients with Traumatic Brain and Spinal Cord Injury

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Functional magnetic resonance imaging (fMRI) was used to evaluate cortical activation in patients ($n = 9$) with severe traumatic brain injury (SHT) at different time intervals (0.2 month to 115 months) as well as in patients with complete ($n = 4$) and incomplete ($n = 1$) spinal cord injury (SCI) for different voluntary movements. The results were compared with normal controls ($n = 10$).

fMRI was performed with a 1.5 Tesla Scanner using echo planar imaging (matrix 96*128, FOV 250 mm, TE 59 ms, scan time 7 sec) of the whole brain with 36 slices of 3 mm thickness and 1 mm gap. 48 measurements (six measurements each alternating four times during movement and rest) were performed per condition. Realignment and statistical

analysis of the functional data was performed using SPM'96 (Dept. of Cogn. Neurology, London). Activated voxels above a threshold of $p < 0.01$ were analysed.

In SHT patients with disseminated frontal lesions (SHT ≥ IV after Soyka) repetitive movement of the right and left hand (fist making) revealed: (1) a lower activation in contralateral M1 and S1 with the presentation of more fractured somatotopic maps, (2) a negative correlation between activation in the supplementary motor area (SMA) and the amount of right hand paresis ($p = .028$) and (3) a lower activation in the left M1 during right hand movement in patients with severe paresis of the left hand ($p = .043$).

Patients with complete and incomplete SCI were investigated during elbow and thumb movement to locate the activation maxima in contralateral M1. Assuming that the cortical elbow representation is more proximal to the deafferentiated body parts than the thumb, we intended to see a shift in cortical organisation. We found a displacement in the direction to the interhemispheric fissure for the elbow but not for the thumb movement in all patients with complete SCI compared to normal subjects. This shift of adjacent located elbow representation into the deafferentiated body area seems to indicate that cortical reorganisation occurs in M1 after complete SCI.

Catecholamine concentrations in CSF and plasma in patients after traumatic brain injury

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Catecholamines (CAT) are widely used in patients during acute management of traumatic brain injury (TBI). Whether catecholamines are endogenously released or, if exogenously administered, diffuse into the intrathecal compartment is unknown. We measured plasma and CSF epinephrine (E) and norepinephrine (NE) concentrations of 13 patients from day one up to 14 days after severe brain injury (GCS < 8). The integrity of the blood-brain barrier (BBB) was evaluated by calculation of CSF/serum ratio of albumin levels. Patients were allocated in two groups: one group was treated with Arterenol^R and Dopamine (I), the other was not (II). Control values were obtained from patients with multiple sclerosis (MS). In group I, two patients with BBB opening, daily administration of Arterenol^R led to an increase of NE in plasma to above 1000 ng/ml and a parallel rise in CSF as well. In group II, one patient with normal BBB function showed increased NE levels in CSF but not in plasma; in two others NE and E levels were increased in plasma, but not in CSF while BBB was intact. In a fourth patient NE levels were elevated in plasma but not in CSF in the presence of BBB impairment. In this patient increase of CAT levels in CSF was observed only at plasma levels exceeding 600 ng/ml. The results suggest, that in principle an exchange of catecholamines between blood and CSF is possible. However, an increasing number of patients is required for further interpretation.

Psychopathological alterations after traumatic brain injury in children and adolescents and therapeutic interventions in the course of rehabilitation

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Psychical impairment and psychopathological alterations after neurotrauma are closely interacting with cognitive and other functional limitations (Rutter, 1981; Lehmkuhl & Thoma, 1989). This interdependence must doubtlessly be taken into account in the course of rehabilitation. Inadequate psychological coping and the development of psychopathological alterations may lead to insufficient success in rehabilitation, leaving the child's remediation much behind the possible.

In this context Prigatano (1991) emphasized the role of psychotherapy in rehabilitation, because the patient's basic emotional and motivational conditions should be taken into account in order to avoid psychopathological alterations. A stable psychosocial environment, namely the family, is most important to enhance psychological coping with the trauma and its sequelae. Rivara et al. (1993) see this as the essential predictor of posttraumatic development. The family's coping with the incident has also to be looked after in the course of therapy to promote stability.

A systematic, controlled and randomized study is carried out since July 1996 to evaluate the effects of a neuropsychological and psychotherapeutic rehabilitation program with respect to functional abilities and quality of life. This program comprises a set of scheduled components for sensory stimulation in coma (if applicable) and neuropsychological remediation. Additionally, systematic support and guidance for parents in their daily interaction with, and support and planning for the child are included, and as well child psychiatric and behavioral interventions, where necessary.

The assessment of psychopathological alterations comprises questionnaires, which allow a differentiated picture of behavioral deviations typically seen after TBI. Separately, Achenbach's Child Behavior Checklist is applied, an internationally recommended tool in general assessment of child psychopathology.

After half of the study's duration, the preliminary results show positive effects of the applied program. Approaches and results concerning psychic problems, coping and psychopathological alterations are exclusively presented in this report as one focus of the study. Patients in experimental and control group showed average results in the retrospective assessment of pretraumatic psychopathological status. In the experimental group this remains mainly unchanged, also through follow up assessments 6 and 12 months after trau-

ma. On the contrary, children and adolescents in the control group show behavioral deviations with a group mean of borderline clinical relevance in the follow ups mentioned.

The components of intervention and differentiating results of the different approaches to psychopathological assessment are presented. Moreover, results of experimental group and controls will be compared and discussed in view of trauma severity and neuropsychological remediation.

This study is part of the "Verbund Neurotrauma NRW-Köln/Projekt III-2: Effects of neuropsychological and psychotherapeutic interventions after traumatic brain injury on functional abilities and quality of life in children and adolescents", funded through the research program "Gesundheit 2000" by the German federal government, FKZ 01 KO 9517. It is additionally funded by the Köln Fortune Program/Faculty of Medicine, University of Cologne.

Motor imagery in the therapy of patients with unilateral central paresis – clinical effects

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In the rehabilitation of patients with lesions in the central nervous system physical therapy based on neurophysiology plays an important role. One of the most significant symptoms of stroke or head injury patients is paresis, often accompanied by changes in muscle tone. Therefore physical therapy deals mainly with the regulation of muscle tone and facilitation of physiologic movements by pure sensorymotor exercises and treatments. Cognitive concepts with the possibility to influence motor programs with motor imagery as shown in sports science have not yet entered in therapy. Main source of cognitive concepts are the motor representations which are built on experience by various feedback sources (mainly visual and proprioceptive) from previous actions. These information are a very important component apart from the real movement. The cognitive model introduced in this study counteracts the phenomenon of learned nonuse by suggesting normal movement to the affected arm and consequently changing the motor representation of the affected hemisphäre in the direction of "normal movement". Object of the here presented study was the influence of motor imagery on the goal oriented grasping movement. A cognitive therapy model was developed which consisted of 2 different phases; in the first (afferent training) a vertically placed mirror was used to simulate normal movement of the affected arm (by moving the healthy arm) and additionally guided movement of the affected arm by the therapist. In the second phase the afferent information of the first one was used as background for the motor imagery, which meant "mental rehearsal" or mental practice of the experienced information. This training was used in 30 patients with hemiparesis, in 20 sessions which lasted 30 minutes.

