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BESA: from raw data to source images and source coherence. - Michael Scherg*^, Karsten Hoechstetter^, Dieter Weckesser^, Harald Bornfleth^, Nicole Ille^, Patrick Berg^+ (*University of Heidelberg, Germany; +University of Konstanz, Germany; ^MEGIS Software GmbH, Munich, Germany).

The BESA (Brain Electrical Source Analysis) program provides a large variety of tools for the complete analysis of EEG and MEG recordings. Using paradigm scripts and a 2D artifact scanning tool, optimized averages can be created for multiple source analysis. A standardized realistic head model, 3D whole head and cortical mapping, and various inverse source algorithms have been implemented in a highly interactive source analysis module. The latest BESA version 5 can transform the surface signals into brain activity using source montages derived from multiple source models. This allows to display the on-going EEG, single epochs, and averages with much higher spatial resolution. The new Source Coherence Module provides an extremely fast and user-friendly implementation of time-frequency analysis based on complex demodulation. Users can create event-related time-frequency displays of power, amplitude, event-related (de)synchronization, and coherence for scalp or source montages. In an error-related negativity EEG experiment a multiple dipole model was applied to transform the surface signals into brain space. The activities of the anterior and posterior cingulate gyrus, visual cortices, basal temporal lobes, and motor cortices could be separated. Time-frequency analysis revealed induced gamma-band synchronization in the visual cortical areas. In a second example, an auditory reaction time experiment, similar multiple source models could be created using EEG alone or location seeds based on fMRI BOLD clusters. The regional source waveforms revealed the sequential activation of bilateral auditory cortices (N100 and N150), SMA, motor cortex, cerebellum, visual cortex, and cingulate gyrus.

Model building and hypothesis testing with EMSE® -R.E. Greenblatt (Source Signal Imaging, Inc., San Diego CA 92102 USA).

Typical steps in the analysis of M/EEG data include data conditioning, data exploration, model building and hypothesis testing. Source estimation (drawing inferences about brain source location, orientation and magnitude from extracranial M/EEG) is often an important step in model building. Source estimation requires solution of forward (brain to scalp) and inverse (scalp to brain) problems. Realistic forward models, such as finite element (FEM) analysis, may represent subject specific anatomy, derived from MRI, and are computationally efficient. Inverse methods may be classified as local vs. global, overdetermined vs. underdetermined, and instantaneous vs. spatiotemporal. In addition, the source space may be constrained using structural and/or functional MRI. Lastly, data may be in the time, frequency, or time-frequency domains. Examples derived from EMSE EEG data analysis will illustrate signal and image preprocessing, source estimation, and statistical hypothesis testing. Strengths and weakness of several forward and inverse methods will be discussed.

CURRY – Multimodal neuroimaging. - M. Wagner (Neuroscan Labs, Hamburg, Germany).

A high-performance, robust tool for electromagnetic source localization and visualization, Curry integrates multiple, complementary modalities (EEG and MEG; MRI, fMRI, CT, PET or SPECT) in a single software package. By combining the latest techniques for measuring electrical activity in the brain with anatomical and functional imaging, Curry provides a powerful method for accurately localizing electromagnetic sources. Curry uses the full physical anatomy from MR and CT to segment individualized three-dimensional models of the skull and brain to be used in source localization. Curry integrates functional imaging such as fMRI with EEG and MEG source reconstruction to allow the comparison of results and to enhance the validity of solutions. Specifications: Integration of EEG, MEG, ECoG with MRI and fMRI/CT/PET/SPECT. Complete analysis of data leading to anatomically constrained source reconstruction. Independent Component Analysis (ICA) and Principal Component Analysis (PCA) for data analysis and filtering. Realistic volume conductor models using the Boundary Element Method (BEM). Finite Element Method (FEM) support. Dipole fits. Dipole confidence ellipsoids are computed. Dipole scans, extended source (patch) scans, and MUSIC scans. Current Density Reconstructions (CDR) based on dipolar or extended sources. Automated data analysis and source reconstruction using macros.

Comprehensive MEG software package for both clinical and research applications. - L. Parkkonen, S. Taulu, M. Kajola (Elekta Neuromag Oy, Helsinki, Finland).

With the advanced whole-head MEG systems, the functionality, usability and quality of the associated software has become increasingly important. The Neuromag software suite is developed both for brain research and clinical work, incorporating both new analysis methods and streamlined clinical protocols. Data acquisition module supports simultaneous preparation and measurement of consecutive patients, continuous head position tracking, and multi-category on-line averaging with artefact rejection. Signals are displayed in selectable layouts, and multiple response categories can be overlayed and subjected to mathematical operations. Continuous data are processed offline with a programmable tool that includes all basic signal processing functions. Source estimation modules feature time-varying multi-dipole modeling, EEG forward modeling, response simulator and minimum current estimation (MCE); all in a sphere or realistic model (BEM). MRIs can be overlayed by dipoles, MCE and electrode locations, and they can be segmented to yield BEM models and 3D renderings with dipoles. Finally, a report can be composed using drag-and-drop from the analysis modules. In addition to graphical user interfaces, all modules are also scriptable and their setups can be recalled, which facilitates routine work. Signal-space projection (SSP) with reconstruction is included for noise compensation and source waveform extraction. Signal-space separation (SSS) is applied for head movement correction and noise compensation. For method developers, MATLAB interface exists for MEG/EEG, MRI, MCE and dipole data. Interfaces to third party software/systems are implemented via standard formats such as DICOM and EPS. The package has demonstrated its applicability to both clinical and research work.

Cortically-constrained minimum-norm inverse solutions. - M.S. Hämäläinen, T. Witzel, F.H. Lin, B.R. Fischl, A.M. Dale (MGH/MIT/HMS Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, Massachusetts, USA).

The FreeSurfer software developed in our center allows automatic segmentation of high-resolution anatomical MRI data. The software produces a topologically correct tessellation of the pial surface as well as the border between the white and the grey matter for each hemisphere. The latter cortical surface is employed as an anatomical constraint in our source modeling procedures. In addition to the locations vertices, estimates for the local surface normals as well as curvature information are calculated. For visualization purposes, an "inflated" surface can also be produced to reveal the cortical sulci. In the estimation of current sources from MEG and EEG data we employ L2 and L1-norm minimum-norm solutions. The current estimates are calculated in a grid with typically 7-mm spacing between source space points on the cortex. We prefer not to use an exact orientation constraint at each source space point, as given by the cortical tessellation, but rather allow some "looseness" in the orientations to account for variation of the normal direction within the cortical patches corresponding to the decimated points. The loose orientation constraint also makes the estimates less sensitive to alignment errors between the MEG and MRI coordinate frames as well as inaccuracies in the forward model. In case of L2-norm estimates we can transform the expected value of the current into a statistical test variable by dividing it with the current standard deviation. We can thus present the results as dynamical statistical parameter maps (dSPMs), similar to the corresponding static maps produced in fMRI and PET.

Spatial filtering in MEG: methods and challenges. - B.D. Van Veen (Department of Electrical and Computer Engineering, University of Wisconsin-Madison).

Several spatial filtering or beamforming methods, including linearly constrained minimum variance (LCMV) (Van Veen et al. 1997) and synthetic aperture magnetometry (SAM) (Robinson and Vrba 1999) have

been proposed for analysis of MEG data. Spatial filtering employs a weighted combination of the sensor data to estimate the signal with a desired spatial amplitude pattern at the sensor, while attenuating signals/noise with undesired amplitude patterns. The desired spatial amplitude pattern is usually determined from an equivalent current dipole model. LCMV, SAM, and several other methods design the weights, or spatial filter, to minimize the spatial filter output power subject to various constraints. The constraints are chosen to preserve the signal of interest and/or other properties of the data. The estimated spatial filter output power or output signal to noise ratio, calculated as a function of location, provides a metric for identifying active regions of the brain. Two key challenges for spatial filtering methods are sensitivity to deviation between the modeled spatial amplitude pattern and actual pattern associated with the underlying activity, and estimation of the spatial covariance matrix from a limited number of measurements. Current research directed toward mitigating these problems, including quadratic weight constraints and subspace mapping, are discussed. Subspace mapping involves passing the data through a bank of fixed spatial filters, designed to pass signals from a region of interest and dramatically reduces the number of data vectors required for covariance matrix estimation.

Exact localization with standardized Low Resolution Brain Electromagnetic Tomography (sLORETA). - Roberto D. Pascual-Marqui (The KEY Institute for Brain-Mind Research, University Hospital of Psychiatry, Zurich, Switzerland).

Scalp electric potential differences and extracranial magnetic fields originate from the primary current density distribution produced by neuronal post-synaptic processes. A solution to the inverse problem, i.e., the estimation of images of electric neuronal activity based on extracranial measurements, would provide important information on the time course and localization of human brain function. In general, there is no unique solution to this problem. However, in particular, a distributed linear solution capable of exact localization of point sources is of great interest, since the principles of linearity and superposition would guarantee its trustworthiness as a functional imaging method, given that brain activity occurs in the form of a finite number of distributed "hot spots". Despite all previous efforts, distributed linear solutions at best produced images with systematic non-zero localization errors. We present a distributed linear solution that yields images of statistically standardized current density (sLORETA) with zero localization error. This property holds for continuous and discrete distributions of the measurement space (with as few as 25 sensors) and of the solution space (with as many as 13,000 voxels), for both the electric and magnetic field cases. sLORETA has been compared to all other published 3D discrete distributed instantaneous linear inverse solutions. Only sLORETA enjoys the "zero localization error" property. In particular sLORETA was compared to the recently developed family of so-called "noise-normalized" inverse solutions based on Dale et al. 2000 Neuron 26:55-67. Except for sLORETA, all variants of "noise-normalization" have systematic localization errors. In addition, sLORETA has highest resolution.

Infomax ICA separates high-dimensional EEG data into temporally independent and spatially compact source projections. - S. Makeig and A. Delorme (Swartz Center for Computational Neuroscience, Institute for Neural Computation, University of California San Diego).

What are the major sources of scalp EEG signals? The short lateral extent of horizontal connections of most cortical neurons, particularly of inhibitory neurons, should produce a strong tendency for near-synchronous patterns of local field activity to emerge in compact cortical domains. Biophysics dictates that the projection to the scalp surface of coherent activity within each such EEG source domain should strongly resemble the projection of an equivalent current dipole. Unfortunately, separating an EEG scalp map into the sum of dipolar projections from multiple source domains is an underdetermined problem. A radically different approach to source separation using independent component analysis (ICA) (Makeig et al. *NIPS*, 1996) considers only the higher-order statistics of the recorded surface maps, rather than the biophysics of volume conduction, based on two assumptions: Over an experimental session, these domains remain relatively fixed spatially, and their time courses are relatively independent. We performed ICA decomposition of fourteen 71-channel EEG data sets from a working memory experiment using over 20 ICA and related algorithms publicly available in Matlab format on the Internet. Several ICA algorithms returned several to many components whose scalp projections were highly significantly more dipolar than the raw EEG data. Most dipolar components were obtained using the Runica algorithm from our EEGLAB Matlab toolbox (sccn.ucsd.edu/eeglab/), which automates extended natural gradient infomax ICA (Jung et al. *Proceedings IEEE*, 2001), and one other ICA algorithm. These results imply that scalp EEG signals predominantly sum partially coherent electrical activity occurring independently in multiple compact cortical source domains.

Introduction to TMS. - R.J. Ilmoniemi (Nexstim Ltd., Elimäenkatu 22 B, FIN-00510 Helsinki, Finland, risto.ilmoniemi@nexstim.com).

The human brain can be stimulated non-invasively by targeted magnetic field pulses that induce small electric currents to flow in the brain, thereby triggering neurons

into action. The popularity of this technique, transcranial magnetic stimulation (TMS), has grown dramatically during the last few years. TMS shows great potential for brain research, diagnosis and therapy. Until now, most TMS experiments have been limited to the stimulation of the motor cortex because the only immediately observable effects of magnetic stimulation have been those reflected in muscle responses. Recently, however, it has been demonstrated that the cortical effects of TMS can also be observed directly, for example by means of electroencephalography (EEG), positron emission tomography (PET), functional magnetic resonance imaging (fMRI) or near infrared spectroscopy (NIRS). To realize the full power of TMS, attempts are being made to develop stimulation systems that combine image-guided targeting (stereotactic navigation), sequential stimulation (scanning) and the recording and display of brain activity evoked by TMS. It is expected that TMS, in particula in combination with EEG or other functional brain mapping techniques, will have wide applications both in basic research and in clinical applications, including diagnosis and therapy.

Combining transcranial magnetic stimulation (TMS) with PET and fMRI. - H.R. Siebner (Department of Neurology, Christian-Albrechts-Universität, Kiel, Germany and Neuroimaging Institute NeuroImage-Nord, Hamburg, Germany).

Transcranial magnetic stimulation (TMS) combined with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) provides a behaviour-independent assay of cortical excitability, connectivity, and plasticity in the intact human brain. By systematically manipulating a specific variable of stimulation such as frequency or intensity, concurrent functional brain imaging can assess the regional excitability profile or the functional connectivity of a distinct cortical area. This opens up clinical applications such as the in-vivo assessment of disease-related or drug-induced changes in cortical excitability. By applying regular trains of magnetic pulses, repetitive TMS (rTMS) is capable of inducing enduring functional changes in a distributed functional network. The time course and the regional pattern of these changes can be readily mapped with PET and fMRI. In addition, one can directly relate rTMS-induced changes in task performance with changes in task-related activation pattern. It will be demonstrated that this approach is suitable to investigate the adaptability of cortical systems and to disclose abnormal patterns of reorganisation in patients with neuropsychiatric disorders.

Neuromodulation of plasticity in human motor cortex. - U. Ziemann, A. Korchounov and F. Meintzschel.

We know from animal experiments that neuromodulators (dopamine, norepinephrine, serotonin, acetylcholin) may powerfully modify plasticity in cerebral cortex. Here we tested in a placebo-controlled cross-over design the effects of a single oral dose of various neuromodulators on associative long-term potentiation (LTP)-like plasticity induced by paired associative stimulation (Stefan et al. 2000, Brain 123:572), and use-dependent plasticity (Classen et al. 1998, J. Neurophysiol., 79: 1117) in eight healthy right-handed subjects. Associative LTP-like plasticity was significantly enhanced by 2 mg of cabergoline (D2 agonist) but suppressed by 2.5 mg of haloperidol (D2 antagonist), 1 mg of prazosine (alpha-1 antagonist) and 8 mg of biperiden (M1 antagonist). Forty milligrams of methylphenidate resulted in a trend towards an enhancement. Use-dependent plasticity was significantly enhanced by cabergoline, methylphenidate and 40 mg of tacrine (AChE inhibitor) but suppressed by haloperidol, prazosine and biperiden. One hundred milligrams of sertraline (selective serotonin re-uptake inhibitor) had no effect on either form of plasticity. These findings suggest that LTP-like plasticity and use-dependent plasticity in human cortex can be predictably enhanced or suppressed by neuromodulation. It is likely that LTP like plasticity and use-dependent plasticity share common mechanisms because a broad variety of neuromodulators exerted very similar effects on both forms of plasticity. Finally, these experiments may be important for strategies to facilitate use-dependent plasticity in neurological patients after lesion.

Transcranial magnetic stimulation (TMS) in neurosurgery: present status and future visions. - M. Fujiki and H. Kobayashi (Department of Neurosurgery, School of Medicine, Oita University, Japan 1-1, Idaigaoka, Hasama-machi, Oita, Japan 879-5593. e-mail: fujiki@med.oita-u.ac.jp).

This study overviews the present status of transcranial magnetic stimulation (TMS) in neurosurgery. After introducing the technical and physiological principles and basic mechanisms of the technique, we demonstrate a representative case of the use of TMS in neurosurgery. Preoperative motor functional evaluation using a mapping technique (integrated with MRI and fMRI) and quantitative evaluation using MEPs are applied as the most important applications of TMS in neurosurgery. We will then discuss how human cortical function can be modified by magnetic stimulation and how this might be used therapeutically in neurological disorders such as cerebral ischemia, epilepsy, chronic pain and Parkinson's disease.

Cortical inhibition in the pathophysiology and treatment of schizophrenia. - J. Daskalakis (Centre for Addiction and Mental Health, University of Toronto, Toronto, Canada).

Background: Cortical inhibition (CI) deficits have

been proposed as a pathophysiologic mechanism in schizophrenia. Moreover, preliminary evidence suggests that antipsychotics, particularly atypical ones, increase cortical inhibition. Three transcranial magnetic stimulation (TMS) paradigms: short interval cortical inhibition (SICI), cortical silent period (CSP) and transcallosal inhibition (TCI) are used to assess cortical inhibition. Methods: In study one, we assessed CI in 15 unmedicated and 15 medicated patients with schizophrenia as well as 15 healthy controls. These results have been previously published. In study two, CI was measured in 27 healthy control subjects before, 6 and 24 hours after being randomly assigned to receive a single dose of either 2 mg haloperidol (n=8), 10 mg olanzapine (n=10) or placebo (n=9). Results: In study one, unmedicated patients demonstrated significant CI deficits compared to normal controls across all inhibitory paradigms whereas medicated patients demonstrated relatively greater CI compared to unmedicated patients. In study two there was no significant effect of olanzapine or haloperidol on CI at any time interval. Conclusions: These results suggest that schizophrenia is associated with deficits in CI and that medications appear to attenuate these CI deficits. In contrast, a single dose of antipsychotic medication does not have any effect on cortical inhibition in healthy control subjects. Potential explanations attempting to reconcile these findings in schizophrenia will be presented. Moreover, we will discuss cortical inhibition as a potential therapeutic target through which novel treatment strategies, such as repetitive TMS (rTMS), exert their antipsychotic effects.

Role of soft bone, CSF and gray matter in EEG simulations. - C. Ramon*, P. Schimpf+, J. Haueisen^, M. Holmes*, A. Ishimaru* (*Departments of Electrical Engineering and Neurology, University of Washington, Seattle, WA, USA; +School of Electrical Engineering and Computer Science, Washington State University, Spokane, WA, USA; ^Biomagnetics Center, Department of Neurology, F.S. University, Jena, Germany).

We examined the effect of the soft skull bone, gray matter and CSF on scalp potentials using a finite element model of the head constructed from the segmented MRI images with 11 different tissue types identified. The finite element model has a 1×1×3.2 mm voxel resolution and a total of approximately 1.5 million hexahedral elements. We used a current dipole model in the motor cortex area and computed the scalp potentials for head models with varying complexities. We used four models: a full model with 11 tissue-types, a model in which the conductivity of the soft bone was set equal to the hard skull bone, a model in which the conductivity of the gray matter was set equal to white matter, and a model in which the conductivity of the gray matter and CSF were set equal to the white matter. The contour plots of the scalp potentials were made. It was found that contour plots of scalp potentials were different for all four models. The differences were the largest for the model where the conductivities of the gray matter and CSF were set equal to the white matter. One possible reason could be that by setting the conductivity of the CSF and white matter same removes the anatomical fine structure in the brain tissue and thereby influencing the volume current flow patterns. These results suggest that for accurate modeling of the scalp potentials one should include anatomical details of the CSF geometry in the computer models of the head.

Cortically-constrained time-frequency analysis of MEG and EEG data. - T. Witzel, S.M. Stufflebeam, F.-H. Lin and M.S. Hämäläinen (MGH/MIT/HMS Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, Massachusetts, USA).

Time-frequency analysis of MEG and EEG waveforms has become a method of increasing interest during the recent years, because it has been shown to reflect higher cognitive processing of sensory input, attention and working memory as well as synchronization processes between distant locations in the cortex. Here we present a method for computing noise-normalized linear minimum-norm estimates in conjunction with time-frequency analysis. Initially, time-frequency analysis is performed by convolution of the measured signals with a complex Morlet's wavelet. The complex result of the convolution is then projected into source space where the power and phase of the narrow-band signal is calculated. In order to yield induced oscillatory activity the solution is calculated on a single trial basis and the across trial statistics is calculated in source space. In order to penalize only environmental spatially correlated noise we use the empty room noise covariance for the regularization of the inverse operator. The noise covariance needed for the noise normalization of the solution is calculated from the baseline of every single trial in source space. Furthermore, this method allows the use of anatomical orientation constraints and spatial priors, such as fMRI activation maps. In order to investigate phase-synchrony in the brain, we calculate the phase-locking statistics between a selected ROI on the cortex or a stimulus phase and all other source locations in the brain. The results are generated in form of activation movies displaying frequency power or phase locking significance. The surface representation of the source space additionally allows cross-subject statistics.

