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# ABSTRACTS

## Neuroinformatics: current activities and future perspectives

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Neuroinformatics is defined, at the international level, as a multidisciplinary research area that combines methods and tools of Neurosciences with Information Technologies. Basic research activities are related to understanding computational processes of the nervous system in normal and pathological functioning through the best techniques of analysis, measurement, modeling and simulation. Applied research is aimed at designing tools useful to analyze brain functions in normal and pathological conditions for diagnosis, and therapy, and to realize artificial systems which emulate brain functioning or complete it through neuro-prostheses. The international scenario is characterized by an increasing level of activity in all these areas and by the formation of Neuroinformatics research groups and centers. Building upon many years of research in bio-engineering and clinical neurophysiology a research group has recently been established in Genova addressing different aspects of Neuroinformatics from a truly multidisciplinary perspective. The goal of the symposium is to present an overview of Neuroinformatics as well as some specific research activities carried out in Genova such as: methodological and computational aspects related to the interfacing of biological systems to silicon devices (neuro-electronic interfaces); the use of artificial systems to understand brain functions;
neurophysiological mechanisms of motor imagery.

## Absence status epilepticus: relationship between EEG pattern and cognitive impairment

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Absence status epilepticus (AS) is characterized by abnormalities of mental status and behavior ranging from mild confusion to coma, in the presence of EEG diffuse paroxysmal activity lasting longer than 30 minutes. The EEG pattern may include not only typical spike-wave and polyspike-wave complexes, but also rhythmic delta activity with intermittent spikes and recurrent triphasic waves with frequency greater than 1 c/s. The diagnosis therefore is based rather on the paroxysmal character of abnormalities and the response to benzodiazepine administration, than on the pattern morphology. AS in adults may occur (a) de novo, usually triggered by toxic and metabolic factors; (b) in patients with a history of absences or other forms of generalized epilepsy; (c) in patients with previous epilepsy generally of non-temporal origin, with bilateral but asymmetrical EEG abnormalities which may raise problems of differential diagnosis with frontal complex partial SE. We report a 57-year-old man with generalized epilepsy (absence and tonic-clonic seizures) since childhood. During the last 8 years he had presented with recurrent confusional episodes lasting 4-30 hours, with slowing, irritability, and subsequent partial amnesia. During a confusional episode (MMSE score = 10/30) the EEG showed sub-continuous slow spike-wave activity, poorly modified by sensory stimulation and subsiding after iv diazepam. On the following days the neuropsychological profile was normal (MMSE score = 28/30), while the EEG showed a sustained spike-wave activity 3-4 c/s, which stopped following sensory stimulation and while performing

complex tasks. Carbamazepine was replaced by lamotrigine (LTG) with improvement. Although these findings are insufficient to establish a relationship between consciousness impairment and EEG pattern, this patient underscores the issue of misdiagnosis of partial and generalized seizures; the variability of EEG pattern and the frequent benefit of LTG treatment in these patients.

**Synchronization of homoclinic chaos and implications for biological clocks**

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All man-made clocks, based on two dynamical variables (spring-mass if mechanical, or inductance-capacitance if electrical) are two-dimensional, which means stable orbits. That is why their period is highly reliable. On the contrary, natural periodic phenomena in biology, ecology as well as economic (business, finance) cycles are ruled by multidimensional dynamics, which approaches sequentially the same saddle focus singularity. Thus these clocks display the so called homoclinic chaos, which consists of regular orbits in phase space repeating themselves with a very small spatial variance, but at erratic times. This geometric regularity makes it difficult to control chaos by exploiting geometric indicators. However at each close return to the singular point, the system is very sensitive to tiny perturbations, therefore it can be synchronized by an external clock. If the clock is too far away from the "natural" repetition frequency of the system, that is, the period averaged over many cycles, then the difference acts as a correction signal that readjust the "wrong" frequency of the external clock. Such a behavior, tested experimentally on a laser system, can be applied to stabilize biological clocks (e.g. circadian rhythms, hormonal clocks, cardiac pacemaker, etc.). For instance, in the case of an external perturbation to the cardiac pacemaker, the perturbation frequency can be re-adjusted automatically to match the working conditions of the patient. In particular we revisit the known facts about neural synchronization, or feature binding, which provide global coherent perceptions out of elementary detection stimuli, and suggest possible applications.

**High resolution EEG: comparison between movement-related potentials and event-related desynchronization/synchronization**

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Functional study of human brain is made possible by the use of advanced neuroimaging techniques such as positron emission tomography (PET), functional magnetic resonance (fMRI), magnetoencephalography (MEG), and high resolution electroencephalography (HREEG). The PET and fMRI have a high spatial resolution (mm) but their temporal resolution (sec) is insufficient for the dynamic investigation of the working human brain. Differently, the MEG has a high temporal resolution (msec) and a good spatial resolution (cm) in the localization of cortical sources oriented tangentially to the sensors. With respect to the MEG, the HREEG has similar temporal resolution and an acceptable spatial resolution (cm) in the localization of both radially- and tangentially-oriented cortical sources. The EEG spatial enhancement is essentially based on the high spatial sampling (64-128 scalp electrodes) and the reduction of head volume conduction effects with surface Laplacian transformation or inverse linear/non-linear estimation of EEG potential distributions over (un)realistic head models. An internally or externally paced sensorimotor event results in the generation of potentials or magnetic fields, which are observable after the averaging of several EEG/MEG single trials with reference to the onset of the event (phase locked event-related potentials, ERPs). Such an event results also in a concomitant non-phase-locked change in the

ongoing EEG/MEG oscillations, called event-related desynchronization/synchronization (ERD/ERS). These EEG(MEG) indicators would be intimately related to a diverse functional weight of cortical-cerebellar-cortical and cortico-spinal pathways (ERPs) as well as of cortical-subcortical-cortical pathways (ERD/ERS). Therefore, they complement each other in the modeling of dynamics of cortical responses.