An expert rating of digitalized randomized video-tapes showed significant improvement of grasping movement after imagery training; the muscle tone of wrist and finger flexors was significantly decreased. Findings of the study support the assumption that cognitive therapy respresents a reasonable supplement in the rehabilitation of paresis.

Demaging effect of occupational lead exposure on vegetative nervous system

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It was the aim to identify alterations with possible demaging effect of the vegetative autonomic nervous system induced by long-term occupational lead exposure, from a modified heart rate.

A group of 135 copper workers (42.6 ± 8.0 years old) with a verified blood-lead load (33.2 ± 10.3 µg/dl for at least 10 years) was compared with 75 neurotoxically unexposed controls (42.4 ± 10.4 years old). Seventeen copper workers with a very high lead exposure (mean BPb 39.4 ± 11.1 µg/dl) were retested a second time after 4 years. The performance at test tasks, physiological strain, and well-being were investigated. The heart rate variability was determinated at rest, test tasks, and recovery. Parameters of analysis were in the time range (absolute sinus arrhythmia) and frequency range (power spectrum of Fast Fourier Transformation FFT).

Repeated heart rate survey at physical rest permitted the subdivision of healthy people in 2 tone groups (vagotonically I and sympathicotonically II dominated). Long-standing lead exposed workers were more vagotonically dominated at rest (55 of 135) than controls (11 of 75). Lead exposed workers demonstrated a prolonged, vagus mediated reset of the vegetative tone after test tasks ($p = 0.047$). This effect depended on the individual occupational exposition ($r = 0.573$, $p = 0.02$). Repeated heart rate measurements (after 4 years) proved a progressing vagus depression in parallel to the proceeding lead exposure ($p = 0.001$).

A long-term occupational lead exposition below the German limit (0,1 mg/m^3 lead in the air) causes a vagus depression which is expressed in a decreased heart rate variability. Repeated heart rate survey (longitudinal study) better verified this effect than the comparison of heart rate in lead exposed and unexposed people (cross sectional study). The heart rate variability is multifactorially modified and depends not only on heavy metal exposition. A prolonged, vagus mediated reset of the vegetative tone after test tasks is a more sensitive parameter than the usual comparison of the heart rhythm at rest in exposed and unexposed people. The induced stiffness of heart rate by occupational lead is to consider as beginning demage of vegetative nervous system.

Arm ability training for traumatic brain injury and stroke patients: therapeutic efficacy. A randomized, controlled study

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Objective: This randomized, controlled trial (RCT) investigates 1. the efficacy of the Ability Training on arm motor function, and 2. the effect of additional augmented feedback (KR, average knowledge of result) with high functioning hemiparetic Traumatic Brain Injury (TBI) and stroke patients. The Arm Ability Training (AT) incorporates training tasks selected to represent different basic arm motor functions such as speed, precision, dexterity, and steadiness.

Methods: Sixty patients were recruited following traumatic brain injury (N = 15) and stroke (N = 45) and randomized to receive either no Arm Ability Training, Ability Training, or Ability Training + Knowledge of Result. A before-after comparison investigates the effects of daily Arm Ability Training (AT) (with or without KR) over a 3 week period on performance (kinematic analysis of aimed movements) and focal disability (ADL test – „TEMPA") with mild to moderate central paresis after brain damage.

Results: Randomized groups were comparable in terms of age, gender, diagnostic group, and degree of paresis. Analysis of variance for repeated measurements for the primary outcome variables, summary time score for unilateral and all (unilateral and bilateral) tasks for the TEMPA test, revealed a superior improvement for those who received the AT ($F(1,56) = 3.82$ and 7.32, $p = 0.0556$ and 0.0090, resp.) and those who received the AT with KR ($F(1,56) = 5.68$ and 8.08, $p = 0.0206$ and 0.0062, resp.) as compared to those receiving no AT. Diagnostic group did not significantly modify these effects. Kinematic analysis of aimed movements showed superior improvement of the initial ballistic movement phase with AT and AT&KR (i.e. maximal velocity: $F(1,55) = 4.86$ and 6.26; $p = 0.0317$ and 0.0153, resp.).

Conclusion: The newly developed Arm Ability Training is efficacious in terms of improving arm function (focal disability) among mildly affected stroke and TBI patients.

Recovery from visual field defects induced by computer-based restitution training in patients with postchiasmatic and optic nerve lesions

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Brain damage is often accompanied by visual field defects, e.g. hemianopia or diffuse visual field loss. In contrast to many other cognitive or perceptual disturbances, restitution of visual functions has been considered impossible for many decades so that most treatment approaches focused on compensation for the lost visual field. Only when animal studies revealed a high degree of plasticity in the visual system, first attempts at inducing recovery by systematic stimulation were made.

In a pilot trial and two clinical studies with brain-lesioned patients, we used computer-based programs for the diagnosis and treatment of visual field defects. Our diagnostic programs (high-resolution campimetry) allow a very detailed characterization of the visual field, including areas of residual vision (transition zones) in or near the "blind" field that seem to be an important basis for visual field enlargement. Nineteen patients with optic nerve lesions and 19 patients with postchiasmatic damage received either restitution training or fixation training (placebo). Restitution training consisted of a systematic stimulation of partially defective areas one hour per day over a period of six months. A significant enlargement of the visual field, both after optic nerve damage (5.8° of visual angle on average) and postchiasmatic lesions (4.9° of visual angle on average) was found in the restitution groups. Furthermore, 72 % of patients receiving restitution training reported a subjective improvement of vision, but only 17 % of control group patients.

In conclusion, the visual system possesses a hitherto little appreciated plasticity which can be utilized for therapeutic goals. We hypothesize that a minimum of residual neuronal structures surviving the lesion represent a possible neurobiological basis for training-induced recovery from visual field defects. During training, attention is shifted towards the (partially) blind visual field so that an improvement of function of these residual visual neurons can be achieved.

Neuroglial activation in the injured central nervous system: role of transforming growth factor-β1

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The Transforming Growth Factor β's is a group of pleiotrophic cytokines with potent neurotrophic and immunosuppressive properties which are expressed in the normal and injured nervous system. In the current study, we examined the role of TGF(1 in the regenerating mouse nervous system after transection of the facial nerve.

Although TGFβ 1 is present in low levels in the normal central nervous system, the expression of this cytokine is strongly upregulated after injury. Transection of the facial nerve also led to the upregulation of the TGFβ receptor II on axotomized motoneurons. Here, the absence of TGFβ 1 in transgenetically deficient mice led to a strong increase of CD44- and GFAP-positive, activated astrocytes in the normal brain and an overall increase in the astrocyte activation after injury. In contrast, there was a severe inhibition in microglial number, their ability to proliferate, the expression of

activation markers, αMβ2 integrin and ICAM-1, and a reduction in their ramified morphology. On the other hand, TGFβ 1 deficient microglia expressed the cell adhesion molecule CD44, which is normally absent in this injury model.

In summary, TGFβ 1 plays an important role in the regulation of the astrocyte and microglial phenotype, which may be mediated by the TGFβ receptor-positive neurons but also provides interesting insights into the cellular network that controls neuroglial activation.