Evaluation of sLORETA in the presence of noise and multiple sources. - M. Wagner, M. Fuchs and J. Kastner (Neuroscan Labs, Hamburg, Germany).

Introduction: Standardized Low Resolution Brain Electromagnetic Tomography (sLORETA) [1] can be used to compute statistical maps from EEG and MEG

data that indicate the locations of the underlying source processes. These maps are derived by performing a location-wise inverse weighting of the results of a Minimum Norm Least Squares (MNLS) analysis with their estimated variances. We evaluate the performance of the method under the presence of noise and with multiple, simultaneously active sources. Methods: Simulated data containing one and two sources at different locations and with different strengths have been computed for an 81 electrode EEG setup. Three spherical shells were used as the volume conductor model. Data were disturbed using Gaussian noise of different levels. sLORETA analyses have been performed using the CURRY software (Neuroscan, El Paso, TX, USA) and their results have been compared with other dipole and current density results. Results: While the method is capable of localizing single sources even in the presence of noise, multiple simultaneous sources can only be separated if they are not too close and their strengths are not too different.

Pascual-Marqui, A.D. Standardized low resolution brain electromagnetic tomography (sLORETA): technical details. Methods and Findings in Experimental & Clinical Pharmacology, 2002, 24D: 5-12.

Extended region spatial-temporal MEG analysis using bayesian inference. -D.M. Schmidt, J.S. George., S.C. Jun, J. Pare-Blagoev, S. Pliz, D.M. Ranken and C.C. Wood (Biological and Quantum Physics Group, MS-D454, Los Alamos National Laboratory, Los Alamos, New Mexico, USA).

We present progress made on extending our original spatial only, extended region Bayesian inference MEG analysis [1] to a spatial-temporal analysis. Beginning with the original formulation of the spatial-temporal analysis [2], we designed, coded and tested multiple generations of analyses. Our testing and evaluation methods were systematic and thorough and with each generation one or more issues were discovered that required modifying the analysis and generating the subsequent generation. Many of the issues identified and the methods we developed for addressing them may be relevant to other MEG analysis approaches as well. Here we describe these issues and methods we developed for addressing them. These include: 1) correlation between size of resulting regions of activity and prior values on the strength of current density, 2) need to limit the temporal extent of active regions, 3) importance of modeling the spatial-temporal correlation of the background noise, and 4) incorporate the uncertainties of the forward model, of co-locating head and sensor coordinates, and of various motion effects.

[1] Schmidt, D.M., George, J.S. and Wood, C.C. Hum. Brain Mapp., 1999, 7: 195-212.

[2] Schmidt, D.M., George, J.S., Ranken D.M. and Wood, C.C. Biomag2000, Proc. 12th Int. Conf. on Biomagnetism, 2001: 671-673.

Dipole analysis on spatiotemporal MEG signals using Bayesian inference. - S.C. Jun, J.S. George, J. Pare-Blagoev, S. Pliz, D.M. Ranken, D.M. Schmidt and C.C. Wood (Biological and Quantum Physics Group, MS-D454, Los Alamos National Laboratory, Los Alamos, New Mexico, USA).

New approaches to the MEG/EEG inverse problem based on Bayesian Inference have been recently described [1, 2, 3]. These approaches yield a probability distribution of solutions upon which all subsequent inferences are based. References [1] and [3] focused on the analysis of data at a single point in time, and demonstrated the utility of Bayesian inference both for including pertinent prior information and for yielding robust results. Reference [1] used an extended region model for neural activity while reference [3] used a multi-dipole model. Reference [2] extended their work to a spatiotemporal Bayesian inference analysis of the full spatial-temporal MEG/EEG data set, using their extended region model for neural activity. Here we present a spatial-temporal Bayesian inference analysis using a dipole model of neural activity that is relatively fast, does not require the use of the subject's anatomical information, does not require prior determination of the number of dipoles, and yields quantitative probabilistic inferences that are one of the hallmarks of the Bayesian inference approach. We added a current time prior probability distribution for the correlation of one time point with another that allows us to include the temporal correlation at nearby latencies. In addition we have incorporated the ability to handle much more complex and realistic estimates of the background noise [4] that reduce the effects of under-modeling this noise. We used Markov Chain Monte Carlo (MCMC) to sample the many possible likely solutions. The spatiotemporal Bayesian analysis is demonstrated using both simulated and empirical whole-head MEG data.

[1] Schmidt, D.M., George, J.S. and Wood, C.C. Hum. Brain Mapp., 1999, 7: 195-212.

[2] Schmidt, D.M., George, J.S., Ranken, D.M. and Wood, C.C., Biomag2000, Proc. 12th Int. Conf. on Biomagnetism, 2001: 671-673.

[3] Bertrand C. et al., IEEE Trans. Biomed. Engin., 2001, 48: 533-542.

[4] Pliz S. et al., Private Communication and abstract this conference.

The signal space separation method. - S. Taulu, M. Kajola and J. Simola (Elekta Neuromag Oy).

Multichannel measurement with hundreds of channels essentially covers all measurable degrees of freedom of a curl and source free vector field, like the magnetic

field in a volume free of sources. This fact is based on the constraint caused by Laplace's equation for the magnetic scalar potential and that the measurable signals are spatially band limited. A functional expansion solution of Laplace's equation enables one to separate signals arising from the sphere enclosing the interesting sources, e.g. the currents in the brain, from the rest of the signals. The signal space separation (SSS) is accomplished by calculating individual basis vectors for each term of the functional expansion solution to create a signal basis covering all measurable signal vectors. Because the SSS basis is linearly independent for all practical sensor arrangements, any signal vector has a unique SSS decomposition with separate coefficients for the interesting signals and signals coming from outside the interesting volume. Thus, SSS basis provides an elegant method to remove external disturbances. The device-independent SSS coefficients can be used in transforming the interesting signals to virtual sensor configurations. This can also be used in compensating for distortions caused by movement of the object by modelling it as movement of the sensor array around a static object. In practice, the SSS method has been found to be a very effective method to remove external disturbances and to calculate various virtual signals without affecting the morphology or decreasing the signal-to-noise ratio of the interesting signals.

Utilizing ICA and MR-FOCUSS to image spontaneous and stimulus synchronized activity. – John E. Moran* and Norman Tepley*# (*Henry Ford Hospital, Detroit, Michigan USA; #Oakland University, Rochester Michigan USA).

A typical current density imaging technique constructs a time series estimate of cortical activation by applying a single pass imaging filter to time series MEG data. This is computationally efficient for imaging long time sequences of MEG data. However, these techniques generate low-resolution images of cortical activity. In contrast, recursively applied imaging techniques such FOCUSS and MR-FOCUSS generate high-resolution estimates of cortical activity by adaptively imaging single time slices of MEG data. However, long sequences of MEG data cannot be rapidly imaged. Designing MEG studies such that ICA techniques can be used to isolate MEG field patterns of spatially distinct sources eliminates this imaging efficiency problem. Combined ICA/MR-FOCUSS imaging of both spontaneous and time synchronized cortical activity will be described. (Supported by NIH/NINDS R01-NS30914).

A combined multi-dipole analysis of simultaneously acquired MEG and EEG. - D. Ranken*, P. Volegov*, E. Best*, R. Kraus*, C.C. Wood* and D. Tucker+ (*Biological and Quantum Physics Group, Los Alamos National Laboratory, Los Alamos, NM; + Electrical Geodesics Inc., Riverfront Research Park, Eugene Oregon, 97403).

As part of a collaboration between the LANL Biophysics Group and Elecrical Geodesics Inc., the LANL SIS MEG system and the EGI EEG system were used to collect data simultaneously in a median nerve stimulation experiment. These data were analyzed using the cortical start spatio-temporal MEG/EEG analysis program CSST (Ranken et al. Biomag 2002). CSST is a multi-start multi-dipole analysis procedure based on MSST (Huang et al. Electro. Clinical Neurophys. 1998). CSST couples a nonlinear simplex search of dipole spatial configurations with a linear fitting to obtain dipole timecourses, using a reduced Chi square as the minimization criterion. Added features in CSST include the ability to run on a computational cluster, subject MRI based selection of starting locations, a fast simplex search, and Monte Carlo analyses. For the combined MEG/EEG analysis, a weighted combination of the MEG and EEG reduced Chi square values was used during the simplex search to obtain an optimal fit to the combined data. Spherical head models were used for both modalities. We show results for the combined analysis, and compare these to results for the individual MEG and EEG analyses.

Realistic spatiotemporal noise covariance model for MEG/EEG source analysis. - S.M. Plis, J.S. George, S.C. Jun, J. Pare-Blagoev, D.M. Ranken, D.M. Schmidt and C.C. Wood (Biological and Quantum Physics Group, MS-D454, Los Alamos, New Mexico, USA).

Accurate characterization of the background noise is important in the analysis of MEG and EEG data as it determines what will be designated as signal. The noise in empirical data typically has a large component from background brain activity and has therefore spatiotemporal correlation not dissimilar from the desired signal. Ignoring this correlation structure in the analysis can lead to spurious sources that merely model the correlated noise or bias offsets in the location and timecourse of true sources. There is generally not enough data available about the noise to determine the full covariance structure given the large number of sensors in modern whole-head sensor systems. We have developed a method for modeling the noise covariance based on a series of orthogonal products of spatial and temporal covariances. By using a series we can model a more complex covariance structure than that from a single product, as in [1]. Furthermore, by using orthogonal products the inverse of the covariance, which is needed in the analysis, can be easily calculated. We describe this approach and demonstrate some of its features using simulated MEG data, and data from an empirical experiment [2] that had a novel stimulus protocol that yields better information about the noise. We use a dipole based

spatiotemporal Bayesian inference analysis to demonstrate the use of this noise model [3]. We compare these results with those from another noise covariance model [1] and from assuming no covariance in the noise.

[1] Huizenga, H.M., de Munck, J.C., Waldorp, L.J. and Grasman, R.P. IEEE Trans. Biomed. Engin., 2002, 50: 533-539.

[2] Pare-Blagoev J. et al., Abstract this conference.

[3] Jun Sung Chan et al., Abstract this conference.

Dynamic neuroimaging with EEG: multi-scale current sources, volume conduction, the inverse problem and the dynamic behavior of macro-potentials. - P. Nunez.

The relationship between micro-current sources at cell membranes and the *meso-sources* or "dipoles" (more accurately dipole moments per unit volume of cortical columns) are considered. EEG dynamic behavior depends on just two underlying variables, the meso-source distribution and the Green's function that fully characterizes the head volume conductor. This physical theory addresses the following contemporary issues of interest in neuroimaging: Dynamic versus static views of brain science and possible physiological bases for dynamic behavior. Why do brains produce oscillations and what physiological time scales underlie these oscillations? These ideas are illustrated with data showing complex changes in coherence patterns during task performance, in which changes can occur in opposite directions in different frequency bands or in short versus long range coherence.

Investigation of dipole localization accuracy in MEG using the bootstrap. - Felix Darvas*, Mikko Rautiainen+, Sylvain Baillet^, Alex Ossadtchi*, John C. Mosher~ and Richard M. Leahy* (*Signal and Image Processing Institute, University of Southern California, Los Angeles, CA 90089,USA; +Ragnar Granit Institute, Tampere University of Technology, Tampere, Finland; ^Cognitive Neuroscience and Brain Imaging Laboratory, Paris, France; ~Los Alamos National Laboratory, Los Alamos, NM 87545, USA).

We used the nonparametric bootstrap to investigate the accuracy of current dipole localization from MEG studies of event related neural activity. The bootstrap is well suited to analysis of event-related MEG data since the experiments are often repeated 100 or more times and averaged to achieve acceptable SNRs. The set of repetitions can be viewed as a set of independent realizations of the brain's response to the experiment. Bootstrap resamples are generated by sampling from these epochs and averaging. In this study we applied the bootstrap resampling technique to MEG data from a somatotopic experiment. Four fingers of the right and left hand of a healthy subject were electrically stimulated, and about 400 trials per stimulation were recorded and averaged to determine the somatotopic mapping of the fingers in the S1 region. Using the single trial recordings for each finger, we performed 5000 bootstrap resamples. We reconstructed dipoles from the resampled averages using the RAP-MUSIC source localization algorithm. To find the correspondences between multiple sources in each resample, dipoles were clustered using a GMM (Gaussian Mixture Model) clustering algorithm, using their combined normalized time-series and topography as feature vectors. The mean and standard deviation of the dipole position and the dipole time-series in each cluster were computed to provide estimates of the accuracy of the reconstructed source locations and time-series. For the 30-60ms time interval the bootstrap method revealed a stable somatotopic mapping on the left and right hemisphere, with spatial standard deviations between 6 mm and 17 mm.

Visual fields of motion-defined stimuli analyzed by a novel blind maximum likelihood estimation algorithm. - B.V. Baryshnikov*, R.T. Wakai* and B.D. Van Veen+ (Departments of *Medical Physics and +Electrical and Computer Engineering, University of Wisconsin-Madison, Madison, WI, 53706, USA).

We present a novel covariance-based algorithm that improves the signal-to-noise ratio (SNR) of multi-epoch data, and we apply it to visual evoked MEG recordings. The algorithm is based on maximum likelihood signal estimation. Its effectiveness lies in its ability to exploit differences in the covariance structure of the averaged and the single-trial data while making very few assumptions. Simulations demonstrated the following advantages: improved SNR, simplicity of implementation, and applicability to recordings in which the signal and noise always overlap in time. The algorithm was then applied to 37-channel MEG data from a study of motion-defined visual contrast. An object consisting of brush strokes (a bird) or dots (a rectangle) was presented over a background composed of identical, randomly distributed brush strokes or dots. The object blended perfectly with the background when stationary and was visible only when moving. Two control recordings were made, first with every element of the image moving independently and randomly and second with the elements of the object moving independently and randomly over a static background. Prominent responses at about 150-180 ms following movement onset were seen for both the motion-defined and the control stimuli, while an additional response in the range 250-450 ms was present for the motion-defined stimuli. The SNRs of both the early and late responses were improved by blind maximum likelihood estimation.

Dynamic spatial filter approach in deep biomagnetic sources localization. - L. Marzetti, M. Demelis and S.N. Erné. (Division for Biosignals and Imaging Technologies, ZIBMT, University of Ulm, Germany).

The reconstruction of deep biomagnetic sources is a challenging topic due the low signal-to-noise ratio of the measured field which falls off at least as $1/r^2$. To obtain a robust estimate of the source parameters, many sources reconstruction techniques accomplish a restriction of the source space over the volume conductor using physiological constraints [1] which can be of limited use in pathological cases, especially concerning brain plasticity. No a priori constraints are necessary in the Dynamic Spatial Filter (DSF) approach. To improve the signal-to-noise ratio the filtering here proposed takes into account only general properties of dipolar sources. Increasing the source depth, the extension of the spatial frequency spectrum decreases. Therefore, a spatial filter with a low pass characteristic in a two dimensional frequency domain has been designed. The filter transfer function is calculated before performing dipole localization using the same first guess. Practically, the procedure is repeated twice, a first run using an analytic volume conductor model and a heuristic first guess, a final run using a realistic model and the previous result as first guess.

[1] Van Veen, B.D., Van Drongelen, W., Yuchtman M. and Suzuki, A. Localization of brain electrical activity via linearly constrained minimum variance spatial filter. IEEE Trans. Biomed. Eng., 1997, 44: 867-880.

Dipole source models for visual ERPs elicited by first and second targets in the pair. - E.V. Mnatsakanian*+ and I.M. Tarkka* (*Brain Research and Rehabilitation Center Neuron, Kuopio, Finland and +Institute of Higher Nervous Activity and Neurophysiology RAS, Moscow, Russia).

Our purpose was to estimate the electrical sources of the evoked activity during the recognition and comparison of pairs of familiar faces and abstract patterns. A total of 18 healthy volunteers participated in the experiment. Each trial began with one of the two cues (S1) followed by consecutive pictures (S2 and S3). Each picture was a photograph of a familiar face on which an abstract dot pattern was superimposed. One cue directed attention to compare faces (Face Task) and another cue to compare patterns (Pattern Task). EEG was recorded using a 128-channel net. Before source modeling, averaged ERPs were filtered (0.3-15 Hz). Spatiotemporal multiple dipole source models were created in BESA2000 for the window of 80-600 ms from S2 and S3 stimuli onsets. The models were initially developed for the Face Task and then applied to Pattern Task data, first for ERPs elicited by S3. Dipolar sources were in the visual cortex, bilaterally in medial temporal and inferotemporal regions, and in the frontal area. The locations and orientations for dipoles from S3 segment were then applied to the S2-elicited ERPs. The residual variances were about 3% for grand average data and around 10-13% for individual ERPs. The temporal dynamics of the source strengths (source waveforms) differed between the models. In both segments, S2 and S3, the task-specific differences were seen. The differences between the models of the segments were observed mostly in frontal and inferotemporal sources.

Adaptability of the brain to TMS gives a direct evidence for a binding between cognitive and motor functions in humans. - J.B. de Graaf, M. Camus, J. Pailhous and M. Bonnard (UMR Movement and Perception, CNRS-University of the Mediterranean, 163 Av de Luminy, 13288 Marseille Cedex, France).

We used TMS both as a reliable tool for quantifying the corticospinal excitability, through the Motor Evoked Potentials (MEPs), and as a central perturbation evoking a movement (because the stimulation intensity was above threshold). The subjects were instructed to cognitively prepare (i.e. without changing their muscle activation) either to "let go" or to "resist to" this centrally evoked movement. We studied the simultaneous evolution of both the motor performance and the Motor Evoked Potentials (MEPs) in the wrist flexor and extensor, separately for the successful trials (on average 66% of the trials whatever the condition) and the unsuccessful trials, allowing us to dissociate the intention-related and performance-related processes. To their own great surprise, the subjects were able to cognitively prepare themselves to resist to a TMS-induced central perturbation. Moreover, because the TMS only evoked short-latency MEPs (and no long-latency components), the amplitude of these short-latency MEPs was found to be related in a continuous way to the actual movement whatever the prior intention. These results demonstrate that prior intention allows an anticipatory modulation of the corticospinal excitability which is not only selective (as already known) but also efficient, giving the intended motor behaviour a real chance to be realized. This constitutes a direct evidence of the role of the corticospinal excitability in the binding between cognitive and motor processes in humans. Moreover, this result shows that the cognitive state of the subject need to be taken into account while interpreting TMS experiments.

Experimental design issues in combined hemodynamic and electrophysiological imaging. - E.J. Pare-Blagoev, J. George, S.C. Jung, S. Plis, D. Ranken, D. Schmidt, D. Sheltraw and C.C. Wood (Biological & Quantum Physics Group, MS-D454, Los Alamos National Laboratory, Los Alamos, New Mexico, USA).

A number of investigators have suggested that combining hemodynamic (fMRI/PET) and

electrophysiological (EEG/MEG) measures of brain activity can improve spatial and temporal resolution over either type of imaging alone. A variety of specific techniques for integration have been proposed, including use of regions of activation in fMRI/PET to constrain dipole solutions for EEG/MEG (e.g., Mangun et al. 1998), the use of fMRI/PET to weight linear inverse solutions for EEG/MEG e.g., Dale et al. 2000), and the use of Bayesian inference to combine fMRI/PET and EEG/MEG into a common estimate of neural activity (Schmidt et al. 1999). In order for both the hemodynamic and the electrophysiological measures to possess information about the same averaged neural activity it is desirable that the same stimulus paradigm be used for both modalities. However, the conventional experimental paradigms used for hemodynamic and electrophysiological are designed to achieve optimal signal-to-noise ratios for each modality, often resulting in different or even contradictory paradigms. Here we present an experimental paradigm, using medial nerve stimulation, that has been used without modification for both fMRI and MEG with good signal-to-noise resulting from each. This makes it appropriate for testing different techniques for combining fMRI with MEG. We discuss the general requirements for such paradigms and describe how this medial nerve stimulus paradigm satisfies these criteria. We present preliminary fMRI analysis results from this data as well.