**Transient human cortical responses to the observation of aimless movements. A high resolution EEG study**

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Mean electroencephalographic potentials related to the execution and observation of unilateral (right and left) aimless finger movements were studied in normal subjects, to investigate the transient cortical processes related to the visuomotor transformations. Electroencephalographic data were recorded from 128 channels and were Laplacian transformed to reduce head volume conductor effects. It was shown that standard components of the mean movement-related potentials (i.e. readiness and motor potentials, etc.) were observed only during the movement preparation and execution. During the movement execution, there were also positive potentials over primary sensorimotor and supplementary motor areas (P300, P350, P400; P=positive, number=latency in milliseconds), which would mainly concern with inhibitory somato-motor processes. Compared to these potentials, the negative/positive potentials accompanying the movement observation (N200, P340, P350, P400; N=negative) were distributed in larger zones overlying primary sensorimotor and supplementary motor areas as well as non-primary frontal and parietal-occipital areas. Remarkably, P350 was preponderant on the right frontal and parietal areas, regardless the side of the movement observation. These negative/positive potentials would reflect excitatory/inhibitory visuomotor processes within a cortical "dorsal stream". It was concluded that in the condition of movement execution, somatosensory (proprioceptive and exteroceptive) information was much more used than visual information (gazing of own moving hand). In contrast, both somatosensory and visuomotor information deeply impinged cortical areas during the movement observation. This might subserve a cortical movement execution/observation matching system for a short-latency pragmatic recognition and possible repetition/imitation of aimless motor acts.

**Perceptual and response bias in visuospatial neglect due to repetitive transcranial magnetic stimulation (rTMS) of right parietal and frontal cortex in normal subjects**

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The role of perceptual and response factors in neglect still needs clarification. In a recent study we showed that rTMS of right posterior parietal cortex can give rise to transitory contralateral neglect in normal subjects. In the present experiment we tried to disambiguate perceptual and response bias in the visuospatial impairment due to rTMS of right parietal or frontal cortex. Nine healthy subjects performed a tachistoschopic task, requiring binary forced choice estimation of the length of the two segments of asymmetrically prebisected horizontal lines. In condition A subjects had to name ("right" or "left") the shorter and in B the longer segment. The task was given in an ABBA order first in basal and then in rTMS sessions. rTMS was delivered in trains of 10 stimuli at 25 Hz frequency with a focal coil positioned over F4 or P6 (according to 10/20 EEG system) and triggered

synchronously with visual stimuli. Both parietal and frontal rTMS gave rise to left visuospatial neglect that in both cases appeared to be due to perceptual *and* (though perhaps to a lesser degree) response factors.

**Single-sweep P3 extraction: use of a new adaptive filter**

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Since the 1950's various methods for ERP extraction have been developed to separate the interesting signal, mainly P3, from the background. Averaging is the commonly employed, but increasing interest in performing the analysis on single sweep appears in last years. An adaptive filter called TALC (Transversal Adaptive Linear Combiner) is proposed and validated to identify P3 in a single sweep. Auditory ERP were acquired using the Odd Ball paradigm. In the test session a primary signal (the measurement epoch to be filtered) and a reference signal (ensemble average of a training session) are required. TALC uses three parameters chosen in the training session. The filter adaptation is based on minimizing MSE between the primary signal and the output of the filter.
Filter selectivity, specificity and robustness for a given subject were proved.
TALC is a simple algorithm, with low computational cost, needs minimal user interaction and can be implement in a real-time processing. It is suitable for the extraction of single sweep P3, needed for inter and intra-individual variability studies. In real-time processing, the filter can be used for studying sleep disease and monitoring the awakening after
anesthesia.

**Disorders of visual processing: an insight on conscious visual perception**

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Objective is to describe two disorders of visual processing: blindsight and acquired achromatopsia and discuss their relationship to conscious visual perception. Blindsight is the ability of a patient to respond to a visual stimulus despite being unaware of its presence. This phenomenon has been previously attributed to either residual visual function related to spared area 17, or subcortical pathways bypassing area 17 (the so called second visual system or retino-tectal system). Two subjects with bilateral infarcts of the occipital lobe including destruction of the fusiform and lingual gyri were studied. Target chromatic and luminance stimuli were presented to the blind field and to the spared but achromatic field. The target were M-scaled and presented along the 45-degree diagonals at 3 and 10 degrees of retinal eccentricity. Patients fixated a central point and were instructed to look at any target appearing in the visual field and return their gaze to the fixation point. Saccades were monitored (via infrared reflection) during the presentation of each stimulus. Luminance and chromatic stimuli presented to the blind fields were not perceived and did not elicit any saccades. Luminance targets were seen in the achromatic field and produced normal saccades. Isoluminant chromatic stimuli were not see but elicited normal saccades. Despite the absence of any subjective color vision both patients were able to make accurate saccades to isoluminant chromatic targets. We concluded that chromatic stimuli reached area V1 and V2 normally and were then transmitted to parietal and frontal areas involved in saccadic programming. Color perception was absent because area V4 was destroyed. Spared area V1 is not sufficient for color perception. The results also suggest that the human dorsal pathway contains cells responding to wavelength information, but these areas do not mediate the perception of color.