Effects of somatostatin, octreotide and cortistatin on ischemic neuronal damage following permanent middle cerebral artery occlusion in the rat

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This study investigated whether peptides acting at somatostatin receptors such as somatostatin-14 (SS), octreotide (OCT) or cortistatin-14 (CORT) can influence the brain damage after focal ischemia in rats. The intracerebroventricular (i.c.v.) application of 0.1 or 1.0 nmol SS 5 min after middle cerebral artery occlusion (MCAO) significantly reduced the infarct size (by 47 and 56 % of the saline control), whereas 10.0 nmol has no protective effect (6 % only). A similar dose-response-relationship was obtained after i.c.v. injection of OCT. The lower doses of 0.1 or 1.0 nmol have a significant neuroprotective effect (reduction of the infarct size by 72 and 56 %), but 10 nmol OCT increased the infarct size up to 46 %. CORT at a dose of 10 nmol was able to decrease the ischemic damage by 53 % of saline control. In comparison with the neuropeptides acting on somatostatin receptors, the kappa opiate agonist enadoline (ENA) at a dose of 10 nmol has a significant protective effect against the development of focal ischemia diminishing the brain damage by 60 % after i.c.v. injection.

Effect of NO on secondary growth of a brain tissue necrosis from focal injury

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Objectives: A cortical tissue necrosis from focal trauma may expand to 140 % or more of its initial volume within the first 24 hrs. It is not yet known, however, whether this phenomenon is a delayed primary process and, therefore, resistant to treatment, or if secondary mechanisms are involved. Aim of our study was to analyse the involvement of NO as a mediator of this process.

Method: A standardized freezing lesion of brain cortex was induced in 50 anaesthetised Sprague-Dawley rats, divided into 5 groups. Animals of two control groups received vehicle only (NaCl i.v. or i.p.; n = 10). Production of NO in the brain was promoted by administration of L-arginine before and after trauma (300 mg/Kg i.v.; n = 10). Animals of two other groups received either L-NNA (100 mg/Kg i.p.; n = 9) as a NO-synthase inhibitor or aminoguanidine for selective inhibition of iNOS (100 mg/Kg i.p.; n = 8). The brain was removed 24 hrs after trauma for assessment of necrosis formation by quantitative histomorphometry.

Results: Administration of the above drugs did not affect physiological variables, as arterial pO2, pCO2, blood sugar or plasma osmolality. Yet, animals of the L-NNA group had an increased blood pressure during preparation ($p < 0.01$), an increase in hematocrit, and body weight loss at 24 hrs ($p < 0.05$). While administration of L-arginine or of L-NNA had no effect on the secondary lesion growth (92.0 ± 8.9% or 104.9 ± 4.9 %), the volume of necrosis in animals with aminoguanidine was attenuated to 72.9 ± 5.8 % ($p < 0.01$).

Conclusions: Selective inhibition of the inducible NO synthase is markedly inhibiting the secondary growth of a traumatic brain tissue necrosis from cold injury. On the other side, since neither administration of L-NNA nor of L-arginine influences the phenomenon, the involvement of NO as a mediator of the secondary lesion growth is not clear as yet. We conclude, nevertheless, that NO plays as a mediator role, although more likely by damaging the injured parenchyma, rather than by a concurrent derangement of the perifocal tissue perfusion. Obviously, further studises on the complex functions of NO in focal brain injury are required. Supported by BMBF-Verbund “Neurotrauma” München, FKZ 01 9704.

Transient retinal ganglion cell size enlargement and recovery of contrast discrimination after an optic nerve crush in adult rats

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After optic nerve crush (ONC) in adult rats, 50 % of the surviving retinal ganglion cells (RGCs), which remain connected with their target, increase slowly their soma diameter. To understand the role of this slow size increase in the adaptive cellular events that appear after neurotrauma, we correlated surviving RGC changes observed in *in vivo* confocal microscopy (ICON) [1] with contrast discrimination performance after a bilateral optic nerve injury.

Rats were first trained to discriminate a vertical grating under different contrast conditions. Thereafter, RGCs were labelled retrogradely by injection of fluorescent beads into the superior colliculus. The rats received either no crush (n = 5) or a bilateral ONC (n = 10 for each crush intensity). After ONC, ICON was applied every five days and contrast discrimination tested every day.

After a mild crush, we observed a similar time course of the slow soma increase and the contrast discrimination recovery. The severe ONC had the same effect than an axotomy. No cells could be seen with ICON and the rats were not able to solve the visual task. After an intermediate ONC,

only few cells had a slow diameter increase and survive. The rats could make the visual test but with very poor results.

Thus, there is a good correlation between RGC anatomic modifications and visual performance recovery after a bilateral optic nerve injury. The slow soma increase observed previously takes part in an adaptive response that enables neural tissue to repair itself.

Reference

[1] * Sabel, B.A., et al. *Nature medicine* **3** (1997) 244–247.

Influence of normobare hypoxia in vivo on potentiation in the CA1 region of hippocampal slices

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Moderate hypoxia protects rats and mice against penthylentetrazol-induced seizures induced seven days afterwards. The mechanism of protection are not fully understood as yet. To determine whether such procedure can preserve neuronal functions during a Mg^{++}-free-medium-time and whether induction and maintenance of long-term potentiation (LTP) in hippocampal slices is altered at appropriate time after a moderate normobare hypoxia *in vivo,* field potential recordings were performed in transversal hippocampus slices 7 days after a conditioning hypoxia. Monosynaptic evoked field potentials were recorded in

CA_1 region after stimulation of the Schaffer-collaterals. The conditioning hypoxia induced protection against ischemic damages, expressed as a lack of field potential decrease, seen in non-conditioned slices. The perfusion with Mg^{++}-free medium induced in all slices a potentiation of the population spike of the evoked field potentials which outlasted the perfusion time of 30 min. In slices of hypoxia-exposed rats this potentiation was significantly greater than in slices of control animals. In separate experiments induction of (LTP) indicate a late phase of potentiation with significant enhancement in slices from preconditioned animals at day 7. A tendential increase of population spike potentiation was also seen in the dentate gyrus of rats *in vivo* 7 days after conditioning hypoxia.

Recording the evoked canine detrusor electromyogram

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Introduction: With increasing interest in detrusor disorders and possible detrusor myopathies, a method for recording the electromyographic activity of the detrusor smooth muscle *in vivo* (detrusor-EMG) would greatly assist the diagnosis of various bladder dysfunctions. Therefore we investigated the electromyographic activity of the canine detrusor during sacral root stimulation and during spontaneous bladder contractions.

Methods: The bladder was exposed in six anesthetized dogs (foxhounds, b.w. 25 to 33 kg) and two modified surface electrodes were implanted subserosal in the bladder dome. After closure of the abdomen and funneling of the connecting wires of the electrodes to the body surface, laminectomy and identification of the sacral roots was performed. The electrical activity of the bladder during sacral stimulation was recorded in all trials. Furthermore, simultaneous detrusor-EMG and bladder pressure recordings were performed in order to evaluate the electrical characteristics of the bladder during detrusor contraction.

Results: A high correlation of detrusor-EMG recordings with bladder contraction was observed in all trials. Analysis in the time domain as well as 3-D power spectrum analysis revealed the most clear correlation of detrusor-EMG with the rise of intravesical pressure in a frequency band above 3 Hz. The spike duration was 100 to 250 ms with an amplitude of 100 to 500 µV. The electromyographic activity below 1 Hz appeared to be random without any correlation with changes in intravesical pressure.

Conclusion: Our trials indicate that the functional relevant frequency band of the canine detrusor EMG could be situated above 3 Hz. Further trials will be carried out to investigate the relevant frequency band in different species and the influence of anticholinergic agents on the detrusor EMG.