Functional correlations between resting EEG and fMRI metabolic changes. - Thomas Koenig*, Lester Melie+, Daniela Hubl*, Werner K. Strik* and Thomas Dierks* (*Department of Psychiatric Neurophysiology, University Hospital of Clinical Psychiatry, Bern, Switzerland; +Cuban Neuroscience Center, CNIC, La Habana, Cuba).

EEG signals originate predominantly from the transient, synchronized activity of cortical neuro-cognitive networks. EEG signals are characterized by their frequency spectrum, their spatial origin extent, and the sequence of events. These variables fluctuate spontaneously, but in a well defined manner. This suggests that they code for a neural homeostasis that is adapted to the individual's physiological state, which depends not only on the momentary external context but also on individual past experience and genetics. In order to further understand the brain state markers provided by EEG (i.e. the synchronization, activation and deactivation of cortical structures), we have begun to correlate the spontaneous and induced fluctuations of EEG state markers with simultaneously acquired 3D measures of blood oxygen level depended signals as measured by fMRI. This work presents on one side the technical aspects of acquiring EEG data (96 channels) during an 1.5T fMRI recording (subject safety, recording technique, artifact removal) and presents on the other side first results, correlating transient, spatially extended EEG events as identified by topographic time-frequency analysis with fMRI bold response changes. Our preliminary results shows that in a given frequency band, typical EEG events also have typical, extended and specific metabolic signatures, but all these events also share activated sites that may be the common pace makers. We conclude that simultaneous EEG and fMRI may become essential to study the temporal, spatial and oscillatory properties of transiently forming neural networks in the brain.

Detection of activation in the motor cortex with high temporal and spatial resolution by multimodal MEG-fMRI recording. - S.N. Erné*, H.-P. Müller*, M. Demelis*, A. Pasquarelli*, E. Kraft+, A. Ludolph+ and J. Kassubek+ (*Division for Biosignals and Imaging Technologies, ZIBMT, University of Ulm, Germany; +Department of Neurology, University of Ulm, Germany).

Functional regions of the human brain are usually mapped by functional Magnetic Resonance Imaging (fMRI). FMRI measures the changes in blood oxygenation with high spatial accuracy in localizing activated regions but restricted temporal resolution. Comprehensive mapping is achieved by magnetoencephalography (MEG). MEG localizes the sources of intracellular electric currents, providing direct information of neural activity with high temporal resolution in the range of milliseconds. Ten subjects performed the identical stimulation paradigm both during MEG (55-channel magnetometer system, AtB, Italy) and fMRI (1.5 T, Siemens, Germany) measurements. As the activation paradigm, simple motor tasks (self-paced flexion of index finger and power grip) were chosen. To pursue synergetic interactions between these two non-invasive recording modalities, it is essential to analyze the data sets in one single software environment. The integrated bimodal imaging analysis was performed using the OMEGA (Open Magnetic and Electric Graphic Analysis) software. Localization sources of MEG and fMRI experiments were integrated and referred to the same individual 3-dimensional MRI (MP-RAGE), acquired during the MRI session: MRI data used as morphological background for fMRI results are also processed to build volume conductor models needed in MEG source reconstruction. The fMRI analysis provides the information for possible sites of sources, whereas MEG data complement the corresponding time course of the activation. Multimodal investigations yield comprehensive information about functional activation from different neuroimaging modalities with high spatial and temporal resolution.

Validation of the new SimBio electromagnetic source localization environment in an animal model. - J. Haueisen*, D. Güllmar*^, L. Flemming*, M. Eiselt+, J.R. Reichenbach^, A. Anwander~, M. Dümpelmann#, T.R. Knösche~ and C.H. Wolters~ (*Biomagnetic Center, +Institute of Pathophysiology, ^Institute of Diagnostic and Interventional Radiology, Friedrich-Schiller University Jena, Germany; ~Max-Planck Institute of Cognitive Neuroscience, Leipzig, Germany; #ANT Software b.v. Enschede, The Netherlands. Email: haueisen@biomag.uni-jena.de).

The central objective of the SimBio project is the improvement of clinical and medical practices by the use of numerical simulation for bio-medical problems. The project constructs a generic environment, running on parallel and distributed computing systems, capable of handling a range of important bio-electromagnetic and biomechanical problems. The outstanding trait of the SimBio toolbox is its extremely modular structure that allows free extendibility without any change to the existing software. This enables a wider community of researchers not only to benefit from the system, but also to contribute to it. Here, we provide a validation of the new SimBio [1] electromagnetic source localization environment with an animal model. We measured simultaneously the electrocorticogram and the magnetoencephalogram after peripheral nerve stimulation in the rabbit. FEM and the BEM models were generated from segmented MR images of the rabbit head. Conductivity tensor information was included into the FEM model. Both focal and distributed source models were used. We found a very good agreement between the results computed with the isotropic FEM and BEM model. The source localization differences were below 1 mm for all source models. For the distributed source models we found the maximums to be identically localized. The anisotropic FEM model yielded slight differences in source localization as compared to using an isotropic model.

[1] Simbio, A. Generic Environment for bionumerical Simulation, Information Society Technologies (IST) Programme, Framework V Project IST-1999-10378, http://www.simbio.de

Distributed current estimates with a cortical constraint. - F.-H. Lin, J.W. Belliveau, A.M. Dale and M.S. Hämäläinen (MGH/MIT/HMS Athinoula A. Martinos Center for Biomedical Imaging, Building 149 13th St. Charlestown MA 02129).

A widely employed distributed source localization approach in MEG is based on the L2-norm prior (probability distribution function, PDF, of normal distribution), resulting in diffuse minimum-norm estimates (MNE). More focal estimates can be obtained by using a minimum-current estimates (MCE), which is based on the L1-norm prior (PDF of exponential distribution) instead. The implementation of MCE requires information about the orientations of the sources, which can be estimated by first applying MNE. Here, we propose using high-resolution anatomic magnetic resonance imaging (MRI) data to improve the estimation of sources in MEG data using both MNE and MCE approaches. MRI provides the local cortical anatomy including the variation of the cortex orientation in the neighborhood of each source location. Using the Dijkstra search algorithm, we were able to define the spatial distribution of the cortical patch associated with each decimated dipole source, the averaged normal direction in the individual cortical patch, the dispersion of the normal direction within a cortical patch, and the area of each cortical patch. This allows one to either use a strict or a loose cortical orientation constraint, both of which can be incorporated in the MNE and subsequently MCE of MEG data. In both auditory and somatosensory MEG experiments, we found that MRI constrained MCE with a loose cortical orientation constraint produced more consistent localization (with respect to single equivalent dipole fitting) compared to either MNE-informed MCE or to a strict cortical orientation constrained MCE.

Dynamic sculpting of brain functional connectivity is correlated with performance measures. -R.B. Silberstein*+, J. Song*, P.L. Nunez*+ and W. Park* (*Brain Sciences Institute, Swinburne University of Technology, Melbourne Australia. +Brain Physics Group, Tulane University, New Orleans, USA).

Rapid changes in the synchronization or functional coupling of neural systems is considered a key mechanism for the integration and segregation of neural systems in cognition. In this study, we use Steady State Visually Evoked Potential- Event Related Partial Coherence (SSVEP-ERPC) to investigate the relationship between cortical functional coupling and speed of cognitive processing while performing a computerized version of Raven's Progressive Matrices (RPM). Fifty-five right-handed subjects (29 males) performed the RPM a nd a matched control task while brain electrical activity was recorded from 64 scalp sites. The SSVEP was elicited by a diffuse 13Hz visual flicker superimposed over the visual fields and the SSVEP-ERPC calculated for all pairs of electrodes. The correlation between SSVEP-ERPC and speed of processing was determined during the 3 sec epoch that subjects selected their task responses. Speed of processing was correlated with SSVEP-ERPC at right frontal and right prefrontal sites only at the time 0.8 msec prior to the task presentation. These findings suggest that speed of processing may depend on the ability to establish functional coupling between right frontal and prefrontal neural networks at specific points in time.

Direct recording of auditory induced gamma/beta oscillations in human temporal cortex. - O. Bertrand*, A. Bidet-Caulet*, F. Bauchet* and C. Fischer+ (*Mental Processes and Brain Activation Lab., INSERM U280, Lyon, France, +Neurological Hospital, Lyon, France).

Neural oscillatory synchronization has been proposed as a dynamic link between the different brain areas engaged into the same perceptual or cognitive process. This hypothesis has mainly been supported by studies in the visual modality, either at the unit level in animals or at a macroscopic level from human scalp EEG/MEG. In this latter case, induced gamma oscillations have been proved to be associated with perception and rehearsal of coherent objects and to be modulated by attention top-down processes. Similar oscillations have been observed in other sensory modalities but have been much less studied. We studied the temporo-spatial characteristics and the attentional modulation of induced beta/gamma oscillations in the auditory system. A precise identification of multiple focal oscillatory sources was obtained by means of direct intracranial EEG recordings in the temporal cortex of epileptic patients in several situations, including passive listening and active discrimination tasks. Focal sources of gamma oscillations have been found in the 20-90 Hz range, between 150 and 350 ms after stimulus onset in the primary auditory cortex and in higher level areas (superior temporal gyrus, planum temporale). These gamma sources showed differential modulations by attention. With similar timing, stimulus induced decrease of on-going beta activity (15-20 Hz) was also observed at different focal location of the supra-temporal cortex. The temporal characteristics of these beta/gamma oscillatory activities and their modulation by attention are described and discussed.

The many faces of the intracranial gamma band response during visual perception in humans. - J.-P. Lachaux (Cognitive Neuroscience & Brain Imaging Laboratory, Paris, France).

While it is known that the perception of visual objects translates in humans into a transient increase of energy in their EEG above 30 Hz (the so-called visually induced gamma response), the neural sources of this response are mostly unknown. We used depth electrodes in humans to record directly from some of those sources in response to face presentations. We found such gamma induced responses in selective occipital, parietal and temporal sites, including the fusiform gyrus and the intra-parietal sulcus. They sometimes modulated frequencies up to 200 Hz and had highly anatomy-specific profiles and latencies; in sharp contrast with the response already observed from the scalp. Such increases were simultaneous with gamma energy decreases in the primary visual cortex, suggesting that a balance between regional cortical gamma activations and deactivations is necessary for face perception.

Sub-millisecond synchronization of fast electrical oscillations in somatosensory cortex. - Daniel S. Barth (Department of Psychology, University of Colorado, Boulder, CO 80309-0345, U.S.A.).

Fast electrical oscillations (FO; > 200 Hz) in sensory neocortex can be recorded in a variety of species, including man, and may reflect extremely fast integration of sensory information. The present work demonstrates that in the whisker representation of rat cortex, multi-vibrissa stimulation produces propagating FO field potential patterns and time-locked unit activity that are sensitive to sub-millisecond delays in inter-stimulus intervals. We propose that FO may be produced by synchronized population spikes and their sub-threshold sequelae in cortical pyramidal cells. FO serve to accurately mark stimulus onset as a phase-encoded excitatory signal, producing phase sensitive interactions that, in the context of exploratory whisking, may extract features of an object under exploration.

Eye movement related activity and connectivity from single trial tomography of awake and sleep MEG data. – A.A. Ioannides (Lab. for Human Brain Dynamics, RIKEN Brain Science Institute (BSI), 2-1 Hirosawa, Wakoshi, Saitama, 351-0198, Japan).

Three subjects were examined in three conditions. During awake state saccades were cued by an auditory tone in one condition and initiated voluntarily in the other. Saccades in each direction and condition were in separate blocks, paced at 0.25 Hz. The third condition used similar saccades during rapid eye movement (REM) sleep. Brain activity was reconstructed from magnetoencephalographic data before, during and after left, right, up and down saccades, independently for each timeslice of each single trial (ST). The tomographic ST solutions were aligned to the EOG onset. Well timelocked activations in each ST were identified in the pons, just preceding saccade onset. These activations were as predicted by the conjugate activation of the gaze centers. Activations in the cortex and pons was identified throughout the one second pre-saccade analysis window, and they were only loosely time-locked to the saccade onset. The mutual information between time-lagged ST timeseries was computed to order in time the activations relative to each other and EOG transients, reflecting ocular muscle activity. The results showed complex cascade of interactions with time lags between related activations well over one hundred milliseconds (Ioannides et al., Cerebral Cortex, 2004). REM saccade onset was preceded by pontine and FEF activity that was related to saccade initiation by 250 and 400 ms respec-

tively. Activity in the same areas in the last 200 ms before saccade onset was related to EOG transients after saccade onset and hence they were likely to relate to fine adjustment and stopping of eye movement.

Corticospinal contributions to static and dynamic motor acts studied by EEG-EMG coherence estimates. - B.A. Conway (Bioengineering Unit, University of Strathclyde, Glasgow, G4 0NW, UK).

During the past ten years many studies have used coherence to investigate the electrophysiological relationships that exist between rhythmic activity arising in the motor areas of the brain and the EMG activity generated by muscles participating in maintained voluntary motor acts (e.g. precision grip tasks). In humans, this work has identified the existence of task related 15-30 Hz coherence between localised recordings of EEG or MEG activity and the EMG recorded during voluntary postural motor acts. The 15-30 Hz coherence is considered to reflect activity transmitted to the spinal motor pools via corticospinal pathways and estimates of the phase or lag time between EEG/MEG signals and EMG activity support this conclusion. Thus it can be argued that the assessment of coherence between cortical activity patterns and motor output provides an opportunity to study aspects (spatial and temporal) of the cortical motor command associated with voluntary movements in humans. Accordingly, we have adapted this approach to study what relationships can be established between the frequency components of EEG and EMG signals recorded during dynamic motor behaviours. The behaviours in question are fast point-to-point wrist movements and locomotion. Although preliminary in nature, our recent data suggest that coherent EEG/EMG activity can be identified during dynamic behaviours and that coherence estimates can provide useful insights into the organisation and temporal structure of some components of the motor command associated with static and dynamic motor tasks.

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Coherent brain oscillations and tremor. - A. Schnitzler (Department of Neurology, Heinrich-Heine--University Duesseldorf, Germany, Email: schnitza@uni-duesseldorf.de).

Functional connectivity between brain areas may appear as correlated time behavior of neural activity. Coherence between signals of sensors covering different scalp areas is commonly taken as a measure of functional coupling. However, this approach provides vague information on the actual areas involved. The analysis approach DICS (Dynamic imaging of coherent sources) proceeds beyond the sensor level to estimate coherences between brain areas [1]. DICS uses a spatial filter to localize coherent brain regions and provides the time courses of their activity. We have applied DICS to explore physiological and pathological conditions in the human sensorimotor system. In general, in these studies simultaneously recorded electromyographic activity serves as a reference signal to calculate cerebromuscular coherence which in turn provides cerebral reference points for the computation of neural coupling with other brain areas. Using this approach we have shown that tremor-like physiological ~8 Hz movement discontinuities occuring during slow finger movements emerge from coupled cerebellothalamo-cortical oscillations representing the neural mechanism of the intermittent control of continuous movements [2]. Likewise, oscillatory networks underlying tremor syndromes, such as parkinsonian, essential and hepatic tremors have been characterized and will be presented [3, 4]. Taken together, the investigation of large scale oscillatory coupling in the human brain has yielded new insights into neurophysiological mechanisms of tremor syndromes.

[1] Gross, J. et al. Dynamic imaging of coherent sources: studying neural interactions in the human brain. Proc. Natl. Acad. Sci. USA, 2002, 98: 694-699.

[2] Gross, J. et al. The neural basis of intermittent motor control in man. Proc. Natl. Acad. Sci. USA, 2001, 99: 2299-2302.

[3] Timmermann, L. et al. The cerebral oscillatory network of parkinsonian resting tremor. Brain, 2003, 126: 199-212.

[4] Timmermann, L., Gross, J., Kircheis, G., Häussinger, D. and Schnitzler, A. Cortical origin of mini-asterixis in hepatic encephalopathy. Neurology, 2002, 58: 295-298.

Non-invasive brain-computer interfaces (BCIs). - Jonathan R. Wolpaw (Laboratory of Nervous System Disorders, Wadsworth Center, New York State Department of Health and State University of New York, Albany, New York, U.S.A., wolpaw@wadsworth.org).

Brain activity produces electrical signals that can be recorded at the scalp, at the cortical surface, or from within the brain. Brain-computer interfaces (BCIs) change these signals from mere reflections of brain activity into outputs that convey the user's intent to the outside world (Clin. Neurophysiol., 2002, 113: 767-791 for review). Because they do not depend on muscle control, BCIs can provide communication and control to people with severe neuromuscular disorders such as amyotrophic lateral sclerosis (ALS), brainstem stroke, cerebral palsy, and spinal cord injury. BCIs can be non-invasive or invasive. Non-invasive BCIs derive the user's intent from specific features of scalp-recorded EEG activity. These features may be in the time-domain

(such as P300 evoked potentials or slow cortical potentials) or in the frequency-domain (such as mu or beta rhythms recorded over sensorimotor cortex). Non-invasive BCIs are already in clinical use for basic communication and control. Invasive BCIs derive the user's intent from neuronal action potentials or from local field potentials recorded within the cerebral cortex. They are being studied mainly in non-human primates. These invasive BCIs face substantial technical difficulties and entail significant clinical risks: they require that recording electrodes be implanted in the cortex and function well for long periods, and they risk infection and other damage. The current efforts to develop them, in spite of these disadvantages, are based on the widespread assumption that non-invasive BCIs will never be able to provide users with real-time multidimensional control of a robotic arm or a neuroprosthesis. New data demonstrate that this assumption is not correct. They show in humans that a non-invasive BCI, using sensorimotor rhythms recorded from the scalp, can provide rapid multidimensional control of a movement signal. The precision and speed of this control is similar to that achieved in monkeys with invasive BCIs. The key element in the achievement of this unprecented control by a non-invasive BCI is an adaptive training algorithm that focuses on those EEG features that the person can best control and encourages the user to improve that control further. We are defining the salient characteristics of this EEG control and the kinematics of the rapid and accurate movements it provides. The presentation will include a video illustrating the movement control achieved. This work extends the potential applications of non-invasive BCI technology to include real-time multidimensional movement control. It indicates that people with severe motor disabilities could use brain signals to operate a robotic arm or a neur.undation, and the James S. Mcdonnell Foundation).

Theories of working memory based on behavioral data. - P. Kyllonen (Educational Testing Service, Princeton, NJ).

Working memory may be defined as the system used for short-term storage and executive processes, such as attention and inhibition, task management, planning, monitoring, and coding (Smith and Jonides 1999). Working memory is exercised in virtually all cognitive activity, but tasks vary in the degree to which working memory (as opposed to other cognitive components, such as knowledge) is the critical performance determinant. Working memory's importance increases to the extent that tasks require the simultaneous processing and storage of information for their success, regardless of content (Baddeley 1986). This means that such tasks may be used to engage or activate the working memory system. In this talk I review evidence for the central role of working memory in all cognitive activity, highlighting reasoning, skill learning, language, and psychomotor performance. I present evidence that performance on working memory tasks is an extremely strong predictor of performance on reasoning, learning, and psychomotor tasks (typically, $r > .70$). Working memory plays a central role in computational models of cognition, such as ACT*, suggesting that a parameter representing the capacity of the working-memory system (e.g., the availability of activation) may be identical to Spearman's g. I also review evidence for the comparative goodness of tasks as measures of working memory, which suggests that a key feature is the minimization of specialized knowledge required.

Selective attention effects on anticipatory and stimulus-evoked activity across cortical and subcortical stages of visual processing. - C.E. Schroeder (Cognitive Neuroscience and Schizophrenia Program, Nathan Kline Institute, and Department of Neuroscience, Albert Einstein College of Medicine).