**Quantitative analysis of sleep-EEG before and during arousals**

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ASDA arousals has been defined as a rapid modification in EEG frequency which can include theta, alpha activity and/or frequency higher than 16Hz but not spindles. They can appear during different sleep stages with different sleep-EEG patterns. The aim of this study is to investigate EEG activity preceding and constituting arousals by means of frequency analysis. In 11 recordings from subjects affected by different sleep disturbances ASDA arousals have been recognized, excluding events with artifacts. For every single event 3 periods of EEG have been studied: 20 seconds before the arousal, the pre-arousal (3.5 sec.) and the arousal. Wavelet analysis has been applied for delta, theta, alpha, sigma and beta band ranges. Chi-square test has been applied to evaluate frequency increase before arousals, ANOVA has been applied for testing differences between subjects. During pre-arousal periods band power was principally stage dependent while the frequency range of the arousal was subject dependent. Pre-arousal delta activity (SWA) was increased respect to basal activity in 75% of the cases ($p<0.001$). Relative sigma power respect to alpha + beta power decreases during arousals. The study confirms the frequent link between brief sequences of SWA or K-complexes during the prearousal period and the arousal themselves, representing a complex of stimulus-responds linked at the sequences of basal synchronization-desynchronization rhythm of the cyclic alternating pattern.

**Hypnotizability, hypnotic analgesia, and psychophysiological mechanisms in pain modulation**

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This report reviews our electrocortical and autonomic findings concerning the effects of hypnotizability and hypnotic analgesia suggestions in pain modulation. Results are seeing as demostrating that hypnotic analgesia is the product of an inhibitory processing which involves focused attention and obstructive hallucination. The first mechanism is mediated by frontal cortical activity, the second is mainly the product of posterior cortical system which modulates mental imagery. This statement is supported by a number of our findings obtained using traditional analyses of EEG rhythms, event-related potentials, and autonomic responses. Experimental evidence is given indicating that different cortical processes are engaged by different suggestions of analgesia, but it still remains obscure how the final product of these different processes give rise to a frontal cortical inhibition. Our most recent results from auditory ERPs have evidenced, during hypnotic analgesia, significant P3 peak amplitude reductions and significant enhancements of a mismatch negativity (MMN) peaking at about 100 ms. These findings indicated that hypnotic analgesia can affect information processing in the brain even at preattentive level, during the discrimination of change in stimulus flow.

**Skilled Performance Task in hemiparetic patients: an electrophysiological follow-up**

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Cortical functions concerned with the execution of skilled movements can be studied through a complex interactive task. Skilled Performance Task (SPT) offers the greatest deal of information about the electrophysiological components which reflect both the pre-programming (Bereitschaftspotential -BP) of a bimanual, skilled motor act and the performance related control processes (Skilled Performance Positivity -SPP). Using SPT we have investigated a sample of ten patients with hemiparesis due to cerebral infarct.
The electrophysiological findings of the patients were then compared with those gathered from a group of age-matched normal subjects. The first recording was carried out only when the patients were able to move the index finger of the paretic hand. In a one-year period four clinical and electrophysiological evaluations were performed. At the first recording, hemiparetic patients scored a smaller number of correct performances ($p<0.03$), associated with a lower BP amplitude ($p<0.002$) and a lower Motor Cortex Potential -MCP (reafferent activity, Papakostopoulos, 1980) amplitude ($p<0.008$), than normal subjects.
However a different trend of BP and SPP was observed during the patients' follow-up. The data has induced us to consider this paradigm as a useful tool in order to evaluate the psycho-physiological assessment during the functional recovery of patients with stroke.

**Non-linear analysis of sleep structure and regulation**

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In the last 10 years, a number of papers has been published in order to characterize the structure of sleep EEG signals. We have also shown that, the sleep modulation mechanisms can be characterized in terms of nonlinear dynamics and that the structure of the profile of the delta band can be explained by the complex interaction of a relatively low number of variables. Regarding the analysis of sleep EEG, it is also well known that there exists a peculiar organization of phasic events during sleep, connected with fluctuations in arousal level, which has been called "cyclic alternating pattern" or CAP (Terzano et al. 1988). For all these reasons, we studied the nonlinear aspects of sleep EEG taking into account the peculiar organization of these phasic events. The dynamical properties of the EEG were assessed by means of the NLCP test recently introduced by Stam et al. (1998). With this test it is possible to reject the null hypothesis that the original time series is linearly filtered white noise and also the hypothesis that the time series represents a static, nonlinear transform of an underlying linearly filtered white noise. Based on the results of this study, we concluded that sleep might be considered as a physiological dynamically evolving sequence of different high/low dimensional states of the EEG, which we could track by detecting nonlinearity mostly in correspondence with CAP sequences; in facts, the occurrence of phasic events, was found to induce the appearance of detectable nonlinearity in the EEG. We also checked for the existence of a similar pattern in premature babies and in infants at-term but failed to find periods of clear nonlinearity in their sleep EEG; however, a certain tendency was found only during quiet sleep. On the contrary, when the sleep EEG of subjects with ESES, a condition characterized by the appearance of continuous spike and waves during NREM sleep, was considered a strong evidence of nonlinearity was found in all subjects analyzed. The nonlinear analysis of the sleep EEG, if correctly performed, is able to provide information on the complexity of functions taking course during this state.

**Psycophysiology of sleep-wake rhythm: models and clinical features.**

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The internal structure of night sleep in subjects with narcolepsy significantly differs as compared to the controls. The differences consist in the presence of sleep onset REM periods (SOREMPs) and in a longer duration (120 minutes versus 90 minutes) of the NREM-REM cycles. Another difference consists in the lack of increase in REM sleep duration during the night, cycle after cycle. With regard to the intrasleep dynamics the actual extension of the Two-process model can't give a satisfactory explanation of these features because REM sleep is included as an external trigger with no intrinsic rhythmic property. The introduction in the Two-process-model extended to the intra-night dynamics of an ultradian oscillator based on a REM-ON - REM-OFF reciprocal interaction model, allows the theoretical possibility to simulate a SOREMP and accounts for the progressive extension of REM sleep-periods duration in the course of the night. The sleep structure of narcoleptic patients can be simulated leaving unaltered the pressure of the homeostatic process and enhancing the REM inducing pressure. Such an enhanced REM pressure can be achieved increasing the value of the numerical coefficient, which represents the strength of connection between the two types of REM-ON and REM-OFF cells, thus obtaining a stronger ultradian oscillator with longer periodicity. Coupling the homeostatic process (process S), considered as normal, to such a modified ultradian oscillator, our model can explain the intra-night sleep dynamics of narcoleptic subjects. A REM-on REM-off dysregulation can be hypothesised to explain the pathophysiological basis of nocturnal sleep features in narcolepsy.