The presented animal model allows pathophysiologic studies of various pathologies of bladder dysfunction and detrusor myopathies.

Effect of hypoxia/reoxygenation on functional intact mitochondria from pig retina

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Isolated mitochondria from pig retina were exposed to hypoxia and reoxygenation of different duration. Progressive decrease of active respiration measured 1 minute after reoxygenation with increasing the time of hypoxia was found. During reoxygenation, the active respiration further declined. The leak-respiration was slightly increased in this *in vitro* ischemia/reperfusion-model indicating changes in the conductivity of the mitochondrial inner membrane. Products of lipid peroxydation (TBARS) and protein oxidation (protein bound carbonyls) as parameters of oxidative stress were elevated. Further, decrease in the activities of the NADH-cytochrome c-oxidoreductase (complexes I and III of the respiratory chain) and of enzymes of the citric acid cycle were found. The water soluble antioxidant ascorbic acid partiallly protected isolated mitochondria from hypoxia/reoxygenation injury. Our data support the suggestion that retina mitochondria were functionally injured due

to deenergetization within the hypoxic phase and the attack of reactive oxygen species which were produced within the mitochondria during reoxygenation.

NO/O_2^--induced neuronal damage: role of glial cells and modes of protection

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It has been reported by Choi's group that pathologically stimulated NO-release from astrocytes contributes to neuronal damage by favoring the formation of $ONOO^-$ in conjunction with O_2^-. Reactive microglial cells represent a potent source for both radicals forming the particularly aggressive peroxynitrate. We studied possible modes of interference in rat glial cell cultures in which a pathological stimulation was mimicked by exposure to lipopolysaccharide or phorbol esters. Treatment with a membrane-permeable cAMP analogue inhibited O_2^- generation in cultured rat microglia, but did not affect the stimulated formation of NO. A similar differential depression of O_2^- but not of NO was observed upon treatment with propentofylline, known to act as cAMP-phosphodiesterase (PDE) inhibitor (Hoechst AG). On the other hand, this pharmacon was also found to inhibit cGMP-splitting PDEs and markedly supported the NO-evoked intracellular rise of cyclic GMP – as observed in nitroprusside-treated astrocytes. Using non purified spinal cord neuronal cultures as experimental model, we found that NO-induced neuronal death could be prevented by propentofylline via a cGMP-linked mechanism. The findings indicate that strengthening of the cyclic nucleotide signaling by selective PDE inhibitors may provide pharmacological protection against glia-related oxidative neuronal damage.

Cytokine release after severe brain trauma with and without multiple injury

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Severe traumatic brain injury induce local as well as systemic inflammatory responses. The aim of this study was to evaluate the relationship between cerebral and systemic mediators after severe brain injury and to compare it with clinical and radiological findings.

Methods: Between 11/96 and 10/98 123 patients were included into a study analyzing patients with severe traumatic brain injury (GCS ≤ 8) with and without multiple trauma (ISS ≥ 18) and multiple trauma alone. 43 patients received an intraventricular catheter for continues CSF sampling.

Results: IL-6- and IL-8-values showed a triphasic time course with an initial increase, a consistent decrease between days 3–5 and a in most patients a subsequent secondary increase.

Conclusion: Il-6 and IL-8 levels were substantially higher in CSF as compared to the corresponding plasma values, thus confirming the brain's ability to generate a separate inflammatory response due to a trauma. The time course of this response and the correlation to structural damage seems to be complex and time-dependant. The relation the analyzed mediators and the morphologic data (CT-Scans) and somatosensory evoked potentials is currently analyzed.

Selective block of urethral sphincter contraction using differently shaped pulses for anodal block stimulation with a Brindley electrode in the dog

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Patients with spinal cord injury present dysfuntion of urinary bladder and urethral sphincter. One treatment option is sacral rhizotomy and sacral anterior root stimulation with a Finetech Brindley stimulator. A major disadvantage of this method is the lack of selective stimulation, resulting in simultaneous sphincter and bladder contraction followed by unphysiological micturition. We investigated the possiblity of selective sphincter blockade and bladder stimulation using a Brindley electrode. Complete posterior rhizotomy was performed in n = 11 male anaesthetized foxhounds. The anterior roots S2 were stimulated with six different quasitrapezoidal (QT) pulses (pulse length range 600 to 1400 µsec, stimulation current 0.1 to 2.0 mA, frequency 20 Hz) using a tripolar Brindley electrode. Sphincter and bladder pressure was urodynamically measured. All 11 animals showed a maximum reduction of the initially high sphincter pressure of over 80 % when QT-pulses with long pulse lengths (> 900 µsec) were used. The sphincter pressure was completely inhibited (100 %) when applying these long QT-pulses in 5 of 11 trials. QT-pulses with short duration (< 900 µsec) showed a sphincter pressure reduction of over 80 % in 2 trails and complete inhibition in one animal. Stimulating at maximal sphincter blockade, the average bladder pressure was 33.48 cm H_2O higher than the average sphincter pressure. In 3 trials, a stimulation-induced micturition was achieved. Selective blockade of the sphincter was possible by applying QT-pulses. The duration of the pulse length should be long in order to achieve minimal sphincter pressure. The bladder remained uninfluenced by this block and excitability was preserved throughout. This study shows that selective bladder stimulation with no or only little coactivation of the urethral sphincter is possible. A physiological micturition can be achieved by using a tripolar Brindley electrode. The fact that the Finetech Brindley electrode is already well established will enable the unproblematical introduction of this stimulation technique into clinical practice.

Regenerative capacity of thalamocortical cocultures after a mechanical impact

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Mechanical injury to axonal connections between thalamic and cortical areas maintained as organotypic cutures (OTCs) has recently been shown by our laboratory to be a suitable model system for neurotrauma *in vitro*. In the present study, the regenerative capacity of neuronal elements following injury was investigated in this system using semi-quantitative measurement of microtubule-associated protein 2 (MAP-2). In cocultures maintained 12 days *in vitro* (DIV) a marked and stable increase (75 %) of the axonally sequestered MAP-2c form occurred within 4 hours after impact in cortical areas, while MAP-2c expression in thalamic areas increased to about the same value (77 %) with a delay of 16 hours. 20DIV OTCs possessed a low basal level of MAP-2c protein, compared with that in 12DIV OTCs. After insult in 20DIV OTCs, basal levels of MAP-2c were only partially enhanced for a short period of 4 hours (33 % in cortex and 43 % in thalamus, respectively). The high molecular weight forms MAP-2a,b were downregulated by 30 % in cortical and thalamic areas in 12DIV OTCs 20 hours after impact. The use of vital stains (Syto 21 and propidium iodide) and DiI-incorporation demonstrated somatic and axonal regeneration in 14DIV OTCs 48 hours after the mechanical impact.

In conclusion, these data indicate a postnatal time window of regenerative capability following axonal injury in the thalamo-cortical system.