In a variety of paradigms selective attention: 1) modulates visual responses in V4/MT, V2 and V1, 2) increases baseline activity in some locations, and 3) differentially depresses low frequency EEG oscillations while enhancing high frequency (γ) oscillations in V4. The generality of the oscillatory effects across areas has not been examined, and their physiological significance is unclear. No electrophysiological effects have been seen in LGN. We examined intermodal selective attention effects on processing in LGN, V1, V2, V4 and MT/MST in 3 monkeys. Laminar EEG and action potential profiles were recorded with multielectrodes spanning the layers of each target structure. We used standard (attend-ignore) comparisons to detect attentional modulation of averaged responses in each area, and also applied Fourier and Wavelet analyses to single trial EEG. In the averaged response analysis, attentional modulation was detected throughout the cortical pathways, but not in the LGN. In going from V1 to V4, effect magnitude increased, and latency decreased. These findings are consistent with a stimulus-driven feedback model of attentional modulation. Concurrent surface ERP recordings revealed a selection negativity, that appears to arise in part from feedback-mediated disinhibition of extrastriate cortex. Our single trial analyses: 1) replicate the earlier V4 finding, 2) find similar results in MT/MST, 3) find more general enhancement in V2 and V1 (These patterns are paralleled in prestimulus baseline activity), and 4) find an indication of attentional modulation in LGN: γ enhancement in P-laminae, and general suppression in M-laminae. Prestimulus baseline effects throughout the system appear to reflect a tonic anticipatory bias of activity due to attention. Differential effects on low

and high frequencies in Area V4 may reflect modulation of inhibition versus excitation.

Neurophysiology of attending and ignoring. - G.V. Simpson (Dynamic Neuroimaging Laboratory, Department of Radiology, University of California San Francisco).

We suggest that selective stimulus processing may operate by enhancing the cortical representations of to-be-attended stimuli and suppressing the representations of to-be-ignored stimuli (distractors). It can be argued that ignoring distractors is a process that automatically accompanies attention, and is stimulus driven. However, it is possible that ignoring may be under top-down control. We have investigated these issues using cued attention designs (S1-S2) in which a centrally presented cue (S1) instructs the subject to deploy attention, following a delay, the second stimulus (S2) is presented. The S2 is either an attended stimulus or a distractor that must be ignored. The use of symbolic cueing ensures that attentional deployment is under top-down control. EEG measures following the cue reveal several processes underlying attentional deployment. The data support both rapid and slow deployment mechanisms of attention under the same conditions. Slow deployment processes consist of frontal and parietal activity followed by sustained activity over the cortical representations of the to-be-attended location, consistent with a bias-signal. At the same time there is an increase in alpha-band activity over the cortical representation of the to-be-ignored location (i.e. location of potential distractor stimuli), consistent with an active process of ignoring. We have begun to examine the processes in common with sustaining attention during cue delay periods and working memory in S1-S2 designs. Extrastriate intracranial recordings (in collaboration with Gregor Rainer) explore the physiological significance of oscillatory activity by investigating the relation between oscillatory activity and single unit firing during these delay periods.

EEG and ERP signals of working memory. - A. Gevins (San Francisco Brain Research Institute and SAM Technology, San Francisco, CA 94108; alan@eeg.com).

Working memory, the conscious effortful process of maintaining and manipulating representations (information) in one's mind for several seconds, is arguably the most fundamental of higher cognitive brain functions. WM involves a hypothetical limited capacity "Central Executive" system and task-specific representational processing systems. Neuroimaging studies of WM tasks show activation of dorsolateral and medial prefrontal and parietal cortex, as well as task-specific areas. Our lab has studied EEG and ERP signals of WM since the mid "80s using the n-back task in which a remembered stimulus, such as a letter or its position on the screen, is compared with a new stimulus (Gevins et al. 1990). (The n in n-back refers to how many trials back the remembered stimulus is.) This task is well controlled in that stimulus and response factors can be held constant while varying task difficulty and type of information. The n-back task evokes well-known EEG and ERP signals (Gevins et al. 1990, 1996, 1997). The magnitude of the continuous load on the attentional resources available for maintaining information in working memory during the n-back task can be measured with frequency domain parameters of the ongoing EEG such as frontal and parietal alpha band power and frontal midline theta band power. ERP peak amplitudes and latencies are modulated by the transient allocation of attention to stimulus processing during the n-back task, in particular the competition between the concurrent demands to maintain and update information while evaluating and responding to new stimuli. The main ERP signals modulated by WM tasks are CNV, P250, P300 and Slow Waves (McEvoy, Smith and Gevins, 1998). These EEG and ERP WM signals are stable after practice (Smith, McEvoy and Gevins 1999), have high test-retest reliability ($r>.90$; $p< .001$) (McEvoy, Smith and Gevins 2000), and their modulation is consistent from childhood to old age (Pellouchoud, Smith, McEvoy and Gevins, 1999; McEvoy, Pellouchoud, Smith and Gevins 2001). The signals have high face validity in that their modulation by variations in task difficulty can be accurately measured in individual subjects (>90%; $p< .001$) (Gevins, Smith, Leong, McEvoy et al. 1998). They have high construct validity in that differences between people in WM task performance and EEG and ERP signals are good predictors of a well-known measure of individual differences in cognitive ability, the Wechsler Adult Intelligence Scale IQ score (multiple $R=.80$; $p < .001$) (Gevins and Smith 2000). Finally, they have high discriminative validity in the sense that the n-back WM task and associated EEG & ERP signals are highly sensitive to transient and chronic changes in neurocognitive function due to a variety of stressors including: antihistamines, caffeine, alcohol and marijuana (Gevins and Smith 1999; Gevins et al. 2001; Gevins, Smith and McEvoy 2002; Ilan and Gevins 2001; Ilan, Smith and Gevins Submitted), anti-epileptic drugs (Chung et al. 2002; Gevins, Meador, et al. In Prep.), and extended Wakefulness (Smith, McEvoy and Gevins 2002). Together, this body of research results suggests that a clinical neurophysiological test of working memory is scientifically feasible.

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Functional brain connectivity with high time resolution sLORETA (Standardized Low Resolution Brain Electromagnetic Tomography). - Roberto D. Pascual-Marqui, Michaela Esslen, Kieko Kochi and Dietrich Lehmann (The KEY Institute for Brain-Mind Research, University Hospital of Psychiatry, Zurich, Switzerland).

The human brain is comprised of a very large number of highly interconnected neurons. Classical functional imaging (PET and fMRI) has emphasized the localization of function, but has practically neglected the role played by functional connections. Oscillations and synchronization, which emerge because of cortical interconnections, have been hypothesized to play an essential role in cognition and consciousness. This work presents a method for the computation and imaging of cortical connectivity. 3D functional imaging of electric neuronal activity is performed with standardized low resolution brain electromagnetic tomography (sLORETA). This method is uniquely capable of exact localization. In addition, it has the lowest spatial dispersion as compared to other published 3D linear, discrete, distributed EEG/MEG tomographies (Pascual-Marqui, Method Find Exp. Clin., 2002, 24D: 5-12). sLORETA provides high time resolution signals of "virtually implanted electrodes" throughout the cortex. Computation of cortical connectivity is then based on the following model: within short time windows, spatial clusters of cortical neurons have the same dynamics of activation, except for location-specific scale factors and for location-specific latency shifts. The method was tested in a visual event related potential experiment to right hemifield pattern reversal checkerboard stimulation, where time lagged connections from left to right visual cortices were demonstrated. In a single subject, eyes closed alpha-EEG study, time lagged connections from right to left posterior cortical areas were observed.

Time-frequency decomposition of ERPs from a visual oddball task: time-dependent delta, theta and alpha oscillations. - E.M. Bernat*, S.M. Malone+, W.J. Williams^, C.J. Patrick~ and W.G. Iacono# (*Department of Psychology, University of Minnesota; + Department of Psychology, University of Minnesota; ^Department of EECS, University of Michigan; ~Department of Psychology, University of Minnesota; #Department of Psychology, University of Minnesota).

Recent work has shown coordinated delta, theta, and alpha activity during visual oddball tasks. To characterize this activity, single-trial time-frequency transforms (TFTs) were decomposed using PCA (Bernat, Williams, Gehring, Lorenz and Casey 2002). Data from 1866 17yo participants in the Minnesota Twin Family Study (979 males) from electrode Pz were used. Target data spanning 0-14 Hz and 1-1312.5 ms were chosen for decomposition. Fifteen PCs evidenced coordinated time-dependent activity as follows. Prior to P300, alpha desynchronization was apparent in two alpha PCs (fast and slow) that transitioned to a single alpha PC ending just before the P300 peak. Also, two delta PCs (100-400 ms/1-2 Hz and 250-400 ms/2-3 Hz) and two interleaved theta PCs occurred before P300. The P300 peak was associated with two delta PCs (375-475 ms/2-3 Hz and 400-600 ms/1-2 Hz). After P300, two delta PCs were evident (1 Hz/600-1000 ms and 1 Hz/1000 ms-end). Alpha resynchronization after P300 occurred in one alpha PC that transitioned to fast and slow alpha PCs. Finally, a theta PC occurred after 900 ms. To assess stability of the solution, odd and even halves of the dataset were decomposed, producing structurally identical solutions. Target task difficulty was assessed. Easy targets produced larger and earlier alpha resynchronization, and simultaneously greater delta and theta activity. Hard targets were associated with greater delta activity preceding P300. In light of the sample size and solution stability, the decomposition appears to offer a stable and rich description of the coordinated TF ERP activity.

Mu-rhythm suppression and enhancement caused by tactile stimulation in healthy volunteers. - E.J. Marttinen-Rossi*+, H. Wikström*+, A. Korvenoja+ and S. Carlson^ (*BioMag Laboratory, Helsinki University Central Hospital, Helsinki Brain Research Center; +Functional Brain Imaging Unit, Helsinki University Central Hospital, Helsinki Brain Research Center; ^Institute of Biomedicine/physiology, University of Helsinki, Neuroscience Unit, Helsinki Brain Research Center).

The mu-rhythm of the primary somatosensory cortex (S1) is momentarily suppressed (event-related desynchronisation (ERD)) and then enhanced (event-related synchronisation (ERS)) when sensory stimulation is applied to a peripheral site (1). A computer-controlled device, which mechanically stimulates the skin with a calibrated von Frey filament was recently developed in our laboratory to study this phenomenon. The produced stimulation is more natural than the commonly used electrical stimulation. Magnetoencephalograms from 13 healthy right-handed volunteers were recorded during tactile stimulation (interstimulus interval 3 s) of the thenar of the right palm. The non-averaged signal from the sensor showing maximum ERD or ERS in the contralateral cortex was filtered using a wavelet centered at the peak frequency of the mu-rhythm in two predefined frequency regions, 8-14 Hz and 15-21 Hz. The average ERD in the first and second frequency regions were 28.3% and 25.7% respectively and the average latencies from the onset of the stimuli to the peak response 313 ms and 219 ms respectively. Respective values for ERS were 40.3% and 46.8% and for the latencies

833 ms and 689 ms. ERD and ERS were elicited in the contralateral S1 and were identified in all subjects. ERD and ERS are reliable indicators of activity in the S1 elicited by tactile stimulation. Compared to electrically induced ERD, ERD elicited by the von Frey filament appears to be shorter in duration (1). Stimulation with the von Frey filament has potential applications in assessing normal and disturbed functions of the somatosensory cortex.

Nikouline et al. Neurosci. lett., 2000, 294: 163-166.

District-related frequency specificity in hand cortical representation as revealed by somatosensory magnetic fields. - Franca Tecchio*+, Claudio Babiloni^, Filippo Zappasodi*+, Fabrizio Vecchio^, Carlo Salustri*, Vittorio Pizzella~, Gian Luca Romani~ and Paolo Maria Rossini+#% (*IFN-CNR, Roma; +AFaR-Dip Neuroscienze, Osp. Fatebenefratelli, Roma; ^Ist. Fisiologia Umana, Univ. "La Sapienza", Roma; ~ITAB, Department of Clinical Sciences and Bioimaging , University of Chieti, Chieti; #IRCCS "S. Giovanni di Dio-Fatebenefratelli", Brescia; %Neurologia Clinica, Università Campus Biomedico, Roma, Italy).

Cortical sensory neurons synchronize their activity at multiple frequency bands after an external stimulation. In the somatosensory cortical areas, previous reports describe more discrete and somatotopically specific neural synchronization at the gamma band. Therefore, an efficient gamma synchronization of the neurons in primary somatosensory cortex (S1) may be expected to characterize the stimulus processing from the thumb, i.e., the hand's most skillful area. To test this hypothesis, neuromagnetic fields were evoked over human S1 by the electrical stimulation of the contralateral thumb or little finger. Neuronal synchronization was indexed by the spectral coherence of the evoked neuromagnetic fields overlying S1. The frequencies of interest were the beta (16–32 Hz) and gamma (36–46 Hz) bands. The global amount of the coherence was defined as the total event-related coherence (ERCoh) among all magnetic sensors overlying the S1. Results showed prevalent increment of beta ERCoh (20–32 Hz) after the little finger stimulation and of gamma ERCoh (36–44 Hz) after the thumb stimulation. These results suggest that the neural synchronization in S1, as revealed by the ERCoh, may vary in frequency as a function of the finger stimulated. In this framework, the neural synchronization at gamma band may characterize the cortical representation of thumb, functionally prevalent with respect to little finger in humans.

An ERP and scalp current density study of spatial or spectral processing of moving sounds. - A. Bidet-Caulet and O. Bertrand (Mental Processes and Brain Activation Lab, INSERM U280, Lyon, France).

Human neuroimaging studies have suggested that posterior temporo-parietal regions are involved in auditory spatial processing forming a putative dorsal "where" pathways. We used EEG to investigate the dynamics of this network during the active or passive integration of a varying acoustic stream in a two-factor paradigm: focused vs diverted attention, spatial vs spectral variations. A stream consisted of successive 35-ms-noise bursts with varying location or pitch. Subjects had either to indicate the final direction of the stream (active integration) or to compare two additional bursts at the end of the stream (diverted attention). Event-related potentials were recorded at 36 scalp electrodes in 14 subjects, and were analyzed by scalp current density mapping (laplacian). During stream presentation, a sustained bilateral temporal activity (polarity reversals across Sylvian fissures) was present and more pronounced for pitch variations over the left hemisphere. When focusing on stream variations, a superior parietal and two bilateral temporo-occipito-parietal components were activated, showing no difference between spatial and pitch processing. Thus, the active integration of either spectrally or spatially moving sounds involved temporal and parietal cortices. These regions are not uniquely implicated in auditory spatial processing but rather in the integration of rapidly varying acoustic streams, thus questioning the actual nature of the auditory dorsal pathways.

Assessing cortical connectivity and information flow from scalp EEG data: a simulation study to address the properties of Directed Transfer Function (DTF). - F. Cincotti*+, L. Astolfi+, F. Vecchio+, A. Basilisco+, C. Babiloni+^, F. Carducci+~, S. Salinari#, P.M. Rossini^~ and F. Babiloni+ (*Fondazione Santa Lucia IRCCS, Rome, Italy; +Dip. Fisiologia Umana e Farmacologia, Univ. "La Sapienza", Rome, Italy; ^AFaR, Ospedale FBF "S. Giovanni Calibita" CRCCS, Rome, Italy; ~Ospedale FBF "S.Giovanni di Dio" IRCSS, Brescia, Italy; #Dip. Informatica e Sistemistica, Univ. "La Sapienza", Rome, Italy).

Besides the research on "where" where sensorial or cognitive take place in the cerebral cortex, techniques that measure the cooperation between cortical regions in carrying on these activities are recognized to be necessary to understand the brain functions. The Directed Transfer Function (DTF) is a spectral index that measures the causal relationship between pairs in a set of signals. Its use has been proposed and applied to electroencephalographic (EEG) data. In this study the performances of this index applied to cortical activity estimates obtained from EEG recordings are evaluated in a simulation setup. The accuracy of DTF estimation from finite and noisy recordings are first investigated, evaluating the difference between estimated vs. analytically computed values of DTF on data of differ-

ent length, corrupted by a variable amount of noise. Also we address the ability of (correctly computed) DTF of being an index of functional coupling, in several cases in which the topology of the network ranges from simple cases one to more complicated ones. The DTF is shown to be rather robust to noise and finiteness of data (8% RMSE in reasonable conditions). Thank to the factorial design of the simulation and to the ANOVA analysis of the results, we also clearly state the limits of the application of DTF the estimation of cortical connectivity in high resolution EEG studies. An application to real data is finally reported in order to show an instance of connectivity estimation between cortical regions from non invasive EEG measurements.

Dynamic cortical patterns during conscious perception in binocular rivalry. - D. Cosmelli.*, O. David#, J.-P. Lachaux*, J. Martinerie*, L. Garnero*, B. Renault* and F. Varela*+ (+Deceased May 2001; *Cognitive Neuroscience and Brain Imaging Laboratory, CNRS UPR 640, Hôpital de La Salpêtrière, 47 bld de l'Hôpital, 75651 Paris Cedex 13, France; #Wellcome Department of Imaging Neuroscience, Functional Imaging Laboratory, 12 Queen Square, London WC1N 3BG, UK).

In the last decades evidence has begun to converge on the notion that the establishment of dynamic relations between distant brain regions underlies conscious experience. According to the synchronous ensembles hypothesis such dynamical relations would be embodied by a transiently coactive network comprising distributed regions of the brain. Anyhow, the study of such integrative processes is far from achieved, specially in the case of spontaneous on-going perception. To be able to study this phenomenon in the human brain it is necessary to have both a good temporal and spatial resolution. The MEG/EEG inverse problem represents a unique non-invasive approach towards this goal. We present an MEG study of binocular rivalry, an experimental paradigm that reveals the endogenous rhythmicity of perceptual experience under reproducible conditions. Here, a subject is presented with non-fusible images, one to each eye, and his perception oscillates spontaneously among both mutually exclusive possibilities. Our aim is the study of on-going neural patterns during the coming into consciousness of a given percept, from an integrative and fundamentally dynamical point of view. Using an adapted inverse problem framework we reveal specific non-averaged patterns of synchronous brain activity that follow dominance periods during visual rivalry in human beings. Such synchronous networks are centered in visual cortex and extrastriate occipital dorsal areas, and comprise parietal, inferotemporal and frontal regions. Moreover, the temporal evolution of the network suggests a dynamical dialogue between the occipital, "visual" cortex and more frontal regions of the brain upon conscious visual perception.

Learning by different strategies modulates prefrontal and temporal brain magnetic activity. - F. Maestú*+^, P. Campo*, P.G. Simos~, A. Capilla*+, N. Paul%, S. Fernandez^, A. Fernández*#, C. Amo*, J. González-Marqués+ and T. Ortiz*# (*Centro de Magnetoencefalografía Dr Pérez Modrego, Universidad Complutense Madrid; +Departamento Psicología Básica II (Procesos Cognitivos), Facultad de Psicología. UCM; ^Departamento de Psicología, Universidad Camilo José Cela, Madrid; ~University of Texas-Houston Medical School, Vivian L. Smith Center for Neurologic Research, Department of Neurosurgery; #Departamento de Psiquiatría, Facultad de Medicina, Universidad Complutense Madrid; %Unidad de daño cerebral, Hospital Beata María Ana de Jesús, Madrid).

Three different verbal learning strategies (serial-order, phonological and semantic) were studied by means of magnetoencephalography. The course of activation elicited by the serial-order strategy showed early activation (between 200 and 400 ms after stimulus onset) of the inferior frontal, sensorimotor, and insular region in the left hemisphere. Furthermore, activation was more prominent in dorsolateral prefrontal cortices bilaterally. Conversely, activation profiles associated with the phonological strategy showed a preponderance activation of the superior temporal gyrus in the left hemisphere between 500 and 600 ms. Finally, the semantic strategy showed activation of the left middle temporal gyrus, between 500 and 700 ms. As a conclusion, the level and type of initial learning processes produce the engagement of different brain circuits.

Studying phase synchrony for classification of mental tasks in brain machine interfaces. - E. Gysels*, J. del R. Millán+, S. Chiappa+, P. Celka* (*CSEM (Swiss Centre for Electronics and Microtechnology), Neuchâtel, Switzerland; +IDIAP (Dalle Molle Institute for Perceptual Artificial Intelligence), Martigny, Switzerland).