**Alcohol intake and vehicle accidents: relationships with alertness fluctuations**

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The aim of this study is to analyse the distribution of alcohol-related accidents over a 24-hour period as related to alertness fluctuations. We examined all alcohol-related accidents ascribed by police officers on Italian highways from 1993 to 1997. Accidents were standardized for traffic intensity. Using the Kolgomoroff-Smirnoff tests on relative cumulative values, we tested the assumption of a significant difference between accident distribution/hour and traffic intensity distribution/hour. The chi-square test was used to detect statistically significant differences at different hours of the day. The distribution of alcohol-related accidents was correlated with an indicative curve of the sleepiness trend over 24 hours obtained from an experimental bed-rest protocol. The distribution of alcohol-related accidents shows a single nighttime peak occurring earlier than that for sleep-related accidents and a drop in the early morning hours. There is no evidence for a minor early-afternoon peak and a drop in the forbidden zone. In conclusion, the daytime distribution of alcohol-related accidents does not seem to be affected by fluctuations in alertness and seems to be more related to social alcohol intake. During evening and night hours, the two effects seem to be cumulative, though with different manifestation times.

**Sleep related vehicle accidents on italian highways**

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The aim of this study was to assess incidence and characteristics of sleep-related vehicle-crashes on Italian highways. The database of the Italian National Institute of Statistics (1993–1997) was the source for the survey (50859 accidents with 1632 (3,2 %) ascribed to sleep by the police). The distribution of accidents was evaluated by means of the analysis of variance considering the year, the day of the week, the age and the time of day and their interactions as main factors. Moreover, using a polynomial regression, we evaluated the relation between accidents (whether sleep-ascribed or not) and sleepiness as derived from a 24-hour sleep propensity curve. The relative risk of sleep-related accidents was also evaluated with reference to the relative traffic density. The counts of sleep-related accidents, and even more the relative risk, revealed the presence of peaks and troughs in zones at a higher level of sleepiness and alertness respectively. Death of the driver occurred in 11.4 % of sleep-related accidents versus 5.6 % in general accidents. The analysis of non-sleep ascribed accidents indicated an estimate of accidents related in some way to sleepiness equal to 18.7%. Considering that the rate of sleep ascribed accidents was 3.2% the total amount of sleep-related accidents reached the value of 21.9%.Therefore, sleepiness appears as a remarkable risk factor and, in our opinion, its incidence as sole or contributory cause of accidents on Italian highways is still underestimated.

**Daytime sleepiness and sleep disorders in a population of italian shift-workers**

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Reportedly, shift-work has a negative effect on both sleep quality and quantity, with excessive daytime sleepiness (EDS) resulting either from fragmented/decreased total sleep time or due to concomitant intrinsic sleep disorders. This study assessed the EDS incidence and correlation between sleepiness and sleep disorders in shift-workers of the Italian State Police (504 male and 101 female shift-workers; mean age 30 ± 5 years). Subjects with pathological daytime sleepiness were identified by the Epworth Sleepiness Scale (ESS). Subjects with scores >11 were asked to fill out a questionnaire to identify symptoms of intrinsic sleep disorders and were informed they could resolve to see a specialist at the Centre of Sleep Medicine. Pathological sleepiness (mean ESS score 12.4, range 11-18) was found in 61 subjects (9.9%). Thirty-two subjects with indications of one intrinsic sleep disorders and ten with more than one sleep disorder were identified. Twenty-five subjects reporting symptoms of intrinsic sleep disorders and 14 subjects without sleep disorders reported being involved in accidents at work or while driving ($\chi^2$, $p<0.02$). Twelve subjects with sleep disorders and 3 subjects without reported EDS-related accidents. In eight subjects, a complete polysomnography confirmed at least one of the suggested disorders. These results suggest a high incidence of intrinsic sleep disorders in shift-workers with EDS. The concurrent effects of shift-work intrinsic sleep disorders may result in health impairment and increased risk of EDS-related accidents during work.

**Pain modulation and the cardiovascular system**

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It is well known that pain may arise from various sites in the cardiovascular system either through mechanical stimulation (e.g. distension of a vessel or a ventricular wall) or chemical stimulation (usually mediated by transmitters such as adenosine and substance P). Common examples of such a kind of pain are observed in acute myocardial ischemia, aortic dissection and arteritis. Perhaps less well known is that the cardiovascular system may also contribute to modulate pain perception and that this is mainly mediated through arterial blood pressure. In fact, a number of studies have consistently demonstrated that high blood pressure and decreased nociception are frequently linked phenomena: a behavioral hypoalgesia (i.e. increased response threshold to noxious stimuli) has been reported in spontaneous and experimental acute and chronic hypertension in the rat and studies in human hypertension have also demonstrated a diminished perception of pain, as assessed as pain thresholds or ratings. Hypertension-associated hypalgesia may be related to stress-induced hypalgesia and possibly reflects an attenuated transmission of noxious stimuli at the spinal level secondary to descending inhibitory influences which are projected from brainstem sites involved in cardiovascular regulation and which may depend on baroceptor activation and/or on a central "drive". Hypertension-associated hypoalgesia may have clinically relevant consequences, especially in silent myocardial ischemia.