Analysis of mRNA populations in the developing brain by means of the PCR-Select cDNA subtraction technique following traumatic brain injury

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In the developing rat brain, focal mechanical trauma to the parietal cortex causes widespread apoptotic neurodegeneration in distant brain regions. Different mRNA/protein expression patterns are suggested to be involved in the pathogenesis of trauma-induced apoptotic neuronal injury. Here we report the use of the PCR-Select cDNA subtraction technology (Clontech) in combination with the SMART cDNA kit with the goal to construct cDNA libraries that contain sequences newly or increasingly expressed in traumatized tissue as compared to controls. Percussion head trauma in female Wistar rat pups at the age of 7 days was produced using a contusive device. Pups were sacrificed at 24 hrs after trauma. Total striatal RNA was extracted, reverse transcribed, amplified and cloned. Sequence analysis of 17 clones revealed one clon for a glutamate transporter, one clon for a mouse seizure-related gene mRNA, one clon for the mss4 protein, one clon for MRC Ox-45, two clones for lactate dehydrogenase, two clones for emerin and five clones for transthyretin. In addition, two unknown sequences were detected. Having constructed specific oligonucleotide primers for each sequence, we are now in the process of verifying differences in mRNA expression. Further effort will be made to isolate full-length cDNA clones of the unknown sequences and pursue their genetic and functional characterization.

Effects of mental training in unilateral central paresis – electrophysiological effects

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From central activation studies it is known that mental motor imagery leads to an improvement of movement performance (Yagüez et al, 1997). During motor imagery patients with central paresis show a significant decrease of Theta, Alpha and Beta-1 Power in comparison to a rest-condition (Weiss et al,1994). Other studies (Hansen et al., 1991, 1993; Petsche et al., 1989) found a significant decrease of alpha- and beta-1-power in the contralateral hemisphere during motor imagery. This phenomenon corresponds to electrophysiological changes observed during performed movement and can possibly be interpreted as activation of the sensorymotor cortex. In relation to the hypothesis of an internal feedback-mechanism it could be seen as correlation of motor representation during motor imagery.

The present study analyses electrophysiological changes before and after a cognitive training program performed during 4 weeks, containing motor imagery of grasping movements. Twenty-eight EEG channels were recorded in different conditions (e.g. observation of a presented glass versus imagery of grasping movements) before and after training. Results showed significant changes during motor imagery such as an increase of desynchronisation of µ-activity in the motor cortex of the affected hemisphere.

As seen in former studies these results point to systematic modulation of EEG-activity in centroparietal regions during motor imagery. In conclusion these changes in EEG-data show that motor imagery is a valuable measure in the rehabilitation of central paresis.

Diagnostic measures in hemiparetic patients performing motor imagery. Relevant information for therapy of grasping movement?

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In the last few years studies clarified the cerebral methods involved in motor imagery and showed the efficacy of imag-

ery in motor learning [1,2]. For implementation of motor imagery in rehabilitation it is important to get an estimate of the patients' ability to use imagery. In this respect it is essential to know to what extent a change in the representation of movements ocurres.

Referring back to Sirigu (1996) we developed two tests to evaluate the patients ability of imagery. Test A contains 3 conditions (imagery of impaired/non-impaired arm; overt movement of non-impaired arm) measuring the time of perfomance of goal oriented movement (or imagery) with equal distance but increasing target width (Fitt's law).

Test B contains sequences of thumb-finger movements in the same 3 conditions as mentioned above – point of interest is the maximal frequency of movement measured by metronome.

A questionnaire provides information about the spontaneously taken perspective of "first person" (motor imagery) or "third person" (visual imagery) in performance of imagery of movement.

First results show that the investigated parameters are important for performance of imagery in therapy because of their high correlation to movement representation

References

[1] Yagüez, L., et al. A mental route to motor learning: Improving trajectorial kinematics through imagery training. *Behav. Brain Research*. 1997.

[2] Seitz, et al., *European Journal of Neuroscienc*e, **Vol. 9**, 1997, pp. 378–389.

Polarisation influence on both an original and modified Brindley book electrode by generator parameter failure

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After spinal cord injury with loss of bladder function, the restoration of reservoir function and voiding control can be achieved by sacral anterior root stimulation with deafferentation. Different animal trials with modified, size-adapted Finetech-Brindley electrodes aim at the optimisation of electrical parameters. Our *in vitro* trial with both, a modified and an original Brindley electrode investigates the possibility of nerve damage caused by false specific generator parameters.

Compared to the original, the modified Brindley book electrode is reduced in size ($7 \times 9 \times 7.5$ mm) with 3 separately controllable slots. The original electrode ($9 \times 9 \times 7$ mm) is larger in size. The lateral nerve slots are connected parallel, the middle and distal slots offer separate electrical control.

The original and modified Brindley book electrodes were mounted in 250 ml physiologic saline solution (NaCl 0.9 %) and in all trials, a biphasic rectangular signal waveform (8 sec stimulus, 20 Hz, 200 (sec pulse length, amplitude 2 mA peak to peak) was applied first by an FHG-IMBT (Fraunhofer Institute, IMBT), and in a following series by an FH generator (University of Applied Science, Mannheim). The FH generator utilizes an optical link between signal generation and current source. To generate signal form, the current source is driven by batteries (± 12 V) with an active current offset compensation. The FHG-IMBT generator is a universal programmable current or voltage generator (Hewlett Packard, HP 32451), which generates a direct arbitrary programmable signal form.

The measurement of polarisation and voltage reply was captured by a long-term storage oscilloscope with continuous computer data recording. Voltage differences, polarisation and rise time of polarisation of the two generators were analysed and evaluated. In proceeding measurement series both the original and modified electrodes presented a maximum exponential negative electrode voltage increase to -1.4 V using the FHG-IMBT generator. The rise time of polarisation was 2.5 sec. No polarisation was recognised in the FH generator.

In the data evaluated, the generator specific parameters showed that the FHG-IMBT generator had an offset current of almost 30 (A, thus causing polarisation at the electrodes. If this generated waveform is applied to the sacral nerve, electrolysis and nerve damage will arise. Thorough examination of the data acquired from experimental equipment is strongly advisable.

In vitro electrode variance with both a modified and original Brindley Finetech book electrode

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Sacral anterior root stimulation by a Finetech Brindley stimulator is an alternative treatment option for patients with spinal cord injury. Different animal trials are necessary for the optimization of electrical sacral root stimulation. An anatomically adapted (e.g. dog) intradural Brindley electrode was utilized. We investigated the electrode variance of both the original and modified Brindley electrode *in vitro*.

The structure of the modified book electrode comprises 3 slots with single compartment control and reduced size ($7 \times 9 \times 7.5$ mm) to avoid compression of the spinal cord. Assembly parameters for optimal nerve stimulation are the slot width (2 mm) and the tripolar electrode width (1 mm). The cable length is 40 cm (71 Ω). In contrast to this, the dimensions of the original book electrode are slightly larger ($9 \times 9 \times 7$ mm). The middle and distal slots have separate electrical control, whereas the lateral nerve compartments are connected parallel. The cable length is 45 cm (87 Ω), the electrode width is 2 mm and the slot width 1 mm. The distance between the electrodes is identical in the original and modified versions (2.5 mm).

The original and modified Brindley book electrodes were mounted in 250 ml physiologic saline solution (NaCl 0.9 %) and in all trials a biphasic rectangular signal waveform (8 sec stimulus, 20 Hz, 200 µsec pulse length, amplitude 2 mA peak to peak) was applied. The measurement of voltage reply was captured by a storage oscilloscope with continuous computer data recording. Amplitude differences and electrical resistance (cable vs. electrode) were analysed and evaluated. In the proceeding measurement series, both the original and modified electrodes gave an identical waveform reply. The amplitude reply of the original Brindley electrode expounded, on average, a 13 % higher voltage course than the modified one. Data evaluation revealed that the correct waveform reply does not, in contrast to the voltage course, depend on higher resistance caused by longer cable length. The adjustment of the difference determined between the original and modified electrode, for example cable length resistance, will enable the introduction of this data into future clinical practice.