Electroencephalogram recordings during imagination of mental tasks allow for developing a new communication device for, e.g., motor disabled people. 32-channel EEG was recorded from 5 healthy subjects while performing, after instruction and in random order, repetitive left-hand movement imagination, right-hand movement imagination and "word generation". In 3 consecutive days, 5 sessions of 4 minutes were acquired, without feedback. Extracted features were based on the Phase Locking Value (PLV), coherence, and the spectral power in the α-, β_1-, β_2- and 8-30 Hz frequency bands. Different feature subsets were considered for classification. The classifier consisted of a combination of Support Vector Machines (SVMs), allowing for classifying the 3 mental tasks. Results were obtained from 5-fold crossvalidation. We ana-

lyzed (offline) data from the last day of recording, when subjects had a training experience of only 40 minutes from the two previous days. Selecting for every subject the best feature subset, often a combination of PLV and power features, we obtained for two subjects correct classification rates of 67.81% and 62.58%, distinguishing the 3 mental tasks. For the other subjects, classification rates were 52.77%, 44.66% and 41.24% only, maybe due to not enough practice. The involvement of the motor cortex manifested itself by a good performance of the features extracted from electrodes located in the centro-parietal region. Sole use of PLV or coherence features yielded good classification, proving phase synchronization appropriate for classifying mental tasks. This shows the importance of studying functional relations between brain regions for further improvement of Brain-Machine Interfaces.

Maintenance of integrated and unintegrated information: a magnetoencephalography study. - P. Campo*, F. Maestú*+, A. Fernández*^, A. Capilla+, C. Amo* and T. Ortiz*^ (*Magnetoencephalography Center Dr. Pérez Modrego. University Complutense of Madrid; +Department of Basic Psychology. Cognitive Processes. University Complutense of Madrid; ^Department of Psychiatry. University Complutense of Madrid).

Working memory (WM) is considered as the ability to temporary maintain and manipulate an active representation of information. Sustained neural activity over memory retention intervals in delayed tasks is generally interpreted as the neural basis of working memory. Evidence from studies with infrahuman primates as well as humans revealed that working memory task performance required the activation of multiple widely distributed regions in posterior perceptual areas, motor cortices, and prefrontal cortex. Maintenance is considered a process of keeping information in mind in the absence of external stimuli, and corresponds to the mnemonic aspect of the WM. Two basic processes are assumed to be involved in the active maintenance of information: storage of material and the rehearsal of material. In the present study participants performed two different tasks in which they had to maintain verbal (letters) and spatial (locations) information, either in an integrated or in unintegrated manner. We investigated the spatiotemporal patterns that characterized the maintenance of integrated information using a neuroimaging technique with a high temporal resolution, as is the magnetoencephalography (MEG). Results are discussed in terms of the activation of different neural networks. We also compared our results with those from a fMRI study in terms of temporal resolution.

Hemispherical differences in middle latency auditory evoked fields. - A. Kult*+, S. Supek+, P. Schneider*^, H.J. Specht^, H.G. Dosch^ and A. Rupp* (*Department of Neurology, University Hospital Heidelberg, Heidelberg, Germany; +Department of Physics, Faculty of Science, University of Zagreb, Zagreb, Croatia; ^Department of Physics, University of Heidelberg, Heidelberg, Germany).

Middle latency auditory evoked fields (MAEFs) occur about 20-80 ms after stimulus onset. Since the MAEF components are relatively small, source identification in that time interval is rather challenging. Some authors reported that the origin of the middle latency evoked activity is located within the primary auditory cortex (PAC) [1,2] while other studies suggest that even the Pa peak, which has a latency of about 30 ms, is too late to be restricted to the activation from PAC [3] only. In this study we tried to localize Pa and Pb sources (around 50 ms) separately and analyze their interhemispherical differences. Stimuli were diotically presented, amplitude modulated, sinusoids with carrier frequency of 1 kHz and a decaying exponential envelope of 4 ms half-life time. Evoked magnetic fields were recorded with a whole-head Neuromag-122 system from 10 normal hearing subjects. Spatio-temporal analysis confirmed that the Pa source received contribution of more than one cortical area, only one of which originated from the anteromedial portion of Heschl's gyrus (HG) which is considered to be PAC. Pb sources were found on the anterolateral portion of HG. Interhemispherical amplitude and latency differences were observed in the measured fields as well as the identified sources. The MRI-based volumetry suggests that these neurophysiological differences might be explained by anatomical differences in HG morphology.

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The human SI activity is related to the input stimulus frequency and perception in a frequency discrimination task. - Li Chan Liu , Peter B. C. Fenwick, Nikolaos A. Laskaris, Marc Schellens, Vahe Poghosyan, Tadahiko Shibata and Andreas A. Ioannides (Laboratory for Human Brain Dynamics, RIKEN Brain Science Institute (BSI), 2-1 Hirosawa, Wakoshi, Saitama, 351-0198, Japan).

We used magnetoencephalography (MEG) to investigate non-invasively whether activity in primary sensory area (SI) of humans is shaped exclusively by the input or it also reflects the subjective perception of the stimulus. Four right-handed males participated in a frequency discrimination task to detect frequency changes of an electrical stimulus applied to the right-hand digits 2+3+4. Pairs of Stim1 (1s; 21 Hz) and Stim2 (1s; 21 Hz (50%) or 22 to 29 Hz) were used. We analyzed the single

trial MEG data using tomographic and pattern analysis, and correlated brain activations with the subjects' responses. The left-SI was the most consistently activated area and showed the first activation peak at 35-48 ms after Stim1 onset and sustained activity during both stimulus periods. During the Stim2 period the left-SI activation started to differ significantly between two groups of trials (21 versus 26-29 Hz) within the first 100 ms and this difference was sustained and enhanced thereafter (about 600 ms). When only correct responses from the above two groups were used, the difference was even higher at later latencies (>650 ms). For Stim2 delivered at 21 and 26-29 Hz but both perceived as 21 Hz, the sustained difference was present only before 650 ms. In addition to the expected SI involvement with the analysis of input frequency, our results show a modulation of SI activity that depends on the subject's perception and decision at late latencies. This is the first evidence from neuroimaging showing perception related correlates in the activity of SI.

Involuntary crossmodal enhancement of preattentive auditory processing is selective in space. - K. Mathiak*, I. Hertrich*, W.E. Kincses+, S. Rothe+, H. Menning*, W. Lutzenberger* and H. Ackermann* (*MEG center, Dept. Neurology, Univ. Tübingen, Germany, +DaimlerChrysler AG, Stuttgart, Germany).

Different sensory pathways are known to interact within the central nervous system. Spatially divergent stimuli may delay responses, whereas a cohesive stimulation design can support correct responses and speed up reaction times. In animal studies, oculomotor, visual, and somatosensory systems were shown to affect auditory processing through distinct subcortical and early cortical pathways. The current study focused on cross-sensory influences on preattentive auditory processing, which detects change and facilitates orienting reactions. We employed an oddball paradigm to assess cortical processing using whole-head magnetoencephalography (MEG) in two series of 20 volunteers each. While subjects performed distraction tasks of varying difficulty, auditory duration deviants occurred randomly at the left or the right ear preceded (200 – 400 ms) by oculomotor, visual, or tactile co-stimulation at either side. Mismatch fields were recorded over both hemispheres. Changes in gaze direction and static visual stimuli cued the most reliable enhancement of deviance detection at the same side, and most strongly at the right auditory cortex. Tactile stimuli at either cheek enhanced the processing of auditory events from the respective ear by the ipsilateral hemisphere. In all three modalities, the lateralized unattended and unpredictive pre-cues acted analogously to shifts in selective attention, but were not reduced by the parametrized cognitive load. Thus, early cognitive representation of localized sounds interferes with other modalities. We suggest that preattentive multisensory integration provides a basis for orienting to objects in space and, thus, for selective attention.

Comparison between tone and phonetic MMN using dichotic listening task. - J. Shinoda, K. Nakagome, Y. Kuwakado, D. Muramatsu, T. Takahashi, S. Ikezawa, S. Kamio and M. Katoh (Showa University School of Medicine, Tokyo Metropolitan Bokutoh Hospital).

It has been acknowledged that dichotic listening task (DLT) is well suited for detecting the interhemispheric difference of brain activity. The aim of this study is to detect the difference in lateralization of automatic mismatch processing between tone and phonetic MMN as well as the similarity of brain regional activities using DLT. The tone MMN task comprised 3 sets of stimuli; 1 kHz stimuli presented to both ears (standard), 1 kHz to the left ear and 2 kHz to the right (right deviant), 1 kHz to the right and 2 kHz to the left (left deviant). In the phonetic MMN task, 1 kHz and 2 kHz tones were substituted to syllables such as "ba" and "da", respectively. The subjects were engaged in a visual task ignoring all the acoustic stimuli throughout the recording. As a result, although there was no significant difference between the tones and phones in terms of discriminability of deviants and standards behaviorally confirmed in the pre-test session, the phonetic MMN was significantly larger than the tone MMN. EEG topographies indicated that the phonetic MMN was distributed predominantly in the left hemiscalp, whereas the tone MMN was distributed bilaterally. SCD analyses revealed a prominent current sink in the left temporal region for the phonetic MMN, whereas it was not evident for the tone MMN. The left hemispheric predominance of the phonetic MMN in DLT was in accordance with the previous reports, suggesting that it may be a good biological marker for left hemispheric dysfunction, which is frequently mentioned in schizophrenia.

Rapid change of tonotopic maps in the human auditory cortex during pitch discrimination. - I. Ozaki*, C.Y. Jin+, Y. Suzuki^, M. Baba~, M. Matsunaga~ and I. Hashimoto# (*Department of Physical Therapy, Faculty of Health Sciences, Aomori University of Health and Welfare, Aomori, Japan; +Department of Neurological Science, Institute of Brain Science, Hirosaki University School of Medicine, Hirosaki, Japan; ^Department of Social Welfare, Faculty of Health Sciences, Aomori University of Health and Welfare, Aomori, Japan; ~Department of Neurological Science, Institute of Brain Science, Hirosaki University School of Medicine, Hirosaki, Japan; #Human Information Systems Laboratory, Tokyo Office, Kanazawa Institute of Technology, Tokyo, Japan.

To study early cognitive processes and hemispheric

differences in the primary auditory cortex during selective attention, we measured auditory evoked magnetic fields (AEFs) to 400 Hz and 4000 Hz tone pips that were randomly presented at right or left ear. Subjects paid attention to target stimuli during pitch (high or low) or laterality (left or right) discrimination tasks. In control session, 400 Hz or 4000 Hz tone alone was presented at left or right ear. We calculated location and strength of N100m dipole for 400 Hz and 4000 Hz tones, based on the AEFs obtained from the hemisphere contralateral to the stimulated ear. N100m amplitude increased in both hemispheres in pitch or laterality discriminating conditions. N100m latency shortened in the right auditory cortex during selective attention. The N100m dipole distance between 400 Hz and 4000 Hz tones was enlarged in the right auditory cortex during pitch discrimination task but was unchanged during laterality discrimination task. We conclude that these dynamic changes in the N100m dipole reflect short-term plastic changes in the primary auditory cortex and right hemisphere dominance of attention, supporting early selection models.

Change in visual brain responses during discrimination of the differences in color or shape of colored letters. - I. Ozaki*, C.Y. Jin+, Y. Suzuki^, M. Baba~, M. Matsunaga~ and I. Hashimoto# (*Department of Physical Therapy, Faculty of Health Sciences, Aomori University of Health and Welfare, Aomori, Japan; +Department of Neurological Science, Institute of Brain Science, Hirosaki University School of Medicine, Hirosaki, Japan; ^Department of Social Welfare, Faculty of Health Sciences, Aomori University of Health and Welfare, Aomori, Japan; ~Department of Neurological Science, Institute of Brain Science, Hirosaki University School of Medicine, Hirosaki, Japan; #Human Information Systems Laboratory, Tokyo Office, Kanazawa Institute of Technology, Tokyo, Japan).

To study early cognitive processes in the visual cortex during selective attention, we measured visual evoked magnetic fields (VEFs) to 4 colored letters (C+G or G+C in green or red letters) that were randomly presented on the screen at 2 sec interval (0.2 sec presentation). Subjects paid attention to target stimuli during color (red or green) or shape (G or C on the left side) discrimination tasks. Total number of the stimuli was 300: 30×2 for target and 120×2 for non-target. In control session, each colored letter alone was presented. The mean reaction time for color discrimination task was 322-333 msec and that for shape discrimination task, 392-411 msec. We calculated location and strength of the dipoles that were identified at 70-500 msec for each colored letter as control and non-target responses, based on the VEFs obtained from the occipital and/or temporal area. For color discrimination, following V1/2 activation, activation of V4 area (the fusiform gyrus) was identified. For shape discrimination, following V1/2 activation, the lateral occipital complex (the occipito-temporal area) was activated. On the other hand, in control session, the V4 area or the lateral occipital complex was rarely activated. In addition, the strength of the dipoles at the V4 area or the lateral occipital complex was much larger in selective attention than in control. We conclude that, even when subjects look at the same colored letter, selective attention to color or shape modifies the information processing pathways in the visual brain as the top-down mechanism, supporting early selection models.

Somatosensory Evoked Fields (SEFs) following finger stimulation are changed by tongue movement or tactile interference to cheek. - I. Ozaki*, C.Y. Jin+, M. Baba+, M. Matsunaga+ and I. Hashimoto^ (*Department of Physical Therapy, Faculty of Health Science, Aomori University of Health and Welfare, Aomori, Japan; +Department of Neurological Science, Institute of Brain Science, Hirosaki University School of Medicine, Hirosaki, Japan; ^Human Information Systems Laboratory, Tokyo Office, Kanazawa Institute of Technology, Tokyo, Japan).

Phantom fingers following arm amputation are known to be frequently represented on the cheek ipsilateral to the amputated arm, suggesting close neural connections in cortical areas between the fingers and cheek. To test the hypothesis above, we analyzed somatosensory evoked magnetic fields (SEFs) to finger stimulation with or without tactile interference to the cheek ipsilateral to finger stimulation or the tongue movement. To elicit SEFs, electrical stimulation at three times of the threshold was applied at the rate of about 1 Hz to the fingers I, II, III and V independently. SEFs were markedly modified by tactile interference to the cheek or the tongue movement. For the interference conditions, SEF power was significantly reduced at around 100 msec where the posterior parietal cortex or SII was activated in control condition. Especially, the response of SII that was identified in control condition diminished in the interference conditions. Furthermore, the reduction in SEF power was of the same magnitude among the stimulated fingers or between tactile interference to the cheek and the tongue movement. On the other hand, the response of SI (<50 msec) was sometimes unaltered in the interference conditions. We conclude that both tactile interference to the cheek and the tongue movement modify the response of SII or the posterior parietal cortex more than that of SI. We therefore speculate that phantom fingers following arm amputation may be the results of altered neural network activities at SII region where activation of a cheek representing area spreads horizontally to the adjacent, formerly hand representing area.

The processing of semantic meaning in Chinese words and evoked brain topography. - W. Skrandies*, M.-J. Chiu+ and Y. Lin+ (*Institute of Physiology, Justus-Liebig University, Giessen, Germany; +Department of Neurology, NTUH, Taipei, Taiwan).

The connotative meaning of words can be quantified statistically by the "semantic differential technique" resulting in statistically defined, independent dimensions where every word is uniquely located on the three dimensions evaluation ("good - bad"), potency ("strong - weak"), and activity ("active - passive"). In an earlier study employing German subjects we demonstrated that there are electrophysiological correlates of these meaning dimensions. Here a group of 55 Chinese adults was investigated in two experiments: first, 210 nouns were rated by 32 subjects, and factor analysis on the questionnaire data yielded three independent semantic dimensions. Semantically unique words stemming from these results were then used as stimuli in electrophysiological experiments in another group of 23 healthy right-handed adults. Words of similar physical appearance belonging to different semantic classes were presented visually in random order. The EEG was recorded from 32 channels, and evoked brain activity was computed for each semantic class. Significant differences in electrical brain activation between semantic word classes were observed as early as 80 ms after stimulus onset confirming earlier reports on similar findings in German subjects. These results illustrate similar early neural activation in subject groups of different language and culture.

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EEG early evoked gamma-band synchronization reflects object recognition in visual oddball tasks. - Gabor Stefanics*, Attila Jakab*, László Bernáth+, Lóránd Kellényi* and István Hernádi*^ (*Dept. of General Zoology and Neurobiology, Faculty of Natural Sciences, University of Pécs, Hungary, +Institute of Psychology, Faculty of Humanities, University of Pécs, Hungary, ^Dept. of Anatomy, University of Cambridge, UK).

In a series of different visual EEG experiment the early evoked gamma activity was found to be insensitive to stimulus type and was suggested to reflect sensory binding mechanisms. However, repetition of both target and nontarget stimuli occured during stimulus presentation in previous studies. Repetition of stimuli usually leads to a phenomenon often referred to as repetion priming and may reflect a neural savings mechanism. Nevertheless, the functional role of early evoked gamma activity is still not clear. In our study EEG was recorded in 3 visual oddball experiments during presentation of natural photos of butterflies and plants in order to study the early gamma activity evoked by familiar and novel stimuli during visual processing of biologically relevant complex objects. In all three experiment picture of one specific butterfly served as target repeating 60 times and subjects task was to silently count them. In Exp 1 neutral stimuli were 180 individial pictures of butterflies from other species, in Exp 2 neutral stimuli were 180 indvidual pictures of plants and in Exp 3 both neutral stimuli were applied. Evoked synchronization (inter-trial coherence or phase-locking factor) was analyzed by sinusoid wavelet based time-frequency analysis. Consistent with other studies, significant phase-locked γ-synchronization was found from 80 to 140 ms postimulus in the 30-50 Hz range at parietal and occipital sites in response to the repeating target stimulus followed by strong desynchronization in γ-band. Nontarget stimuli did not evoke similar activity in the γ–frequency range. The observed difference can be explained if we assume that the repeated experience of an object may lead to rapid formation of a neural assembly representing the object causing the repetition priming effect. In our study the single target stimulus was introduced to the subjects before the expirement whereas individual nontargets were unfamiliar images. Thus, subjects probably had a neural representation of the target only. We suggest that the early phase-locked γ-activity in the 30-50 Hz range might reflect the top down activation of the neural representation of the familiar target.We found strong evoked γ-band synchronization which was significantly higher for target than nontarget stimuli. γ-synchrony was reported to reflect sensory and task processing and was suggested to be involved in top-down processing. In line with previous findings the evoked γ-synchrony was sensitive to stimulus type probably reflecting attentional mechanisms.

Neuromagnetic studies on emotional and inverted faces in an oddball paradigm. - A. Susac*, R.J. Ilmoniemi+^, E. Pihko+ and S. Supek* (*Department of Physics, University of Zagreb, Zagreb, Croatia; +BioMag Laboratory, Helsinki University Central Hospital, Helsinki, Finland; ^Nexstim Ltd., Helsinki, Finland).

Faces are socially very important visual stimuli and the detection of a change in face identity or facial expression is an evolutionary very important skill. Non-target neutral face presented as a deviant in an oddball paradigm with happy face standard and face with glasses target deviant elicited negative shift around 280 ms in EEG (electroencephalography) an MEG (magnetoencephalography) recordings [1]. If the neutral face of another person was used as the standard the amplitude of the observed negativity was smaller and at a later latency. Face inversion is known to disrupt face processing. The aim of the present study was to investigate the effect of face inversion on mismatch activity [1]. Neurodinamic measurements

were conducted at the BioMag laboratory using 306-channel Vectorview system in the parallel with a 60-channel EEG. MRI scans were available for all 8 young male subjects that participated in the study. The spatio-temporal localization of neuromagnetic sources of the observed effect was carried out with standard Neuromag software. Four experimental conditions were employed: 1) happy standard, neutral deviant; 2) neutral standard, neutral deviant; 3) inverted happy standard, inverted neutral deviant; 4) inverted neutral standard, inverted neutral deviant. The task was silent counting of the face with glasses deviant in all conditions. Mismatch activity observed in condition 1 and 2 was attenuated or disappeared in condition 3 and 4. This paradigm provides means for studying inversion effect on recognition of facial identity and facial expression.