**EEG correlates of CAMCOG score in Alzheimer's patients**

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Among the several neuropsychological scales employed to evaluate cognitive impairment in Alzheimer's disease (AD), the short CAMCOG scale is computerised, has an Italian version and offers the advantages to be administered in a short time. However, the relationships between the CAMCOG score and the neurophysiological indexes of the severity of AD are scantly known. Thirty-three AD patients (27 women, 6 men, mean age: 76.8, SD 5.1) underwent short CAMCOG

evaluation and quantitative EEG in the same week. Correlation was searched for between three CAMCOG indexes (total score, a language index and a praxis index) and the relative power of two quantitative EEG (qEEG) bands (2-7.5 Hz and 8-12 Hz) in the two posterior temporal channels. Total CAMCOG score was more significantly correlated with the 2-7.5 Hz band (left side: r= -0.63, p<0.001; right side: r= -0.58, p<0.001) than with the 8-12 Hz band (left side only: r= 0.42, p<0.02). The language score correlated more significantly with the left-side (2-7.5 Hz: r= -0.63, p<0.001; 8-12 Hz: r= 0.56, p<0.001) than with right-side (2-7.5 Hz: r= -0.52, p<0.01; 8-12 Hz: r= 0.29, p=0.5) bands. Finally, the praxis score correlated with a similar significance level with the two bands irrespective of the hemisphere (left-side 2-7.5 Hz: r= -0.53, p<0.01; 8-12 Hz: r= 0.54, p<0.01; right-side 2-7.5 Hz: r= -0.50, p<0.01; 8-12 Hz: r= 0.48, p<0.01).Language function is mainly related to the left-side qEEG bands, whereas the praxis function are expressed by qEEG bands of both sides. It is concluded that the CAMCOG score is an adequate tool to detect the functional impairment in AD.

**A MEG study of stroboscopic alternative motion**

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We compared MEG event-related fields induced by an ambiguous pattern reversal with externally induced perceptual switches in an apparent motion paradigm. Event-related fields of 10 subjects were recorded and frequency analyses in the alpha range were carried out. Patterns evoking ambiguous motion perception are well suited to study the human visual system. Since the same physical stimulus is constantly presented to the visual system, the perceived changes in motion direction are completely endogenous in origin and do not result from stimulus changes. Therefore, it is an interesting question whether it is possible to find neurophysiological correlates of the switching process which may reveal bottom-up or top-down influence. Our results show a slow wave in response to the perceived changes of motion direction which was larger for the externally induced pattern change. This result corresponds nicely to previously found ERP results. In addition, we found that prior to the reported changes of motion direction the induced (non phase-locked) alpha activity decreases steadily for the ambiguous pattern, while for the externally induced pattern change the induced alpha activity remained stable until the pattern reversed. This finding may indicate that the ambiguous pattern reversal is related to a decrease in the alpha-band. These findings are compatible with the satiation theory of figure reversal claiming that the percept switches when one percept is satiated which is referred to as a bottom-up process.

**ERD and motor programming: clinical applications**

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Movement preparation and execution is related to the reduced expression of the electroencephalographic rhythms of the alpha and beta bands, over the related sensorimotor areas. This phenomenon, defined as Event-related desynchronization (ERD) is considered as a sign of cortical activation. Following movement termination, a synchronization (ERS) of the same rhythms occurs, which is considered as a sign of cortical idling or inhibition. Both these phenomena show different abnormalities in pathologies involving motor behavior, such as Parkinson's disease, focal lesions, motor neuron disease, frontal disturbances or fatigue during the course of Multiple Sclerosis, obsessive-compulsive disorder.

**Psychophysiological and behavioral correlates of anger**

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In this report results will be presented from two studies of our research concerning the debated relationship between anger/hostility traits and cardiovascular illness.
In the first study, heart rate (HR), systolic and diastolic blood pressures (SBP and DBP) were analyzed in 24 volunteer Belgian college students during mental imagery of personal events inducing neutral, anger, and fear sensations. Subjects with high control over aggressive reaction showed greater anticipatory reactivity of the cardiovascular system and lesser increases from baseline during imagery. Subjects with low control of aggressive behavior and Ss with higher anger-out style showed greater reactivity during imagery.
The second study investigated the relationship between anger/hostility and cardiovascular reactivity in 28 woman volunteer students. HR activity was recorded during mental imagery inducing neutral, anger, and fear feelings. From the spectral density function of HR activity, peak amplitudes for three frequency bands were measured: 1) Low-Band: 0.03-0.08 Hz (simpathetic activity); 2) Mid-Band: 0.08-0.15 (simpathetic-parasimpatetic balance); 3) High-Band: 0.15-0.5 Hz (parasimpathetic activity). During self-generated mental imagery inducing anger episodes anger-out subjects showed high level of activity in both sympathetic and parasympathetic branch of the autonomic system. The deregulation in the autonomic balance is suggested as a possible precursor of cardiovascular illness in anger-out individuals.

**Topography and estimated sources of the oscillatory ~20-35 Hz cortical responses to visual stimulation: a human MEG study**

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Models and experiments indicate a functional role of synchronized cortical oscillatory activity above 20 Hz in early visual processing. Oscillatory (~20-35 Hz) mass responses to contrast stimulation are recorded in man and cat, with suggested cortical origin and with time dynamics anticipating the broadband responses (VER). Ten healthy subjects were recorded during transient foveal stimulation with sinusoidal vertical gratings presented to each visual field quadrant (reversal mode at 1Hz; spatial frequency: 5cpd; contrast: 70%). Data acquisition and processing were through a Neuromag$^{TM}$ 122 probe system and standard software [*]. Oscillatory responses at ~20-35 Hz were recorded in all subjects and proved maximal after inferior nasal field stimulation. The topographic distribution and estimated sources were comparable to those of the VER. However, the amplitudes of the oscillatory responses and VER were not correlated on longitudinal and latitudinal gradients at the same occipital location; the sources of oscillatory responses and VER differed in orientation; and the oscillatory response field reached a structured pattern 20-40 msec before the VER. These findings further support a predominant cortical origin of the ~20-35 Hz oscillatory responses to contrast stimulation and suggest differences from conventional broadband VER in the mechanisms of generation and function.
* Measurements were done at the Brain Research Unit, Low Temperature Laboratory, HUT, Espoo, Finland, with partial support from the EU's Large-Scale Facility Neuro-BIRCH III.