The functional anatomy of auditory lexical decision and its plasticity after left hemisphere damage: A PET-study

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In a PET-study of 15 healthy right-handed volunteers we investigated the brain activation during auditory lexical decision. There were two experimental conditions: First, the subjects had to discriminate between real words and nonwords, which consisted of Finish and Czech words played back in reverse. Second, real word varied with pseudowords, i.e. phonologically legal words without meanings. Comparing each of these tasks to a control condition, consisting of a high and low tone discrimination, we found bilateral activation of the whole superior temporal gyrus and of the inferior third frontal gyrus including Broca's area and the frontal operculum.

Comparing the two lexical decision tasks, distinctive lateralization effects were found. The more complex and language specific realword/pseudoword decisions activated the left frontal language zone (BA 44, 45, 47) together with the dorsal anterior cingulum (BA 32). In contrast, the unspecific global real word/nonword decisions were lateralized to the auditory cortex (BA 42) of the nondominant right hemisphere.

In the second part of this study, we included 13 aphasic patients, who were recovered well enough for performing at least 80 % correct on all three tasks. In patients with anterior and central lesions of the left MCA territory, all activations being significant were restricted to perisylvian areas of the unimpaired right hemisphere. In patients with posterior lesions, the unimpaired anterior language zone on the left remained active in addition to the same right hemisphere involvement as seen in the other patient group. We postulate that the right hemisphere involvement is due to unimpaired 'protolanguage' functions, which became expanded during recovery from aphasia.

Electrophysiological correlations of auditory perception of temporal phenomena and its implications for aphasia therapy

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Within the last few years auditory temporal order, e.g., the ability to perceive the temporal order of two clicks, has been shown to be of significance in the diagnosis and therapy of patients with receptive speech problems. Phonetic decoding requires a hearing sensitivity in the milliseconds range. However, electrophysiological aspects of auditory perception in this temporal range remain largely unclear. These electrophysiological correlates may serve as important indicators for diagnosis and therapy of patients with aphasia. In our study the following parameters in neurologically healthy subjects and in patients with fluent aphasia will be examined: 1) psychophysically measured temporal fusion (simultaneity vs. non-simultaneity) and temporal order thresholds (sequentiality) upon the presentation of two clicks, 2) the ability to discriminate between phonemes (stop-consonant vowel syllables with varying voice onset times and inverted speech signals), and 3) electrophysiological correlates of auditory evoked potentials of these psychophysically assessed parameters. On the basis of psychophysical measurements and electrophysiological correlates objective, sensitive, and reliable markers should be extracted for diagnosis of temporal processing deficits in patients with aphasia. Furthermore, a sensitive marker for feedback in the training of temporal deficits in these patients should be developed and tested.

Restitution of locomotion and functional motor performance in children after severe traumatic Brain injury

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It is proposed that due to a higher plasticity of the central nervous system in the childhood, the restitution of motor functions after Brain damage is faster than in adults. Therefore the purpose of the study was, on one hand to investigate the restitution of a distinct motor function, i.e. locomotion and on the other hand to follow the recovery of more generalised motor functions in children after severe traumatic Brain injury. Functional motor skills comprising different items such as stance, locomotion, postural functions, muscle tone, hand movements and transitional movements in different body positions have been scored in a standardised manner.

Gait was analysed both, on a walkway and for kinematic recordings on a treadmill. These investigational tools were applied to nine infant patients with severe brain injury after a mean posttraumatic interval of 12 months. The results were compared to the data of eight age-, sex-, and body dimension matched healthy children. The patients were reinvastigated after two months of rehabilitational therapy. In the first investigation several gait parameters (velocity, step frequency, stride length and kinematics) were found to be reduced in the patients. Although these differences did not reach significance, in some individuals they were distinct. In contrary to that we discovered significant differences in the motoscopic assessment between patients and control subjects (total score, stance, locomotion and balance, hand and transitional movements). In the reinvestigation after two months of rehabilitational therapy no improvement was found in the gait parameters. However, in the functional motor score, significant improvement was found for the items total score, stance, locomotion, balance and hand movements. In conclusion, we assume that multidimensional investigations of motor function are necessary to describe the restitutional capability of the motor systems. An improvement in the gait pattern was only seen in patients who were investigated relatively early after the trauma, whereas for the whole group the restitution of locomotion could not be observed. We propose that locomotion seems to be a rather stable and robust motor function, which restitutes relatively early after a trauma.

Improvement of the gait pattern in normal pressure hydrocephalus after CSF tapping

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Gait disturbance is the most striking symptom of the treatable disease of normal pressure hydrocephalus (NPH). It is assumed that NPH is caused by an enhanced outflow-resistance of the cerebral ventricular system. Thus, the gait disorder and other motor symptoms are most likely due to impairment of supraspinal motor regions and pathways. The aim of the study was characterise and to quantify the gait disorder in NPH and investigate the improvement of the locomotion pattern after tapping of cerebrospinal fluid (CSF-tap test). We analysed the gait pattern of ten patients with NPH and nine age matched healthy controls on a walkway (temporal and spatial gait parameters) and in addition on the treadmill for the recording of the kinematics of locomotion. Compared to the healthy controls, patients with NPH walked significantly slower, with shorter steps and a somewhat reduced step frequency. Balance-related gait parameters (step width, foot rotation angles) were significantly enhanced while the foot-to-floor clearance during swing-phase was poor. In addition the variability of the stride length was much higher in the patients. After tapping of 30 ml CSF on average, we found significant improvement of the following gait parameters: Walking speed increased by 21 %, due to an enlarged stride length (19 %). The phases of the walking cycle changed according to the higher gait velocity. In parallel to the augmented stride length the variability of this parameter decreased. The cadence, the step height and the balance related gait parameters were unaffected by the treatment. We assume that only those gait parameters respond to CSF-tapping which are thought to be generated and controlled supraspinally (e.g. stride length) while others (step frequency), which are likely generated by intraspinal networks remain unaffected by treatment.

Functional reorganisation after training of alertness

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Five patients with right vascular brain damage and one TBI patient, all presenting with deficts of alertness, were trained by the subprogramme “ALERTNESS” of the AIXTENT computerized attention training. The training was administered for 14 sessions of 45 minutes each. Before and after the training either a PET or fMRI activation and a comprehensive neuropsychological test battery for attention functions and neglect were carried out. We wanted to assess training induced changes in the individual functional networks involved in intrinsic alertness. After the training all patients showed an improvement either in the median or in the intraindividual variability of reaction time in the intrinsic alertness test. The PET and fMRI activations in most patients after the training revealed a partial or complete restitution of the right hemisphere functional network known to control intrinsic alertness in normal subjects.