[1] Susac, A., Ilmoniemi, R.J. and Supek, S. Emotional faces in the visual oddball paradigm: A possible mismatch negativity (in preparation)

Dynamic movement of N100m dipoles in evoked magnetic field reflects sequential activation of isofrequency bands in human auditory cortex. - Y. Suzuki*, I. Ozaki+, C.Y. Jin^, M. Baba^, M. Matsunaga^ and I. Hashimoto~ (*Department of Social Welfare, Faculty of Health Sciences, Aomori University of Health and Welfare, Aomori, Japan; +Department of Physical Therapy, Faculty of Health Sciences, Aomori University of Health and Welfare, Aomori, Japan; ^Department of Neurological Science, Institute of Brain Science, Hirosaki University School of Medicine, Hirosaki, Japan; ~Human Information Systems Laboratory, Tokyo Office, Kanazawa Institute of Technology, Tokyo, Japan).

To investigate spatiotemporal features of the isofrequency bands for 400 Hz and 4000 Hz tones in human auditory cortex and on the hemispheric differences in the arrangement of the isofrequency bands, we recorded auditory evoked magnetic fields (AEFs) to 400 Hz or 4000 Hz tone pips presented at right or left ear from 31 normal subjects. The dipole location for the N100m sources was successively calculated from the AEFs obtained from the hemisphere contralateral to the stimulated ear. In the right hemisphere, the current sources for 400 Hz and 4000 Hz moved toward anterolateral direction before the N100m peak, showing parallel arrangement of the isofrequency bands (4000 Hz in medial location). In the left hemisphere, the movement direction of 400 Hz dipoles was anterolateral, while that of 4000 Hz dipoles was lateral. This difference in the organization of isofrequency bands between right and left auditory cortices reflects distinct functional roles in auditory information processing such as pitch vs. language discrimination.

Spatiotemporal dynamics of lexico-semantic processing in left perisylvian cortex. - T.W. Wilson*+^, P.J. Pardo*+~ and A.C. Leuthold*+# (*Brain Sciences Center, Veterans Affairs Medical Center, Minneapolis, Minnesota; +The Domenici Research Center for Mental Illness; Departments of ^Psychology, ~Psychiatry and #Neuroscience, University of Minnesota).

Numerous functional neuroimaging experiments have investigated the neural substrates of lexico-semantic processing. These predominantly metabolically-based studies have greatly enhanced our understanding of the neuroanatomy subserving linguistic functions, but have not provided insight into the temporal dynamics that likely mediates our language processing capacities. Moreover, although much investigated, the precise neural correlates remain an area of contention due to the inconsistent results that have plagued this domain of inquiry. The present study furthers this research by focusing on the temporal behavior of neural responses common across-condition in a within-subject design. Using whole-head magnetoencephalography, we recorded the brain processes evoked when participants view high-frequency concrete nouns, pronounceable pseudowords, and consonant strings (i.e., nonwords). In each participant (n=10), dipole-modeling techniques were employed to characterize the spatiotemporal dynamics of word-level language processing. Within-subject, we observed substantial overlap in the tissue underlying word and pseudoword processing; however, these left perisylvian neural regions were recruited much earlier (~100 msec) in the processing of words relative to pseudowords. In addition, the cell populations activated by pronounceable stimuli exhibited reasonable spatial variance when compared across-subject, which may reflect the origin of the replication problems emerging in metabolic studies. The nonword stimuli activated mostly right hemisphere structures, thus displaying little systematic relationship with the other stimuli classes. We conclude that all pronounceable stimuli activate a common neural circuit in left perisylvian cortex dedicated to lexico-semantic processing, and that the time-course by which this circuit is recruited may vary as a function of the linguistic stimuli's frequency.

Fetal and neonatal magnetic auditory evoked responses. - R.T. Wakai (Department of Medical, University of Wisconsin-Madison, Madison, WI, USA).

Over the last few years, there has been growing interest in recording fetal brain activity with MEG. In the fetus, magnetic detection provides much higher signal quality than electric detection. Furthermore, MEG is an ideal technology in that it records neuronal activity directly, has high temporal resolution, and is completely

safe and noninvasive. Our group has mainly attempted to record fetal auditory evoked responses (AERs). Of the various AERs, long-latency cortical responses have been the easiest to record in the fetus. In one study, fetal AER recordings were obtained from 23 fetuses at gestational ages 28-40 weeks, using a 37-channel biogradiometer. The stimuli were 1500 Hz tone bursts of duration 50 msec and intensity 100 dB. The fetal AERs had amplitudes on the order of 25 fT and were recorded with a success rate of approximately 50%. The responses were dominated by a component with approximate latency 250 msec. The fetal AERs were consistent with AERs recorded postnatally from the same subjects. Generally, AER latency decreased with increasing conceptional age; however, the polarity of the dominant component appeared to reverse polarity from N to P during the last month of pregnancy. Fetal MEG research is at a very early stage. Signal quality and detection rate need to be improved. We have shown, however, that under favorable circumstances fetal MEG signals can be recorded with reasonable signal-to-noise, allowing initial studies of human brain activity throughout the perinatal period.

MEG recordings of fetal and infant auditory short-term memory. - M. Huotilainen (Cognitive Brain Research Unit, Department of Psychology, University of Helsinki, Finland).

The functioning of the auditory short-term memory is manifested in the mismatch negativity (MMN) event-related response in adults and children of various ages. MMN correlates well with behavioural measures of auditory change detection, and measures of higher cognitive abilities needed in, for example, speech perception. MMN is also promising in studying defects in general cortical functions, decay of memory trace duration in, for example, Alzheimer's disease, and problems of specific auditory perceptual abilities in, for example, autistic and Asperger children. MMN can be recorded also in infants and even in prematurely born babies. Magnetoencephalography (MEG) is a non-invasive method to record the neuronal activity. We aimed at determining whether the magnetic counterpart of the MMN, the MMNm, could be obtained in infants of 1 to 5 days old, and in fetuses of 35 to 40 weeks GA. We were able to obtain statistically significant MMNm responses in both subject groups. We regard this result as a promise for the future of neonatal and fetal MEG since it proves that even such cognitive skills as change detection and short-term memory can be studied in these subject groups.

Optical activation studies of newborn infants. - I. Nissilä, *, K. Kotilahti*, M. Huotilainen+, L. Lipiäinen*, T. Noponen*, V. Fellman^~ and T. Katila* (*Laboratory of Biomedical Engineering, Helsinki University of Technology, Finland; +Cognitive Brain Research Unit, Department of Psychology, University of Helsinki, Finland, ^Hospital for Children and Adolescents, University of Helsinki, Finland, ~Department of Pediatrics, Lund University, Sweden).

Imaging techniques based on near-infrared spectroscopy (NIRS) have been researched for the past decade for use in functional brain imaging. Due to the different absorption spectra of oxy- and deoxyhemoglobin, it is possible to determine the local changes in these concentrations using at least two wavelengths in the near infrared. In addition to changes in attenuation, frequency-domain optical imaging devices can measure the mean optical pathlength of the photons between the source and the detector. Optical imaging is at least in theory well suited for studies on neonates, who can be investigated during sleep. The optical attenuation of tissue is lower than with adults, and the cortex is closer to the surface of the head, allowing a higher signal-to-noise ratio. The compactness of optical imaging technology may lead to bedside applications. We have studied neonates using auditory, somatosensory, and visual stimuli. The idea is to compare the block and event-related paradigms, and study the reliability and accuracy of optical imaging for the study of cortical hemodynamics and brain activity in neonates. We plan to compare responses of full-term neonates to pre-term ones, as well as young children and adults. Simultaneously recorded EEG will be used as a reference during the event-related optical studies.

Quantitative EEG norms for the first year of age. - T. Harmony*, L. Díaz-Comas+, E. Porras*, S. Ocampo*, E. Santiago*, L. Galán+ and T. Fernández* (*Institute of Neurobiology, National Autonomous University of Mexico, +Cuban Neuroscience Center).

Quantitative EEG norms for school-age children have shown to be very useful for the evaluation of many disorders, as learning disabilities, attention deficit disorders, mental retardation, etc. We are involved in a project for early diagnosis and neurohabilitation of children with prenatal and perinatal risk factors of brain damage. Our main purpose is to try to reduce, as much as possible, neurological sequels in children. For this reason very early treatment should continue for at least one or two years. Therefore it is necessary the longitudinal evaluation of the infants. The obtention of a normative data base might be very useful for these evaluation. The EEG of normal infants between oneweek and one year of age was recordedin the 10/20 system. Children had no pathological antecedents and a normal neuropediatric examination. 24 EEG segments of 2.56 s were edited and analyzed. Spectral parameters each 0.78 Hz were calculated. AbsolutePower, relative Power and Mean Frequency for the classical EEG bands were obtained. Regression equa-

tions in function of age were obtained for the narrow spectral power and for the broad band parameters in the referential (A1A2), Laplacian and Average montages. Topographic maps of the raw and Z values for absolute and relative power and mean frequency were developed.

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Brain's plastic changes caused by speech intervention in bilingual SLI children. - Elina Pihko*+, Annika Mickos^, Teija Kujala~+, Paavo Alku#, Roger Byring^ and Marit Korkman% (*BioMag Laboratory, Helsinki University Central Hospital; +Helsinki Brain Research Centre; ^Folkhälsan; ~CBRU, University of Helsinki; #Helsinki University of Technology; %Åbo Akademi).

We studied the effect of a new intervention program on the ability of bilingual children to discriminate speech sounds. In addition, we studied if the possible rehabilitation effect is reflected in the brain activity measured by magnetoencephalography (MEG). Subjects were Finnish-Swedish preschool children with specific language impairment. Two sets of syllables (/su/- standard, /so/ and /sy/-deviants, and /da/-standard, /ba/ and /ga/-deviants) were used as stimuli in the oddball paradigm. After the initial MEG measurement behavioral test on sound-pair discrimination was carried out. After an intervention period of 8 weeks MEG and behavioural tests were measured again. Half of the children had language-related intervention, the other half a physical exercise program. The language-group improved on behavioural sound discrimination of one pair (/da/-/ba/). This improvement was accompanied by increased dipole moments to the /ba/-deviant on both hemispheres (P1m at 210 ms). In addition, dipole moments of P1m after /ga/, and of MMNm after /sy/ (at about 520 ms) were increased in the right and left hemisphere, correspondingly. The results show that children receiving language-related intervention improved on discriminating sounds according to the behavioural tests. In addition, this positive rehabilitation effect was reflected in their brain activity. Both hemispheres seem to participate in the analysis of the speech sounds in these children.

Selective attention induces immediate changes in finger representation in human area 3b. - Isao Hashimoto* and Yoshinobu Iguchi+ (*Human Information Systems Laboratory (Tokyo Office), Kanazawa Institute of Technology, Tokyo, Japan; +Department of Integrated Neuroscience, Tokyo Institute of Psychiatry, Tokyo, Japan).

In order to clarify whether selective attention induces immediate changes in finger representation in human area 3b, somatosensory evoked magnetic fields (SEFs) were measured during selective attention tasks. In one experiment, we used vibratory stimuli to the index or middle finger with a frequency of 100 or 400 Hz for selective discrimination of finger and frequency attribute of stimuli. Equivalent current dipole (ECD) for the first M50 SEF component originating in area 3b indicated that the cortical regions for the fingers were specifically segregated in the finger discrimination task but not in the frequency discrimination task or in the control condition. The task dependent and immediate switchover of cortical finger-representation demonstrates a dynamic SI activation for spatial information processing. In another experiment, two tasks were performed under simultaneous electric stimulation to the index and middle fingers. In the attention task, tactile stimuli were randomly (20%) presented to one of the two fingers simultaneous with the two-finger electric stimuli and the subjects were requested to respond to the tactile stimuli in order to induce selective attention to the target finger. In a control task, the subjects ignored the tactile stimuli. In spite of the two-finger stimulation, the M50 ECD localization showed that the attention task induced a distinctive cortical somatotopy for the target finger, while the control task did not. The M50 amplitude showed no change between the attention and control task. These results suggest that selective attention not only enhances the activity of the representation for the target finger but also actively suppresses that for the non-target finger.

Pharmaco-EEG of $GABA_A$-receptor modulators and its application in experimental epilepsy research. – Rob A. Voskuyl*+ and Meindert Danhof* (*Leiden/Amsterdam Center for Drug Research, Leiden University; +Dutch Epilepsy Clinics Foundation, Heemstede, The Netherlands).

Benzodiazepines are allosteric modulators of the $GABA_A$ receptor, exhibiting anxiolytic, anti-epileptic, hypnotic and anaesthetic properties. In humans and animals they increase at moderate doses the β frequency band (11.5-30 Hz). This EEG change serves as effect measure in pharmacokinetic-pharmacodynamic (PK-PD) modelling, which is used to characterize the concentration-pharmacological effect relation of drugs in terms of receptor activation and the ensuing transduction pathway. The *in vivo* concentration-EEG effect relation is sigmoid and can be described by the Hill equation. Investigation of full, partial, silent and inverse agonists, demonstrated good correlation between *in vivo* parameters and receptor affinity and intrinsic efficacy. Thus, the β band is a good biomarker for enhancement of $GABA_A$-mediated inhibition. Neurosteroids are more potent modulators, displaying a bi-phasic EEG effect, i.e. at high concentrations the amplitude decreases. This

was modelled by describing the transduction step by a parabolic function. This confirmed two predictions: (1) the *in vivo* potency of different neurosteroids correlated well with *in vitro* binding and (2) compounds with a lower intrinsic efficacy, such as benzodiazepines, do exhibit a *mono*phasic concentration-effect relation. Relative to neurosteroids, benzodiazepines behave as *partial* agonists. Changes in concentration-effect relations may also reveal disease progression and associated processes. In kindled rats, which exhibit only increased seizure susceptibility, and in kainic acid treated rats, which develop spontaneous seizures, the benzodiazepine-induced increase in β activity is reduced or virtually eliminated respectively. This result suggests that impairment of GABAergic inhibition is in part responsible for pharmacoresistance development in certain types of epilepsy.

QEEG predictors of treatment response. - L.S. Prichep and E.R. John (Brain Research Laboratories, Dept. Psychiatry, NYU School of Medicine, NY, NY, USA and Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, USA).

It has been demonstrated that clinically homogeneous populations may contain heterogeneous quantitative electrophysiological profiles. Such findings are suggestive of distinctive patterns of underlying brain pathophysiology, which could be expected to be related to differential treatment responsiveness. Using QEEG features derived from 19 channels of eyes closed resting artifact-free EEG collected from drug-free states; we have shown significant relationship between electrophysiological subtype membership (multivariate QEEG profiles of abnormality) and prediction of treatment outcome for many diagnostic groups. In a study of Obsessive Compulsive Disorder (OCD), response to SSRI treatment was predicted with accuracy greater than 80% using pre-treatment QEEG subtype [1]. These findings have been prospectively replicated [2] with sensitivity of 98% and specificity of 89%; and extended to include follow-up QEEG evaluations on treatment. Responders belonged to the QEEG subtype which would be moved in the "normalizing" direction by SSRIs, as would be predicted from the work of Saletu et al. [3]. Using Variable Resolution Electrical Tomography (VARETA), clear differences were seen in very narrow band theta and alpha sources for the responders and non-responder subtypes, in the same regions identified by PET scans in these patients. Similarly, using this approach for predicting relapse in cocaine dependence, for predicting response to stimulants in attention deficit disorder and for prospective prediction of conversion to dementia in normally elderly, has led to high predictive accuracy. Thus, these results suggest that QEEG represents a cost-effective, non-invasive evaluation tool that appears highly sensitive to treatment responsiveness in psychiatric patients.

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Somatosensory evoked potentials and magnetic fields during active and quiet sleep in newborns. - L. Lauronen*+^, E. Pihko*+, H. Wikström+, S. Taulu~, J. Nurminen*+, S. Kivitie-Kallio# and Y. Okada% (*BioMag Laboratory, Helsinki University Central Hospital, P.O. Box 340, FIN-00029 HUS, Finland; +Helsinki Brain Research Centre, ^Department of Clinical Neurophysiology, Helsinki University Central Hospital, Helsinki, Finland, ~Neuromag, Ltd., Helsinki, Finland, #Department of Social Pediatrics, Hospital for Children and Adolescents, Helsinki, Finland, %Department of Neurology, University of New Mexico School of Medicine, Albuquerque, NM, USA).

We investigated the effect of sleep stages on the somatosensory evoked potentials (SEPs) and magnetic fields (SEFs) of newborn babies. The subjects were 14 full-term healthy newborns. The tip of the left index finger and/or thenar eminence were stimulated by movement of a plastic membrane touching the skin. The inter-stimulus interval was 2 seconds. MEG from the contralateral hemisphere was measured simultaneously with eight-channel EEG-recording. The data were analyzed off-line for active and quiet sleep stages. The responses consisted of three main deflections. The first deflection, N1, peaked at about 30 ms. The following more prominent deflections peaked at about 80 ms (P1) and 260 ms (P2). The amplitudes of P1 and P2 were significantly reduced in active sleep compared to quiet sleep (P1: p = 0.003 and p= 0.02; P2: p= 0.018 and p = 0.000004, for EEG and MEG, T-test). In conclusion, our study shows that MEG is feasible in studies of the newborn somatosensory system. Furthermore, the marked differences in response strengths in active and quiet sleep demonstrate the need to carefully monitor the newborn's sleep stage in at least the studies of the somatosensory evoked responses.

Effect of skull holes on scalp potentials. - C. Ramon*, J. Haueisen+, P. Schimpf^, M. Holmes* and A. Ishimaru* (*Departments of Electrical Engineering and Neurology, University of Washington, Seattle, WA, USA; +Biomagnetics Center, Department of Neurology, F.S. University, Jena, Germany; ^School of Electrical Engineering and Computer Science, Washington State University, Spokane, WA, USA).

The effects of a skull holes on the scalp potentials was examined using a finite element model of the head constructed from the segmented MRI images. The whole head model has a 1×1×3.2 mm voxel resolution and we identified 11 different tissue types in the model including, scalp, hard and soft skull bone, gray and white matter, CSF, fat, muscle, cerebellum, etc. A square hole of a size of 20 mm filled with air on top of the head was used. The electric potentials and currents in the whole head were computed using an adaptive finite element solver. We used a current dipole of 5 μA mm in the motor cortex area. From the computed fields the scalp potentials were extracted and contour plots were made. We used two models, one with a hole and the other one with no hole. The maximum and minimum of the contour vales for the model with hole were -0.45 μV and 0.65 μV, respectively. Similarly, for the model with no hole the maximum and minimum contour values were -0.6 and 0.85, respectively. The dynamic range of the difference is about -0.15 to 0.25 μV for a dipolar source in the motor cortex area. The spatial patterns of the contours were also different for the two models. This shows that the scalp potentials are affected by the presence of a hole in the skull.

Evaluation of the distortion of EEG signals caused by a hole in the skull mimicking the fontanel in the skull of human neonates. - L. Flemming, Y. Wang and Y. Okada (Biomagnetic Center Jena, Friedrich-Schiller-University, Jena, Germany, Department of Neurology, University of New Mexico, School of Medicine, Albuquerque, NM, USA).

Brain functions of human infants, including pre-term and term babies, have been traditionally evaluated with EEG as part of the neurological examination carried out on infants with risk factors. EEG is also used in staging the development of the nervous system to detect delays in the brain development. The interpretation of the EEG of newborns is very difficult because it is strongly affected by the different conductivity of fontanels and sutures compared to the skull. This effect was studied in 10 farm swine. The fontanel was mimicked by a hole, which was filled with materials of different conductivities (air, sucrose-agar, saline-agar). Cortical areas beneath the hole, at the edge of the hole and far away from the hole were electrically stimulated. 30 stimulations were averaged and used for the analysis. EEG signal of the cortical area beneath the hole was strongest affected by the different conductivities compared to the other areas. The further away from the hole the area was the smaller was the influence of the hole. The leakage of the current through the hole shown by the laplacian transformation was strongest for the sucrose-agar conductivity in all cases. The conductivity of sucrose-agar was in the middle between air and saline-agar. It was comparable with the conductivity of the skull. We also investigated the influence of the hole to different components of the EEG signal for the stimulated cortical area beneath the hole. The second component (p20) was strongest influenced and the third component (n50) was weakest influenced.

Neurofeedback effect on EEG current sources. - T. Fernández, T. Harmony, L. Díaz-Comas, E. Santiago, L. Sánchez, A. Fernández-Bouzas, W. Herrera, G. Aboytes, J. Bosch and S. Ocampo (Instituto de Neurobiología, Universidad Nacional Autónoma de México and Centro de Neurociencias de Cuba).