**Cholinergic effect on relationship between cerebral perfusion and cognition in Alzheimer disease**

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Dementia has a growing incidence in western countries, mainly due to increasing life expectancy. The recently introduced acetylcholinesterase inhibitors, such as Donepezil, have been shown to slow down the course of the Alzheimer disease (AD), when administered at early stages. Nineteen patients (4 males, mean age 75.3 years +- 6.4,) affected with probable AD (NINCDS-ADRDA criteria) were examined twice, before and after a period (mean 10.6 +-2.9 months) of Donepezil oral administration (5 mg/day), by routine clinical and neuropsychological examination. At each time point, brain perfusional SPECT scan was performed. According to the variation of Mini-Mental State Examinations (MMSE) score, the group was divided into two subgroups: "responders" (MMSE variation ranging between +2 and -1, mean 0.18: 11 subjects) and "non responders" (MMSE variation between -2 and -7, mean -4.38). There was no difference between the two subgroups either for age or sex distribution. In each subgroup, the correlation between the MMSE score and perfusional value variations were assessed in Frontal and Parietal-temporal areas in each hemisphere. In responders there was a correlation between cerebral perfusion and cognitive changes, more significant in right ( frontal, $p<0.01$, and parietal-temporal areas, $p<0.02$ ) than in left ( $p<0.05$ in both areas) hemisphere, whereas in non responders no correlation was found. These preliminary data confirm that the cognitive effect of the anticholinesterase therapy, obtained only in a part (approximately a half) of AD patient, is supported by neural activity, that is tightly coupled to the perfusional levels.

**Periodicity of arousal complexes in the modulation of sleep structure and in the pathophysiology of sleep disorders**

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The conventional definition of arousal relies on transient EEG changes mostly characterized by patterns of wakefulness. In the scoring of arousals, the abrupt appearance of slow wave activities, i.e., K-complexes or delta bursts, is basically neglected. Lately, the definition of arousal has been revised by the increasing evidence that vegetative modifications, such as changes in heart rate and blood pressure, can occur in concomitance with EEG shifts towards high-voltage low-frequency activities. In other words, transient synchronized EEG patterns, whether or not associated with an ASDA arousal, can be endowed with arousal-like properties. The activating properties of both slow and rapid EEG rhythms suggest to extend the stereotyped definition of arousal to a number of complex features (intermittent alpha rhythm, vertex sharp waves, bursts of K-complexes, K-alpha complexes, delta bursts, arousals), which share graded activating properties along a hierarchical continuum. Most of these EEG features appear exclusively during NREM sleep and are orderly arranged in a spontaneous 20-40 s rhythm, defined as cyclic alternating pattern (CAP) in relation to the repetitive emergence of the arousal complexes. Due to the involvement of CAP in the structural organization of sleep, CAP parameters provides basic information on the regulatory mechanisms of normal sleep and on the pathophysiology of sleep disorders.

**Event-related potential studies on language comprehension: a selective review**

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Language comprehension requires the activation, coordination and integration of different kinds of linguistic knowledge. There are several hemodynamical and neurophysiological approaches to study the postlexical processing of word recognition. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are useful to localize brain regions of interest in word comprehension but have a low time resolution. Although event-related brain potentials (ERPs) are limited to determine neuroanatomical aspects of cortical and subcortical regions implicated in linguistic processes, their data provide informations for a number of specific components that can be linked to distinct aspects of language understanding. In particular, the separation of meaning and structure in language is associated with different ERP features (LAN, N400, P600), providing a neurobiological basis for models of comprehension. Since the first researches of Kutas and Hillyard (1980) many semantic ERP studies were conducted to detect age effects on semantic memory and language dysfunction in patients with senile dementia, Alzheimer's disease (AD) and left hemisphere lesions. So, used together with other neuroimaging techniques, the ERP method could be a useful tool to better understand the cognitive processes underlying the linguistic knowledge, and could also find clinical applications in assessing lexical-semantic impairments in several pathological conditions, like AD, aphasia and dyslexia.

**MMN and P300: recording standards.**

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Event-Related Potentials (ERPs) recorded in Humans can provide important information about cognitive processes both in normal subjects and in clinical populations. Mismatch Negativity (MMN) and P300 are the most popular components and the most widely studied. A multiplicity of factors affects the quality of the investigations: the recruitment of subjects and patients, the types of stimuli and responses, the electrodes, the features of the recording system, the artifacts rejection/compensation strategy. Also, the design of the experimental paradigm should be carefully tailored on the cognitive process to be explored. Recent guidelines for recording ERPs have been published (Picton et al., Psychophysiology, 2000) and should be followed by researchers in the field.

**The effects of noise in multistable perception: a neural network model.**

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This work describes two different aspects of noise effects in an artificial neural network modeling some peculiar aspects of human perception in the presence of so-called *ambiguous figures.* When one of such patterns is observed, the same visual input can elicit two different interpretations, *A* and *B,* giving rise to a cyclic perceptual alternation of the two competitive percepts. The basic unit of the model is an autoassociative network (SLN) with continuous neuron activation and with a two dimensional energy landscape. The SLN network consists of two sets of neurons: the first one is made up of n(A) elements or neurons associated with the perceptual features of the first *A* interpretation of the ambiguous figure; the second set is made up of n(B) neurons associated with the alternative *B* interpretation. In this way, we can associate the two alternative percepts *A* and *B* with two minima in the energy of the network, corresponding to two stable states.
The network can be operated at either zero or non zero temperatures which represent an internal system noise. As a first result, we show that, under the influence of a weak periodic external signal,

the network exhibits a maximum in the signal-to-noise ratio at an optimal noise level: the characteristic signature of Stochastic Resonance phenomenon.
In order to reproduce some other experimental characteristics of the perceptual alternation phenomenon, and in particular the stochastic behavior shown by the experimental data, we must increase the structure of the network by designing a multilayer neural network (MLN). The lower layer of the MLN is made up of a set of SLN working in parallel, without any interconnections, and the upper layer is made up of only one SLN, identical to the lower ones. Computer simulations have demonstrated that the MLN network allows one to obtain stochastic Gamma distributions similar to those of experimental data and also results in good agreement with some other characteristics of the perceptual alternation phenomenon.