Temporal constraints of cognition in patients with Broca’s aphasia

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We report experimental evidence, using a subjective rhythmization paradigm, on temporal constraints of information processing in the domain of presemantic temporal integration (TI). This mechanism appears to be limited to intervals up to approx. 3 sec and is referred as the “subjective present”. The aim of the present study was to test whether temporal processing in this time domain is related to language deficits following acquired brain lesions. 56 patients with pre- or postcentral, left or right hemispheric brain damage grouped beats generated with various frequencies by a metronome. They were asked to listen to exposed beats and to mentally accentuate every x-th beat, to create a subjective rhythm. Patients reported verbally how many beats they

were able to integrate into a perceptual unit. The measured integration interval length was defined as the number of reported beats multiplied by the time distance between two successive beats. Results indicate temporal processing disturbances depending on the lesion location. Specific disorders were found in Broca's aphasics who integrated the information for longer intervals than other patients at lower frequencies of beats, accompanied by shorter ones for the highest frequency. We postulate, thus, that the Broca's patients used a different strategy than other participants and did not rely mainly on presemantic TI, but rather on mental counting. These temporal processing disorders appear to be related to language deficits characteristic for this aphasia syndrome.

From phenomenological to molecular events during axonal regeneration in adult retinal ganglion cells

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Adult retinal ganglion cells can be protected from axotomy-induced death and those surviving are able to regenerate an axon under favoured conditions. We have analysed several steps of the cellular response to axotomy and monitored techniques to prevent the cell death and support regrowth of the axons. In the first part of the work inhibitors of proteases were injected into the vitreous body at the day of optic nerve injury. In a second part inhibitors of endonucleases were injected at or shortly after injury. In both experimental series more ganglion cells survived the axotomy 14 days later. Treatment with the aforementioned neuroprotectives and delayed explantation for axonal growth in culture revealed massive extension of axons. In terms of quantity, more than 5 % of axotomized ganglion cells regenerated their axons *in vitro*. Analysis revealed differences to control, non-regenerating explants. Metabolic staining of the proteins with radiolabelled aminoacids is currently performed in order to purify and clone the regeneration-specific gene products.

Hypothetical pathophysiological mechanism of omeprazol associated visual disorders

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Pharmacological activity of omeprazole, a proton pump inhibitor (PPI), depends on non-specific binding to thiole-containing chemical structures, such as the sulfhydryl-cysteinyl groups of the gastric K^+-H^+-ATPase. The selectivity of the PPI for the parietal cells results only from the acidity in the canaliculi of these cells providing a rapid conversion of the prodrug into the active sulfenamide. Based on clinical and experimental findings a pathophysiological mechanism is proposed which may explain the occurrence of visual disorders including irreversible damage despite a proper drug use. Omeprazole and other PPI inhibit proton secretion not only in K^+-H^+-ATPases from parietal cells, but also from other tissue including brain and vascular smooth muscle even under moderately acidic conditions. Resulting intracellular acidification may trigger ischemia by vasal constriction in terminal vessels and, thereby, with a parallel direct effect on nerve tissue, may cause reversible functional or irreversible structural damage in structures such as the optic nerve. To prove this mechanism, more *in vitro* data have to be collected followed in perspective by a prospective controlled randomised trial to estimate the clinical importance of the adverse drug reaction.

Prediction of neuropsychological 4-6 month outcome following TBI from clinical, neuroradiological and early neuropsychological data

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Sixty patients (42 male, 18 female, median age 26.5 years (range 16–68), initial GCS 14 (range 3–15)) out of a consecutive series of 138 suffering from traumatic brain injury could be assessed clinically at days 1, 4, 10 and neuropsychologically at day 10–14, and were reassessed 4–6 months later. CT scans were performed initially and according to clinical necessity .

The initial GCS score was correlated with outcome measures of memory functions, performance in the Stroop task, and performance in the frontal lobe score of Ettlin & Kischka.

The presence of traumatic frontal lobe lesions was associated with more pathological scores in behavioral assessments such as the frontal lobe score and the Neurobehavioral rating scale.

Worse performance at outcome in the Wisconsin Card Sorting Test and the Stroop task was present both with diffuse and focal injury. An increased number of perseverations in the WCST occurred only with focal frontal lesions.

Presence of focal neurological symptoms was not predictive of the neuropsychological outcome six months after injury.

Neuropsychological tests performed 10–14 days post TBI correlated highly with neuropsychological performance at outcome. There were also strong intercorrelations among tests. The most sensitive neuropsychological measures are highly intelligence-dependent, which limits their value for outcome prediction.

In summary, although both the early clinical phase and the neuropsychological pathology following TBI is dominated by the effects of diffuse injury (including some typical "frontal lobe tests"), the behavioral pathology seems to de-

pend to a high degree on the presence of focal lesions in areas related to behavioral control. Behavioral scales such as the NBRS and the frontal lobe score of Ettlin and Kischka seem promising tools for identifying patients at risk for residual behavioral deficits.

On interaction of voluntary movements and tremor

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The study of movement disorders is part of the Forschungsverbund Kiel. Our group will in the future assess the rehabilitation of hand functions and gait in patients suffering from brain trauma. This poster is to demonstrate the methods applied for the movement analysis of hand functions in these patients. As this study has not yet started we present data from another study of patients with tremors of various origin. Essential tremor was long been considered a pure postural tremor. As this does not fit with the clinical observations we decided to analyze this movement disorder in a simple reaching paradigm. We present data of the kinematic analysis of hand movements taken from healthy individuals, patients with essential tremor and from patients with diseases of the cerebellum. Hand transport and grip formation can be studied separately. The hand path is more curved and the deviations from an idealized trajectory increase when approaching the target in cerebellar patients. Similar findings can be obtained in a subgroup of patients with essential tremor. Overshooting of the wrist is common and the grip aperture is affected similarly. In simple movements of the elbow and wrist, these symptoms of ataxia and intention tremor are known to follow deficits of the coordination of synergistic and antagonistic muscles. The data demonstrate, that a disturbance of hand function is found in part of the patients with essential tremor similar to the findings in cerebellar disease. This might suggest that the cerebellum is affected in advanced essential tremor. The method seems to be appropriate to demonstrate typical abnormalities of cerebellar functions.

Molecular constituents of regenerating growth cones of mouse facial motoneurons

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Peripheral nerve axotomy is usually followed by axonal regeneration. While disconnected axons and associated myelin are rapidly destroyed in the distal part of the nerve, in the proximal part the tip of the injured neurite is transformed into a growth cone, a semi-autonomous cellular structure capable of rapid elongation into and through the distal part of the nerve. In the current study, we examined the molecular make-up of regenerating growth cones in the mouse facial motoneurons.

Regenerating motor growth cones were identified with immunofluorescence against vesicular acetylcholine transporter (VAChT), an anterogradely transported protein which accumulates in the motor neurite terminals. Immunofluorescence double-labeling revealed a colocalization with α7 and β1-integrin subunits on VAC-immunoreactive growth cones in the proximal nerve stump and extending into the distal part of the cut facial nerve. In contrast, there was no colocalization with CD44, a cell adhesion molecule strongly induced on perikaryal surface of the injured motoneurons. Interestingly, peripheral axonal injury was also associated with a formation of long axonal sprouts in and around the affected facial motor nucleus, beginning at day 7, with a maximum at day 14 and a disappearance 42 days after axotomy. These intra- and perinuclear sprouts also expressed no CD44 but clear α7β1- and VAChT-staining and very strong immunoreactivity for Galanin and CGRP, neuropeptides which are strongly upregulated in injured mouse motoneurons.