Neurofeedback (NFB) is an operant conditioning procedure, whereby an individual can learn to modify the electrical activity of his/her own brain. In one hand, it has been shown minimum alpha absolute power is necessary for adequate performance; in the other hand, Learning Disabled (LD) children have higher values of theta EEG absolute and relative power than normal children do. Therefore, reduction of (theta/alpha) ratio may improve cognitive deficits. Eleven LD children were selected with higher than normal (theta/alpha) ratio at least in one lead. Test Of Variables of Attention (TOVA) and WISC-R were applied. NFB was given in the region with highest ratio, triggering a sound each time the ratio fell below a threshold value. Twenty half-hour sessions were applied. Two months after the end, TOVA, WISC-R and EEG were obtained again. EEG current sources were computed. After NFB, current decreased at frequencies 2.34-7.02 Hz, principally in occipital areas, and increased at frequencies 8.58-18.72 Hz, more on the left hemisphere. Significant increase was observed in ADHD score from TOVA and in verbal scale from WISC-R These results suggest that NFB of (theta/alpha) ratio produces an important spurt on EEG maturation, and as a consequence, behavioral improvement in LD children. Although NFB treatment was applied according to the activity of one lead, different for each child, EEG changes were observed on wide regions, suggesting that the treatment affects the whole cortex.

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Improving P300 latency determination by 128-channel EEG measurements: results in mild-to-moderate head injury patients. - N.M. Maurits, J.W. Elting, J. van der Naalt and T.W. van Weerden (Groningen University Hospital, Department of Neurology, P.O. Box 30.001, 9700 RB Groningen, The Netherlands).

The P300 event related potential is a measure of cognitive function and its latency and amplitude are thought to quantify information processing. P300 latency is known to be increased in patients with dementia and severe head injury. Recently subcomponents of P300 have been defined; the more frontally distributed P3a (novel stimuli) and the centro-parietal P3b (stimulus processing). The large intra-individual inter-trial P300 latency variation in normal controls makes it hard to distinguish between normal and abnormal P300 results. One of the causes of variation is the overlap in P3a and P3b potentials resulting in inaccurate latency determination of P3b (P300). Conventional P300 registration only allows for separation of the two potentials in approximately 25% of the measurements. We have used 128-channel EEG and a new dipole source analysis technique for data reduction, to overcome this problem. We are able to separate the P3a and P3b components and thereby reduce the spread in P3b (P300) latencies compared to single-channel analysis in normal controls (n=16). Using these results, in a group of mild-to-moderate head injury patients (n=23, EMV 4-14, duration of PTA 1-60 days), we find that increased (conventional) P300 latency actually corresponds to diminished P3a activity (pseudo-delay). The P3b latency appears to be normal. We have also investigated the predictive value of these results for outcome based on psychological test results (Stroop test and word-recall) after three months. These results indicate that our method may help interpret P300 results in head injury patients and improve the prognostic value of abnormal P300.

Event-related correlations in learning impaired children during a hybrid go/no-go choice reaction visual-motor task. - J.M. Peters*, D.P. Waber+,G.B. McAnulty^ and F.H. Duffy^ (*Department of Neurology, Leyenburg Hospital, The Hague, Netherlands; Departments of Neurology^ and Psychiatry+, Harvard Medical School and Children's Hospital, Boston, MA).

169 learning impaired (LI) and 71 non-learning impaired (NLI) children underwent a hybrid go/no-go choice reaction time visual-motor task to study the behavioral and physiological fundamentals of learning disorders. A left button was pressed for Left Arrow (LA) stimuli, a right for Right Arrow (RA) stimuli, none (no-go) for a non-directional arrow. Stimulus specific visual evoked potentials were formed and, with PZ as index electrode, were lag-correlated to frontal electrodes to form Event-Related Correlations (ERC). Exploratory t-statistic significant probability maps (t-SPM) were used to define regions of interest (ROI). Behaviorally, there was a right hand advantage over the left in the NLI group, but less in the LI group. Electrophysiologically, RA and LA conditions increased correlation between visual areas (PZ) and contralateral frontal areas (F3 and F4). A unilateral ROI, at electrode FC1, also preceded both left and right-handed responses. Neurobehaviorally, increased visual-motor correlation was associated with better performance, especially for the left hemisphere, at F3 and FC1. Surprisingly, visual-motor correlations were not associated with performance for the NLI group in the RA and no-go condition. Our data support previously reported difficulties of learning impaired children in low-level information processing. Furthermore, we hypothesize that LI, in contrast to NLI children, demonstrate difficulty in automatizing routine tasks.

Aging effects on auditory processing in an oddball task: an MEG study. - S. Kovacevic, J.M. Stephen+*, C.C. Woodruff*, C. Qualls+*, J.C. Adair+*, D. Hudson*, J. Knoefel+* and C.J. Aine+* (*University of New Mexico, Albuquerque, NM; +New Mexico VA Health Care System, Albuquerque, NM).

A possible explanation for age-related changes in performance is that aging is accompanied by a general slowing in cognitive processing. We examined changes in amplitude of the sources located in the superior temporal gyrus (STG) while subjects performed an oddball task. Our hypothesis was that the attention effects on amplitude of the STG sources would be more prominent later in elderly than in young subjects as a result of cognitive slowing. Fifteen healthy subjects (20 – 84 yrs) were presented with frequent (1000 Hz) and rare (1050 Hz, 20% probability) tones binaurally at a rate of 1 tone/s. MEG data was collected and online averaged while subjects silently counted the rare tones using 122-channel Neuromag magnetometer system. Active brain regions and their associated timecourses were characterized by using the multi-start spatial-temporal algorithm (MSST). In agreement with previous studies, both elderly and young subjects showed overall stronger STG responses to the rare than to the frequent tones. The latency of the early response (~ 100 ms) to the tones did not differ between young and elderly. However, the peak latency in the 180-600 ms time interval was longer for the elderly. These results indicate that although the timing of the early (sensory) processing in the STG was not affected by normal aging, the subsequent processing of the relevant stimuli occurred slightly later for elderly. Although STG activity has traditionally been associated with early sensory processing, our results suggest that the STG activity is also important for later processing, as a part of the attentional network.

Age-related changes to median nerve stimulation measured with MEG. - J.M. Stephen*+, D.M. Ranken^, C.C. Woodruff*+, S. Kovacevic*+, D. Hudson+, J.C. Adair+, J. Knoefel+, C. Qualls+ and C.J. Aine*+ (*University of New Mexico, Albuquerque, NM; +New Mexico VA Healthcare System, Albuquerque, NM; ^Los Alamos National Laboratory, Los Alamos, NM).

Studying sensory processes provides a critical step to understanding age-related changes in cognitive function. Using multi-dipole analyses to analyze MEG data provides a unique opportunity to characterize age-related latency and amplitude changes in the primary and secondary areas responsible for the somatosensory response. Based on previous EEG and ERP studies, we hypothesized increased amplitude with age and increased latencies between primary and secondary areas as a function of age due to increased central conduction times. Currently data from 9 elderly (65 + years) and 7 young (20-29 years) healthy subjects have been collected. The left and right median nerves were stimulated with a current pulse and the magnetic responses were measured with a 122- channel Neuromag biomagnetometer. The data were analyzed using a multi-dipole multi-start spatio-temporal modeling technique (Ranken et al. 2002). The amplitude of the first peak of the primary somatosensory response was greater for the old than the young ($p < 0.02$). We also found that the variability of the response from trial-to-trial was greater for the young for the first peak of the response ($p < 0.02$). There was also considerable inter-subject variability in responses in secondary areas. Drechsler (1978) and others suggested that the increased amplitude of the responses in older subjects could be related to a decrease in inhibition with age. An alternative is the larger variability in the trial-to-trial responses in the young, which could lead to a lower amplitude averaged response due to poor time-locking.

MEG studies of memory in healthy aging. - C.J. Aine*+, J.C. Adair*+, J. Knoefel*+, D. Hudson^, C. Qualls*+, S. Kovacevic*+, C. Woodruff*+ and J.M. Stephen*+ (*New Mexico VA Healthcare Systems; +University of New Mexico SOM; ^BRINM, Albuquerque, NM).

Preliminary data from our laboratory and others suggest that lower-level auditory areas play a major role in cognitive processing. A group of 17 healthy subjects (20-40 and 65-85 years) completed two different verbal memory tasks while MEG recordings were obtained. It was predicted that the late sustained activity localized to putative auditory association cortex would reveal activity of greater amplitude and longer duration for younger subjects. Subjects decided whether the words, representing common objects, were larger than a television set. After a 15 minute delay, subjects were asked whether or not each word, embedded within a larger list of words, was one they heard previously. The timecourses of activity from multiple cortical regions were determined via multidipole, least-squares minimization procedures. A main effect of age ($F=4.54$, $p=.05$) for the late sustained activity revealed earlier peak latencies for the elderly, compared to the young and poorer performance (i.e., fewer percent correct and longer RTs). An unexpected finding was greater peak amplitude and duration of activity around 60 ms which did not correlate with performance on the tasks. These results suggest that activity in the superior temporal gyrus (in the vicinity of Heschl's gyrus) is important for early complex processing, beyond simple sensation. Supported by VA MERIT Review, The MIND Institute, NIH COBRE.

Symmetry and non-symmetry in the brain. - M.J.A.M. van Putten (Department of Neurology and Clinical Neurophysiology Ziekenhuis Leyenburg, Leyweg 275, 2545 CH The Hague, The Netherlands. email: M.van_Putten@lumc.nl).

The EEG of the physiological brain is characterized by a relative strong symmetry between the two hemispheres. The EEG in the pathological brain, however, often shows a particular non-symmetry. Various parameters can be defined that characterize brain symmetry or non-symmetry. Measures range from parameters based on, e.g., the spectral density, coherence and phase synchronization to the recently proposed Link Rates [1]. We evaluate the dynamic behavior of several symmetry measures in their application to controls and patients with various neurological conditions, such as epilepsy, dementia and (threatening) brain infarctions. In addition, task specific asymmetry will be studied using a control group of healthy medical students. We will show that the dynamic behaviour of symmetry measures shows characteristic differences in the application to the EEG of neurological patients. This adds to the store of knowledge about physiological and pathological brain function and allows improved differentiation between various EEG patterns of neurological patients. From a clinical point of view, we foresee additional applications in continuous EEG monitoring in stroke and ICU patients.

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EEG global field power spectrum changes after a single dose of atypical antipsychotics in healthy volunteers. - Keizo Yamada*, Toshiaki Isotani*, Satoshi Irisawa*, Masafumi Yoshimura*, Aran Tajika+, Takami Yagyu*, Akemi Saito* and Toshihiko Kinoshita* (*Department of Neuropsychiatry, Kansai Medical University, Osaka 570-8506 Japan and +Department of Public Health, Kansai Medical University, Osaka 570-8506 Japan).

The EEG effects of 4 different novel atypical antipsychotics were compared with 2 conventional typical antipsychotics and a placebo in 14 male, right-handed, nor-

mals (24.1±4.1 years). All subjects went through 7 sessions. In each session, a subject received orally either 0.5mg risperidone, 4mg perospirone, 33mg quetiapine, 1.25mg olanzapine, 50mg chlorpromazine, 1mg haloperidol or placebo according to a single-blind, crossover, Latin-square design. EEG was recorded from 19 scalp-electrodes prior to as well as 2, 4 and 6 hours after drug administration. Twenty sec/subject/drug/time-point EEG were analyzed into FFT Global Field Power spectra (GFP) (Lehmann and Skrandies 1980). GFP waveforms (one tracing measures the strength of the whole brain electric field) were computed for 7 frequency bands (Kubicki et al. 1979). Assuming the maximal effect would correspond to serum-concentration, 2-hours after perospirone and quetiapine, 4-hours after risperidone, olanzapine, and chlorpromazine, and 6-hours after haloperidol were chosen. Difference from pre-drug GFP-values were compared using one-way repeated measures ANOVA, then post-hoc multiple comparisons (LSD) and LORETA (Pascual-Marqui et al. 1999) were applied. Relative GFP in delta (1.5-6 Hz) increased ($p<0.05$), (a) after quetiapine compared with perospirone, olanzapine, chlorpromazine, haloperidol and placebo, (b) after risperidone compared with haloperidol and placebo. LORETA showed ($p<0.05$) cortical posteriorization of delta after olanzapine and anteriozation of delta after haloperidol. Thus, quetiapine and risperidne showed sedative effects on the brain, which may reflect the strength of both receptor A_1 and H_1 bindings. The LORETA result of olanzapine indicating posterior inhibition, i.e., frontal shift of brain electric activity, might include a function against the negative symptoms in schizophrenia.

Topographical analysis of spectral EEG and late visually evoked brain activity in patients with benign rolandic epilepsy of childhood. - W. Skrandies and D. Dralle (Institute of Physiology and Department of Neuropediatrics, Justus-Liebig University, Giessen, Germany).

A group of 11 young patients (7-15 years of age) with benign rolandic epilepsy of childhood was studied. We recorded the interictal spontaneous background EEG and flash evoked potentials from 19 channels distributed according to the International 10/20 system. Following visual stimulation, five of the patients displayed a late sustained component over temporal and central scalp regions at a mean peak latency of 194.8 ms. In the other patients this pattern of activity was absent while early VEP components were comparable in both groups. We related the occurrence of this N200 component to the spectra of spontaneous EEG and clinical parameters. Significant topographical differences were observed in the spectra of the spontaneous EEG of patients with and without a visual N200 component. The effects were most evident in the lower alpha (7.5-9.5 Hz) and beta band (13-15 Hz) when the spectral amplitudes obtained over temporal, parietal and occipital regions of the left and right hemisphere were compared. There was also a tendency that children without N200 displayed more hypersynchroneous activity in the spontaneous EEG than children with N200 activity. This suggests a protective role of interictal spike activity, and probably coincides with a benign prognosis of epilepsy.

Propagation of epileptic activity in patients with juvenile myoclonic epilepsy. - E. Santiago-Rodríguez, T. Harmony, A. Fernández-Bouzas and T. Fernández (Instituto de Neurobiología, UNAM).

Juvenile myoclonic epilepsy (JME) is a syndrome beginning in puberty, characterized by myoclonic jerks in the morning, tonic-clonic seizures (TCS), and, less frequently, absence seizures. Generalized spike-wave (SWC) and polyspike-wave complexes (PSWC), with fronto-central accentuation are the typical EEG pattern shown in JME. Frontal alterations have been detected with anatomophatological studies, MRI voxel-based morphometric analysis and magnetic resonance spectroscopy. In opposition to partial epilepsies, invasive monitoring in JME is not indicated. The objective in this study was to use a VARETA (Variable Resolution Electromagnetic Tomography) for determining the electric current sources in the propagation of epileptogenic activity in patients with JME. Five patients with all clinical criteria for JME were included. Four were female and one male with mean age of 23 + 11 years. All patients had myoclonic and TCS with mean age of onset at 13 years. Nineteen referential leads were recorded using a linked earlobe reference. One solution with VARETA each 5 ms of all paroxysmal events was calculated. Initial localization of sources in medial frontal gyrus was observed, corresponding to initial spikes of PSWC. In the next 5 to 10 ms a cyclic propagation to right or left temporal lobe was showed. Always, the temporal sources were less intense than frontal sources. The cyclic propagation of electric sources was observed independently of synchronic or asynchronic spikes in visual analysis. In synchronic spikes the time of cyclic alternation was shorter.

The use of hidden markov models for detection of paroxysmal activity propagation in interictal MEG data. - Alexei Y. Ossadtchi*~, John C. Mosher+, William W. Sutherling^ and Richard M. Leahy* (*Electrical Engineering, University of Southern California, Los Angeles, CA, 90089; +Los Alamos National Laboratory, Los Alamos, NM, 87545; ^Epilepsy and Brain Mapping program, Huntington Medical Research Institute, Pasadena, CA, 91105; ~Source Signal Imaging Inc., 2323 Broadway, San Diego, CA, 92102).

Automatic spike detection techniques applied to interictal MEG data often discover several spike clusters

that represent potentially epileptogenic regions in the brains of patients with partial epilepsy. For the purposes of treatment planning, it is important to determine which of the detected regions are the most likely primary generators of seizure activity. Analysis of the patterns of paroxysmal activity propagation between the detected regions may allow for detection of these primary epileptic foci. We have developed a Hidden Markov Models (HMM) for estimation of the propagation patterns between several spike clusters or regions. Analysis of the estimated transition probability matrix allows us to determine the probabilities of a spike in each region being followed by a spike in each of the other regions. From these we can determine the most likely primary foci as those which occur spontaneously and have a relatively high probability of being followed by spikes in one or more of the other regions. We applied the HMM to four independent interictal datasets collected from a patient with multi-focal epilepsy. Several spike clusters were automatically detected and the propagation detection technique was applied to determine the pattern of propagation of abnormal interictal activity. In all four datasets propagation from the temporal lobe to the frontal lobe was detected. Statistical significance of these results was established using a permutation test.

Focality of extratemporal neocortical epileptiform EEG studied with 256 scalp channels. - K.J. Eriksen*, M.D. Holmes+, S. Vanhatalo+ and D.M. Tucker* (*Electrical Geodesics, Inc., Eugene, OR, USA;+Harborview Medical Center, Seattle, WA, USA).

The appearance of diffuse scalp EEG suggests widespread simultaneous activity, but volume conduction can mask or smear focal activity. We wished to examine whether the use of high density scalp EEG and cortically constrained source modeling in a realistic head model could demonstrate focality of extratemporal, neocortical epileptiform activity. Five epilepsy patients were recruited for this study, selected for frequent interictal activity and a diagnosis of medically refractory extratemporal epilepsy. We recorded 30-90 minutes of 256 channel EEG at 500 samples/second using a comfortable electrode net that allowed the subject to lie on a bed in a sleep lab. We acquired high resolution structural MRI scans covering the whole head and used then to build realistic boundary element models of each subject's head, including a parameterization of the individual cortical gray matter. Source modeling of interictal spike and sharp waves was done using a weighted minimum norm inversion onto the cortical surface. We repeated this modeling with subsets of 128, 64, and 32 EEG channels. The visually observed focality of the epileptiform activity increased as we increased the number of scalp electrodes from 32 through 256, concentrating in smaller and smaller areas of cortex. We conclude that with 256 channels we are getting closer to meeting the spatial Nyquist criterion and achieving adequate sampling of the spatial distribution of the underlying activity.

Validation with depth EEG recordings of spatio-temporal algorithms for the localization of the sources of interictal activities with MEG. - J.-M. Badier, M. Gavaret, D. Schwartz, F. Wendling and P. Chauvel (UMIU9926 INSERM, Laboratoire de Neurophysiologie et Neuropsychologie, Faculté de Médecine, 27 bd Jean Moulin, 13005 Marseille, France).

Localization of the sources of the paroxysmal activities in epileptic patients candidates for surgery is still a challenging task. A first series of 10 patients suffering from various type of epilepsies, excluding the common and considered as easier to cure mesial temporal lobe epilepsie, have been studied. They all had simultaneous EEG and MEG although MEG data are presented here. Various techniques had been applied to the data, including non linear dipole fit and a more recent spatio-temporal algorithm developed in our laboratory. This algorithm uses a linear approach by calculating a metric, based on the decomposition of the signal, over the cortical surface segmented from each individual MRI. This technique allows complex reconstruction of source distributions in time as well as in space. Results of the localisation are compared to the depth recordings made prior to surgery. This is done by the mean of automatic detection of the activities recorded in the depth and automatic extractions of typical patterns of activation of the different brain structures involved. This allows not only to determine the distribution of the abnormal activity but also to reconstruct the dynamic of the activities. This study confirmed the power of the MEG to give a good image of the localization as well as the dynamic of paroxysmal activity especially when using the linear spatio-temporal fit algorithm.

Clinical contribution of interictal source localization using high-resolution EEG in 2 cases of pharmacoresistant frontal lobe epilepsies without any MRI structural lesion. - M. Gavaret, J.-M. Badier, P. Marquis, F. Bartolomei, J. Bourien, F. Wendling and P. Chauvel (Department of Clinical Neurophysiology, Timone Hospital, Marseille, France).