**Oscillatory responses obtained by texture stimuli in different perceptual conditions**

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The data of two texture Visual Evoked Potential (tVEP) experiments, which were originally performed using standard broad-band (1-250 Hz) filters, were reconsidered applying off-line narrow-band digital filters (19-40 Hz) in order to analyze oscillatory responses (OR). The stimulation paradigms were aimed to identify such pre-attentive perceptual processes as edge detection and surface filling-in (first experiment) and amodal completion (second experiment). Results concerning broad-band obtained tVEPs have been reported elsewhere (Vision Research, 1999, 39, 31-39; Clinical Neurophysiology, 1999, 110, 86-91). OR were obtained in all stimulation conditions and consisted of 9 components (from N0 -mean latency 43 ms- to N4 -mean latency 234 ms-). The last two components (P4, N4) were not detectable in some cases, not depending on stimulation condition. In the first experiment OR did not vary with stimulus features, thus reflecting low-level aspects of stimulus. No effects specifically related to edge detection and surface filling-in were found. In the second experiment an enhancement of some middle-range components (N1, P2, N2) was detected, specifically reflecting amodal completion. This enhancement preceded in time the broad-band component associated with the same perceptual process (around 170 ms). The results suggest that OR may be particularly linked to functional binding of separate neuronal aggregates when the different patches of the stimulus are components of a perceptual unity.

**Spontaneous blinking in the assessment of awareness disturbances in patients with severe post-traumatic syndrome**

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It is known that in normal subjects the frequency of spontaneous eyeblinking (blink rate, BR) is affected by arousal levels, basal cognitive processes (attention, identification, information-processing, memory) and more complex cognitive functions (concentration, mental calculation, reading, conversation). Moreover, BR is believed to be a good index of central dopaminergic activity and mental workload. In this work, the inter-blink interval (IBI) (inversely related to BR) was daily tested for a 5-minutes period in 4 patients with severe post-traumatic syndrome. The aim was to validate the blinking observation in the assessment of cognitive networks activity in wakefulness-without-awareness patients.
In all patients the mean IBI of each test was often statistically different with respect to controls; moreover, a meaningful inter-test difference was often found in contrast with the stability of BR

pattern reported for normal subjects. In 2 out of 4 patients (with the best GCS score at the income and successively improved) the mean IBI of each test was higher than controls, instead in the other 2 (with the worst GCS without successive improvements) was lower or floating around controls mean. Moreover, patients with positive outcome showed a higher intra-test variance than patients with negative outcome and controls as an expression of the irregularity of blinking rhythm. In conclusion, up today collected data appear linked enough both to the severity of coma and to the possible improvement of awareness level. Therefore, the study of the spontaneous blinking could play a complementary role in the total evaluation of the cognitive state of scarcely or not at all collaborating patients with awareness disturbances and unaffected wakefulness.

**Sex differences in pain perception**

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It is commonly retained that females are more sensitive to pain as compared with male. Moreover literature about gender differences on pain perception is relatively scarce and conclusions not homogeneous. This has been attributed to different stimulation modalities (type of stimulus, electrical or termic, body sites stimulated, spatio-temporal mechanisms, etc), socio-cultural factors and affective-emotional impact produced on subjects. We tried to investigate the possible role of basal physiological mechanisms in sex perception differences by studying the somatosensory system with low intensity electrical stimulation (both painful and non-painful) so as to focus on sensory-discriminative rather than affective-motivational aspects of pain. To do this, intracutaneous electrical stimulation of the index finger tip was performed in 10 not paid healthy volunteers (6 females and 4 males), enrolled among the staff of our Department, including the authors. Absolute values of either tactile (Tt) or pain (Pt) thresholds and also Pt/Tt ratio (or Relative Pt) were considered. Compared with males, females showed significantly lower Tt ($p<0.001$) and slightly smaller Pt ($p<0.05$) than males. Nevertheless, females exhibited higher Relative Pt values ($p<0.0001$), resulting relatively less sensitive than males. In conclusion, by considering Pt/Tt ratio as a measure of the tactile system activation at painful threshold levels, one could hypothesize that the lower sensitivity observed in females could depend on a higher activity of the "gate control" system in modulating afferent nociceptive inputs.