In summary, injury to the facial nerve leads to the de novo appearance of cell adhesion molecules and neuropeptides in the growth cones of the sprouting motor axons. These molecules may play a strategically important role in mediating changes in the adhesive properties of regenerating neurites and the intercellular communication between the axonal growth cones and their direct cellular environment.

Regulation and function of α7β1 Integrin in the injured nervous system of the mouse: impaired regeneration in the α7-deficient animals

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The α7β1 integrin is a cellular receptor for the basement membrane proteins laminin 1, 2 and 4. Since integrins of the β1-family are important for neurite outgrowth *in vitro*, we examined the role of this cell adhesion molecule in the normal and injured nervous system.

In the normal mouse nervous system, α7 immunoreactivity was found primarily on cerebrovascular pericytes and the astrocytic processes in the glia limitans. Peripheral axotomy led to a rapid increase of α7 on the affected motoneurons in the axotomized facial nucleus, vagal nucleus, hypoglossal nucleus and on motoneurons in the lumbal spinal cord. A similar upregulation was also observed on the axotomized sensory neurons of the dorsal root ganglia and on their central processes in the spinal cord. In contrast, no increase of α7 was observed on axotomized central neurons in the retina or cerebral cortex and was rarely present on the injured septohippocampal neurons. The increase of α7 after peripheral axotomy was also accompanied by an increase of the β1 integrin subunit, indicating the presence of functionally com-

plete α7β1 integrin. Here, transgenic deletion of the α7 subunit led to an impairment of the axonal regeneration of the facial motoneurons, with a 33 % reduction of the regeneration distance ($p < 0.01$).

In summary, injury of the nervous system leads to a general increase of α7 on the regenerating sensory and motoneurons but not on centrally projecting neurons of the CNS. Here, the impairment of axonal regeneration in the absence of α7 underlines the important role of this adhesion molecule for the successful, peripheral regeneration.

From psychophysics to speech perception: Detection of temporal jitter in stochastic pulse trains and jitter speech coding strategies for cochlear implant patients

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Psychophysics of temporal jitter detection in cochlear implant (CI) patients is relevant for assessment of their temporal processing capabilities and thus for the design and parametrization of speech coding strategies. For improvement of CI users' consonant recognition two jitter speech coding strategies were developed on the basis of the Continuous Interleaved Sampling (CIS) strategy. The Novoicing-Jitter CIS strategy (NvJitCIS) uses pulse trains with a speech-periodicity-dependent jitter of equally-distributed interpulse intervals (IPI jitter) to improve the discriminability of voiceless and voiced consonants. Within the Jitter CIS strategy (JitCIS) a constant speech-periodicity-independent equal-distribution IPI jitter is applied aiming at general improvement of consonant recognition by the more physiological excitation of the auditory nerve compared to CIS. For parametrization of both jitter strategies thresholds of IPI jitter detection in stochastic pulse trains were obtained from 12 patients with the implant C40+ (Med-El) in psychophysical studies. Jitter detection was investigated at an apical and a basal electrode and for two stimulus durations. Most patients were able to detect IPI jitter in stochastic pulse trains and performed jitter detection better for apical than for basal electrode stimulation as well as for the longer stimulus duration. Both jitter strategies were also evaluated in comparison with the CIS strategy in 4 CI patients using a /vCv/-consonant identification test. Consonant identification was only 1 % better for the JitCIS and NvJitCIS strategies compared to CIS.

The role of $p75^{NTR}$ in modulating neurotrophin survival effects in developing motoneurons

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Neurotrophins exert their biological functions on neuronal cells through 2 types of receptors, the trk tyrosine kinases and the low-affinity neurotrophin receptor ($p75^{NTR}$), which can bind all neurotrophins with similar affinity. The $p75^{NTR}$ is highly expressed in developing motoneurons and in adult motoneurons after axotomy, suggestive of a physiological role under such conditions. In order to characterize this specific function of $p75^{NTR}$, we have tested the effects of NGF on embryonic motoneurons from control and $p75^{NTR}$ deficient mice. NGF antagonizes BDNF- and NT-3-mediated survival in control but not in $p75^{NTR}$-deficient motoneurons. Survival of cultured motoneurons in the presence of 0.5 ng/ml of either CNTF or GDNF was not reduced by 20 ng/ml NGF. Dose-response investigations revealed that 5 times higher concentrations of BDNF are required for half-maximal survival of $p75^{NTR}$ deficient motoneurons in comparison to motoneurons from wildtype controls. After facial nerve lesion in newborn wildtype mice, local administration of NGF reduced survival of corresponding motoneurons to less than 2 % compared to the unlesioned control side. In $p75^{NTR}$ deficient mice, the same treatment led to enhanced survival of more than 35 % of the facial motoneurons on the lesioned side. Thus $p75^{NTR}$ appears as a component of the high-affinity neurotrophin receptor complexes in motoneurons which enhances specificity for BDNF and NT-3. The observations that CNTF and GDNF survival effects are not reduced by $p75^{NTR}$ signaling and that the number of motoneurons in the facial nucleus of postnatal mice is reduced argue against a physiological role as a cell death receptor in developing motoneurons.

System Analysis of the pre- and early clinical management in patients with severe head injury in Southern Bavaria

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Purpose of this project is a system analysis of the preclinical and early clinical management of patients with severe head injury in Southern Bavaria (5.6 mio. inhabitants) on a population-based level. A complex network has been established involving all trauma and neurosurgical hospitals, 10 dispatch centers, 5 forensic medicine laboratories, and 5 emergency helicopter stations in the study region.

Beginning August 1998, a total of 408 patients suspected to have traumatic brain injury have been reported until now. Head injury was confirmed in 190 patients. Victims dying at the site of an accident were included, if severe head injury was confirmed by autopsy.

The patient management and care was protocolled from alarming the dispatch center until completion of the acute clinical phase, including the first CT-scan, surgical interventions, and transfer into an intensive care unit. The detailed

clinical documentation is continued until day 8. The subsequent course in medical or rehabilitation centers is also protocolled, finally the outcome by using the Glasgow-Outcome-Scale (GOS) at 3, 6 and 12 months.

Objective of the population-based study is to gather information on the current management efficiency of all components of the preclinical and early clinical care of patients with severe head injury – also as a basis of further improvements, if necessary.

Superoxide dismutases in rat brain – perinatal development and cellular distribution

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Superoxide dismutases (Mn and Cu/Zn) are considered to belong to the major antioxidant enzymes in the brain. We followed the developmental profile of these enzymes in isolated brain mitochondria and homogenates by activity assays and western blots. It could be shown that the perinatal development of MnSOD in rat brain mitochondria is completely different compared to heart and liver mitochondria. Remarkable is the delayed increase of MnSOD in brain not before the 10th day of postnatal development. The late expression of SOD is in correspondence with the late development of the cytochrome c-oxidase, which proves a close connection between energy metabolism and antioxidant capacity.

In addition to the biochemical studies, the cellular distribution of Mn SOD and Cu/Zn-SOD was investigated by immunocytochemistry during the postnatal period (days 0–40). Cu/Zn-SOD was homogeneously distributed through nervous tissue without significant regional or temporal differences. On the cellular level astrocytes expressed the highest amounts of Cu/Zn-SOD immunoreactivity. Mn-SOD was found to be concentrated in neuronal mitochondria. It was shown that neuronal Mn-SOD expression is dynamically regulated with regional and temporal differences between day 5 pp and 20 pp.