Pharmacoresistant epilepsies of extra-temporal origin can represent a difficult therapeutic challenge in particular in case of apparently non lesional focal epilepsies. We report here 2 cases of frontal lobe epilepsy without lesion visible with the structural MRI which presented usually full and abundant paroxysmal interictal events. These paroxysmal interictal events were recorded in High Resolution EEG (64 electrodes, high sampling rate) and source localizations were calculated with several algorithms

(spatio-temporal dipoles, moving dipole, MUltiple SIgnal Classification) and a realistic head model of the electrical activity propagation mediums. SEEG (stereo-electro-encephalography) showed abundant, sub-continuous paroxysmal interictal events with a spatial distribution restricted. Source localizations highlighted were confirmed by an automatic detection of paroxysmal interictal events performed on SEEG signals. The anatomopathologic examination demonstrated a dysplasic lesion which was not visible on MRI including T1, T2, IR and FLAIR sequences. Source localization tools can provide spatial information in the pre-surgical assessment of medically intractable epilepsies specially in difficult cases of extra-temporal epilepsies apparently non lesional.

An MEG/EEG examination of the generality of the gating deficit in schizophrenia. - J.C. Edgar*+, S. Moses+^, R.J. Thoma+^, M. Huang+~, F. Hanlon+^, M.P. Weisend+~, G.A. Miller*%, L.E. Adler$ and J.M. Canive+# (*Department of Psychology and Beckman Institute, University of Illinois at Urbana-Champaign, Urbana, IL, USA; +Center for Functional Brain Imaging, New Mexico VA Healthcare System, Albuquerque, NM, USA; ^Department of Psychology, University of New Mexico, Albuquerque, NM, USA; ~Department of Radiology, University of New Mexico, Albuquerque, NM, USA; #Department of Psychiatry, University of New Mexico, Albuquerque, NM, USA; %Department of Psychiatry, University of Illinois at Urbana-Champaign, Urbana, IL, USA; $Department of Psychiatry, University of Colorado Health Sciences Center, Denver, CO, USA).

Auditory paired-click studies have established a clear relationship between schizophrenia and impaired sensory gating using the P50 component of the event-related brain potential (ERP). However, the presumed cross-modal generality of the gating deficit has not been systematically tested. The current study did so by investigating the M20 component of the somatosensory ERP. Patients were expected to show impaired auditory and somatosensory gating, but positive correlations were expected between auditory and somatosensory gating ratios. 122 channels of magnetoencephalographic (MEG) and 19 channels of electroencephalographic (EEG) data were simultaneously collected from 27 subjects with chronic schizophrenia and 21 control subjects. Subjects were administered: (1) the standard paired-click auditory paradigm (500 ms ISI) to assess P50 gating and, (2) a recently developed paired-pulse somatosensory paradigm using a 500 ms or a 75 ms ISI to assess M20 gating. Using Magnetic Source Imaging (MEG + structural magnetic resonance imaging), left and right S1 and S2 M20 somatosensory responses were localized and the sensory gating ratio (S2/S1) was calculated. Groups did not differ in M20 gating in either hemisphere or at either ISI. Patients failed to show normal P50 gating. Negative correlations were observed between M20 and P50 gating ratios in controls but not in patients. Thus, neither gating nor the schizophrenia gating deficit appears to be cross-modal.

Fast ripples in hippocampal epileptogenicity. - J. Engel, A. Bragin, C.L. Wilson and I. Mody (UCLA).

Fast ripples (FR) are abnormal, brief, high frequency (200-600 Hz) oscillations recorded from epileptogenic hippocampus and parahippocampal structures in patients with mesial temporal lobe epilepsy, and rat models of this condition. FR is usually associated with interictal EEG spikes, and preferentially occurs in structures capable of generating spontaneous seizures. FR, therefore, permits distinction between interictal epileptiform events that identify the epileptogenic region and those which are nonspecific propagated events, or indicative of epileptically abnormal tissue that does not have the capacity for spontaneous seizure generation. Because the temporal development of FR following intrahippocampal kainate injection in rats precedes the development of behavioral seizures, and because FR is seen at the onset of both low-voltage fast and hypersynchronous ictal events in these animals, it is believed that they represent the pathophysiological substrate of epileptogenesis, and epileptogenicity. The topographical distribution of FR activity within epileptogenic tissue is not homogeneous, but, rather, discretely localized within small neuronal clusters imbedded within hippocampal and parahippocampal tissue that does not exhibit FR activity. The size and/or density of FR clusters, as measured by the number of multiple microelectrode contacts recording these events, correlates directly with seizure frequency in rats. Furthermore, although the location of microelectrode contacts recording FR is stable over weeks to months, hippocampal slice recordings demonstrate that treatment with small amounts of bicuculline increases the size of FR neuronal clusters. This observation is consistent with the in vivo observation that paired-pulse perforant path stimulation, which produces suppression in epileptic hippocampus, produces facilitation and FR activity in discrete FR neuronal clusters. These data suggest that spontaneous seizure generation could be initiated by relatively generalized nonspecific disinhibition, which would permit FR clusters to increase in size, coalesce, and/or synchronize to create the critical neuronal mass necessary for seizure initiation and propagation.

Spikes and slow waves recorded with MEG in patients with epilepsy. - J.C. de Munck, A. de Jongh, D. van't Ent, I. Manshanden, M. Pulligedhu, J.C. Baayen, C.J. Stam and F.H. Lopes da Silva.

Interictal spikes represent only a very small part of the MEG/EEG data. In some cases, the spike rate is less

than two per hour. It has been proposed in the literature to make use of another pronounced property of the MEG/EEG data of patients with epilepsy: the enhanced delta band activity. The purpose of this work was to investigate whether pathological delta band activity can be localized using simple dipole models and detection techniques, and whether its sources coincide with the dipole sources found with the analysis of inter ictal MEG spikes. To localise the delta band activity efficiently, MEG data were band-pass filtered, the large amplitudes were detected and a global search algorithm was applied to find a good initial guess for the final non-linear dipole search step. Spikes were detected by a human observer and submit to a clustering algorithm to group the spikes into groups with high similarity. Spikes within each cluster were averaged to reduce the noise, before dipole localisation. The fully automatic delta band analysis was applied on the MEG data of a group of patients with intracranial tumours and epilepsy. In 70% of the patients clear dipole clusters were found adjacent to the tumour. These clusters were quite robust and in post-operative MEG data it was found that these clusters are hardly influenced by medical treatment. Only a few data sets of the tumour group showed both abnormal delta and epileptic spikes. In all these data sets the delta activity agreed on the lateralization and on the lobe. Furthermore, most spikes sources (70%) were located at the same side of the structural lesions as the delta sources. This study shows that the delta band sources carry pathological information that is of potential clinical applicability. Furthermore, it shows that slow waves and inter-ictal spikes are related, but more data is required to establish the automatic delta analysis as a substitute for the inter-ictal spikes.

Challenging MEG source imaging with simultaneous depth recordings in epilepsy. - S. Baillet*, C. Adamm*+, A. Ducorps^, D. Schwartz^, R.M. Leahy~, J.C. Mosher#, B. Renault*, M. Baulac+ and L. Garnero* (*Cognitive Neuroscience and Brain Imaging Laboratory, CNRS Hôpital de la Salpêtrière, Paris, France; +Epilepsy Unit, Hôpital de la Salpêtrière, Paris, France; ^MEG Center, Hôpital de la Salpêtrière, Paris, France; ~Signal and Image Processing Institute, University of Southern California, Los Angeles, USA; #Design Technology Group, Los Alamos National Laboratory, USA).

Simultaneous MEG and depth electrode recordings in patients under evaluation for epilepsy surgery will be presented. We will specifically discuss how MEG source imaging at the individual cortical surface can predict the potentials recorded from the depth electrodes. Sensitivity to deeper structures such as the Hippocampus and Amygdala will also be discussed in this context.

A new look at the dynamics of the epileptic brain: prediction of epileptic seizures and resetting of the epileptic brain leads to intelligent brain pacemakers. - L.D. Iasemidis*, J.C. Sackellares+, D.S. Shiau+, P.R. Carney+ and P.M. Pardalos+ (Brain Dynamics Lab, The Harrington Department of Bioengineering, Arizona State University, Tempe, AZ; +Brain Dynamics Lab, Departments of Neurology, Neuroscience, Biomedical Engineering, Pediatrics, Industrial and Systems Engineering, University of Florida, Gainesville, FL).

Epilepsy is considered a dynamical disorder of the brain. Epileptic seizures and spikes occur intermittently, and seemingly in a random and unpredictable fashion. In the last 15 years, we have provided evidence that seizures may be deterministic and predictable [1]. Recently, we presented the first automatic, prospective seizure prediction system [2] on continuous long-term EEG data. Spatiotemporal analysis of a total of 2,000 hours of continuous EEG recorded from depth (hippocampal), subdural (temporal and frontal), and/or scalp electrodes in 10 patients with focal epilepsy showed that a progressive dynamical entrainment (convergence of measures of chaos like the maximum Lyapunov exponents) of the focus with critical normal brain sites occurs hours to days prior to seizures onset, and reverses after seizures end (brain dynamical resetting). From 80% to 100% of a total of 160 focal seizures of temporal lobe origin could be predicted at the 99% confidence level, approximately 70 minutes in advance, with 0.2 to 0.1 false warnings per hour respectively. Detection of seizure susceptibility periods of days in duration prior to sequences of seizures was also observed. The significance of these findings for brain research, understanding of the mechanisms, diagnosis and novel methods of treatment of epilepsy will be discussed.

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Mapping distributed sources of cortical rhythms in mild Alzheimer's disease. A multi-centric EEG study. - C. Babiloni*+, G. Binetti+, G. Dal Forno~#, R. Ferri%, B. Lanuzza%, C. Miniussi+, D.V. Moretti*, F. Nobili$, R.D. Pascual-Marqui&, G. Rodriguez$, G.L. Romani!, S. Salinari?, F. Tecchio@, P. Vitali% and P.M. Rossini+^~ (*Dip. Fisiologia Umana e Farmacologia, Univ. "La Sapienza" Rome, Italy; +IRCCS "S. Giovanni di Dio-F.B.F.", Brescia, Italy; ^A.Fa.R. Osp. FBF; Isola Tiberina, Rome, Italy; ~University "Campus Biomedico" Rome, Italy, #Department of Neurology, Johns Hopkins University School of Medicine, Balti-

more, Maryland, [%]Dept of Neurology, Oasi Inst. for Research on Mental Retardation and Brain Aging (IRCCS), Troina-Italy; [$]Division of Clinical Neurophysiology (DIMI), University of Genova, Italy; [&]The KEY Institute for Brain-Mind Research, University Hospital of Psychiatry, Zurich, Switzerland; [!]ITAB Univ. Chieti and INFN, UdR L'Aquila, Italy; [?]Dipartimento Informatica e Sistemistica Univ. "La Sapienza", Rome-Italy, Roma, Italy; [@]IFN-Consiglio Nazionale delle Ricerche (CNR) Unità MEG - Osp. Fatebenefratelli Isola Tiberina).

This study aimed at mapping (i) the distributed EEG sources specific for mild Alzheimer's disease (AD) compared to vascular dementia (VaD) or normal elderly people (Nold) and (ii) the distributed EEG sources sensitive to the mild AD at different stages of severity. Resting EEG (10-20 electrode montage) was recorded from 48 mild AD, 20 VaD, and 38 Nold subjects. Both AD and VaD patients had 24-17 of mini mental state examination (MMSE). EEG rhythms were delta (2-4 Hz), theta (4-8 Hz), alpha 1 (8-10.5 Hz), alpha 2 (10.5-13 Hz), beta 1 (13-20 Hz), and beta 2 (20-30 Hz). Cortical EEG sources were modeled by "Low resolution brain electromagnetic tomography" (LORETA). Sources of EEG rhythmicity were defined as specific for mild AD group when their current density values were different than those for VaD and normal groups. Regarding issue (i), There was a decline of central, parietal, temporal and limbic alpha 1 (low alpha) sources specific for mild AD group respect to Nold and VaD groups. On the other hand, occipital alpha 1 sources showed a strong decline in mild AD compared to VaD group. Finally, distributed theta sources were largely abnormal in VaD but not in mild AD group. Regarding issue (ii), there was a lower power of occipital alpha 1 sources in mild AD sub-group having more severe disease. Future studies should evaluate the clinical usefulness of this source mapping in early differential diagnosis, disease staging, and therapy monitoring.

MEG-migraine studies: update. - Norman Tepley*[+], Susan M. Bowyer*[+] and John E. Moran* (*Department of Physics Oakland University, Rochester, MI 48309 USA; [+]Department of Neurology Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI 48202 USA).

The Spreading Cortical Depression (SCD) of Leão has long been implicated in migraine headache. In 1987, K.M.A. Welch suggested MEG could be used to detect SCD during migraine, and soon after Okada used a SQUID magnetometer to detect SCD in turtle cerebellum. Since 1988 our laboratory has used MEG to study SCD. We have observed DC shifts and suppression of spontaneous cortical activity in MEG signals from humans during migraine aura, results similar to those of Leão in animal models of SCD. We have used a whole head Neuromagnetometer and visual stimulation to confirm the hyperexcitability of widespread regions throughout occipital cortex in M+A and M-A patients during spontaneous and induced aura. This hyperexcitability explains the susceptibility of these patients for triggering migraine aura. We are studying the effects of prophylactic medications on cortical activity in migraine patients. We have monitored visually excited cortex pre and post treatment with divalproex sodium, a medication known to suppress cortical excitability. Our studies suggest a relationship between this drug and underlying hyper-excitability of cortex in migraine patients. MEG is uniquely suited to the study of Migraine and SCD. Unlike fMRI, MEG directly measures neuronal activity occurring over millisecond intervals rather than the secondary changes in blood oxygenation taking place over the course of minutes. Being electrodeless, MEG is better able to measure DC changes than EEG. These characteristics may make MEG useful for selecting clinically applicable prophylactic medications that will be effective in reducing the hyper-excitability in particular patients. (Supported by NIH/NINDS R01-NS30914.)

The neurophysics of consciousness. - E.R. John (Brain Research Laboratories, NYU School of Medicine, New York, NY; Nathan Kline Institute for Psychiatric Research, Orangeburg, NY).

Consciousness combines information about attributes of the present multimodal sensory environment with relevant elements of the past. Information from each modality is continuously fractionated into distinct features, processed locally by different brain regions relatively specialized for extracting these disparate components and globally by interactions among these regions. Information is represented by levels of synchronization within neuronal populations and of coherence among multiple brain regions that deviate from random fluctuations. Significant deviations constitute Local and Global Negative Entropy, or information. Local field potentials reflect the degree of synchronization among the neurons of the local ensembles. Large-scale integration, or "binding", is proposed to involve oscillations of local field potentials that play an important role in facilitating synchronization and coherence, assessed by neuronal coincidence detectors, and parsed into perceptual frames by cortico-thalamo-cortical loops. The most probable baseline levels of local synchrony, coherent interactions among brain regions, and frame durations have been quantitatively described in large studies of their age- appropriate normative distributions and are considered as an approximation to a conscious "ground state". The level of consciousness during anesthesia can be accurately predicted by the magnitude and direction of reversible multivariate deviations from this ground state.

An invariant set of changes takes place during anesthesia, independent of the particular anesthetic agent. Evidence from a variety of neuroscience areas supporting these propositions, together with the invariant reversible electrophysiological changes observed with loss and return of consciousness, is used to provide a foundation for this theory of consciousness. This paper illustrates the increasingly recognized need to consider global as well as local processes in the search for better explanations of how the brain accomplishes the transformation from synchronous and distributed neuronal discharges to seamless global subjective awareness.

Theory of mind: the interface of emotion and language in schizophrenia. - N.C. Andreasen.

The concept of "theory of mind" (TOM) refers to the ability to infer and attribute mental states to one's self and to others and to recognize that behaviors are guided by these mental states. Examples of mental states include beliefs, wishes, thoughts, goals, and knowledge. This ability is also referred to as "mentalizing." TOM or "mentalizing" requires the understanding that those mental states reflect a subjective reality rather than the real world. This capacity, which is related to the capacity to put oneself in another's place, or to have empathy, is an important component of social interactions. It appears to be impaired in many individuals with schizophrenia. Because of its philosophical and clinical importance, we undertook a study of TOM in a group of healthy volunteers and patients with schizophrenia, using PET to identify the neural circuits used during a language task that required subjects to attribute a mental state to another person. Specifically, they were asked to "imagine that you sat next to a woman on an park bench and you realized she was crying. Make up a story about what led up to her crying." (The gender of the person was changed to female if the subject was a male.) The comparison task consisted of reading a neutral story aloud, in order to control for the speech component of the task. In normal individuals this task activated a distributed group of nodes that included anterior cingulate and paracingulate regions, L anterior frontal regions, L anterior temporal lobe, and R cerebellum. Many of these regions are implicated in the identification of goals and associative memories. The large cerebellar activations add further evidence to the importance of the cerebellum in a many types of mental activity. The patients with schizophrenia had decreased flow in multiple regions (lateral cerebellum and vermis, visual association cortex, and a nonsignificant decrease in the thalamus) and increases in others (R inferior frontal, R dorsolateral frontal, R parietal, and R putamen). The areas of decreased flow are consistent with many previous studies indicating problems in recruiting cortical-cerebellar circuits in schizophrenia. The areas of increase may reflect a need to draw on right hemisphere regions to perform the task, in order to compensate for deficits in left frontal and cingulate regions.

MEG evidence for cortical reorganization in schizophrenia. - M. Reite, P. Teale, D. Rojas, D. Abrams and A. Bennett (Neuromagnetic Imaging Laboratory, Department of Psychiatry, Univ. of Colo. Health Sciences Center, Denver CO 80262).

MEG evoked field components generated in primary and secondary sensory cortex in response to auditory and tactile stimuli in patients with schizophrenia frequently have source location estimates at variance with those recorded from non-schizophrenic control subjects. Schizophrenic subjects tend to exhibit a decrease in normal left-right brain asymmetry in source location, and sources often appear somewhat further anterior in the left hemisphere. When source locations are compared with MRI based brain anatomy, auditory sources appear to be dissociated with expected locations in Heschl's gyri, and somatosensory sources, at least in the left hemisphere, often appear to be generated in locations anterior to the central sulcus in subjects with schizophrenia. These findings raise the possibility of sensory cortical disorganization, or possibly sensory cortical mosaicism, accompanying schizophrenia. Supported by USPHS MH 47476.

Development of MEG neuroimaging phenotypes. - R. Coppola (Clinical Brain Disorders Branch, NIMH).

Advances in both genetics and functional imaging have cross-fertilized into "imaging genomics". FMRI allows the investigation of individual variations in complex cognitive behaviors. These variations identify individual phenotypes that can be related to genetic polymorphisms. Magnetoencephalography can add fine temporal resolution to the study of brain activation patterns. An adaptive beamforming technique is used to examine and localize variances between active and control states. Once in 3d brain space, group maps can be formed by appropriately registered structural images. Results with group data for several cognitive tasks will be presented. The time comparison of block and event related designs shows response related maps that also suggest group differences with a COMT polymorphism that has been identified as a possible susceptibility allele for schizophrenia.

Neurophysiological hints to understand psychosis. – W. Strik (Department of Psychiatric Neurophysiology, University Hospital of Clinical Psychiatry, Bern, Switzerland).

Traditional event-related potential measures such as amplitudes and latencies are statistically sound, but the

changes are non-specific in psychotic groups. Topographical analysis has added specific features for psychopathological subgroups and indications for the possible differential mechanisms of the underlying dysfunction. Own results will be presented to demonstrate the functional difference of acute remittent psychosis (cycloid psychosis), chronic schizophrenia and manic disorders which indicate a distributed hyperarousal, regional left-hemispheric functional deficits and frontal disinhibition, respectively. The results will be interpreted in the context of the respective clinical symptoms. It is concluded that a necessary strategy in the neurophysiological study of psychoses is the definition and understanding of physiological behavioural and perceptional complexes, and their central control, and to define psychotic subgroups in terms of a partial system failure. As an outlook, finally, the example of a paradigm apt to study the top-down control of perception is presented.