**Pattern electroretinogram (PERGs) in response to equiluminant red-green and blue-yellow gratings in normal subjects**

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Pattern electroretinograms (PERGs) were recorded more than twenty years ago using luminance-contrast stimuli to detect both physiological responses of retinal ganglion cells in normal observers and optic nerve dysfunction in patients. More recently, PERGs to chromatic-contrast stimuli have been recorded. The properties of chromatic-contrast PERGs differ substantially from those of luminance-contrast PERGs. Aim of this study was to better characterize the features of chromatic PERG to red-green (R-G) and blue-yellow (B-Y) stimuli in healthy subjects in a attempt to establish a set of normative values, suitable for clinical applications. In eleven normal volunteers (5 females, 6 males; mean age 41.1 ± 14.2 yrs) we have recorded chromatic PERGs in response to both equiluminant R-G and B-Y and luminance-contrast (Yellow-Black: Y-Bk) horizontal gratings. All stimuli (spatial frequency 0.3 c/deg, Michelson contrast 90%, mean luminance 15 cd/m$^2$, 1Hz

reversal) covered a field of 59.2*59 deg and were presented monocularly at a viewing distance of 24 cm. The equiluminant point was established psychophysically by determining the relative luminance of Red and Green or Blue and Yellow at which the perception of flicker for stimuli alternating at 15 Hz was minimal. Retinal signals were recorded with cup electrodes taped over the inferior eyelid and referenced to the contralateral, occluded eye; the ground was positioned over the central forehead. Two-hundred sums were averaged to extract signal from noise. Responses were digitally smoothed to eliminate high-frequency noise originating from eyelid muscles. Transient chromatic PERGs showed a typical positive-negative (P1-N1) waveform for both R-G and B-Y stimuli and had a smaller amplitude and a longer latency that luminance PERGs to Y-Bk stimuli. Mean values (± 1SEM) for P1 latency and P1-N1 amplitude, respectively, were: R-G, 74.4 ± 1.0 ms, 3.2 ± 0.2 μV; B-Y, 70.8. ± 1.3 ms, 2.5 ± 0.2 μV; Y-Bk, 60.7 ± 1.4 ms, 4.2 ± 0.3 μV. The above findings indicate that chromatic PERGs, in spite of their smaller amplitude as compared to luminance PERGs, may be reliably recorded in normal observers by means of skin electrodes. The response variability is of the same extent as that of luminance-contrast PERGs. Data provide a set of normative values to be employed in the clinical routine.

**Motor program and preparatory set**

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Central problems in the analysis of higher brain function in the context of planning of motor activity are: 1) from where does the motor cortex get its instructions, 2) how the elements of a movement pattern are spatially and chronologically sequenced, 3) what is the role of behavioral context in the modulation of the motor programs and of their execution, 4) how is the appropriate co-ordination of goal-directed movements and postural muscle activity achieved. Less concern is normally devoted to the planning of the modulation in excitability of the reflex activity triggered by the movement, which can intrude into the motor plan itself: sensory and motor signals normally interact during the execution of many motor acts, except perhaps of the most rapid and short-lasting ones. Planning of movement is the first step in the production of any motor activity, be it a short-lasting 'voluntary' motor act as reaching or pointing to a target, or a long-lasting 'automatic' motor behaviour such as locomotion. In the former case, the control of the re-afferent input can be of less momentum, in the latter, this control would be crucial. Conversely, in order to successfully achieve the goal, the planning one or the other motor act must depend on the state of the effector, which can be, say, fatigued or not fatigued. The modulation of the spinal excitability appears to be one major aspect of the motor plan. This appears to be true in particular for the proprioceptive input: 1) the termination of a prolonged muscle contraction critically depends on the depression of the input from the muscle spindles, 2) the reflex responses to leg muscle stretch during stance are depressed whenever posture is stabilized. These events appear to be altered in movement disorders. 3) locomotion is unaffected by artificially enhancing proprioceptive input from the moving legs, a sign of powerful suppression of spindle inputs during gait.

**Multistable perception and cognitive order formation**

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Multistable perception is a paradigm for psychophysics without physical change, i. e. we find in certain patterns a dramatic cognitive reversal process without any change in the stimulus. There are different categories of mulitstable patterns: figure-ground-reversal (Rubins face-vase), reversals in perspective (Necker-Cube), semantic reversals (duck-rabbit-figure) and the stroboscopic alternative

motion (i. e. switching between horizontal and vertical phi-phenomena). Recent results show that the reversal rates of the different categories can be influenced by cognitive efforts in a very different amount, generally the semantic changes more than the structural reversals. We found positive correlation between the switching rates in divergent tasks (creativity/flexibility) and negative correlation in convergent tasks (finding analogies). Furthermore there is a significant age dependency of the reversal rate increasing from 3-5 to 20 years of age and decreasing form 60 years on. There is a correlation between the reversal rates and gamma band EEG-activity at the frontal area, which might be an indicator of cognitive flexibility of the brain.

**Electrophysiological studies of multistable visual perception**

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Multistable visual perception, i.e. the spontaneous oscillation between different stable percepts of the same physical stimulus pattern, is a useful paradigm for studying perceptual order formation. In a series of studies we investigated potential and frequency changes in the EEG induced by figure reversals during continuous viewing multistable patterns. We used the Necker cube (NC) and a bistable dynamic motion display, which is called Stroboscopic Alternative Motion (SAM). The results were: 1. Figure reversals are related with a slow positive wave in the EEG, which shows a central-parietal amplitude maximum for the SAM, but no distinct topographical effects for the NC. 2. The amplitude of this „perceptual switching related positivity“ is higher and the duration longer for the SAM than for the NC. 3. In comparison with an unambiguous figure reversal (alternating presentation of two unambiguous versions of the ambiguous pattern) the slow positive wave induced by the ambiguous pattern (SAM) has a smaller amplitude and a longer duration. 4. There is a frontal gamma-band (30-50 Hz) enhancement during naiv observation of the SAM and NC (subjects were not informed about the multistability of the patterns) compared to spontaneous EEG. 5. During active observation of the SAM (subjects were informed and had to press a button following the figure reversal) the frontal gamma-band increase is higher in the time window, which includes the figure reversal (reversal phase) compared to the time window, which contains no figure reversal (non-reversal phase). NC results have a similar tendency. The results indicate evidence for consistent changes in the EEG related to multistable visual perception. The reported potential and frequency changes are similar for both the static NC and the dynamic apparent motion display (SAM).

**Time distribution (1966-1999) of ERPs published reports and the Decade of the Brain**

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The impact of ERPs in neuroscience was indirectly estimated by assessing the time distribution (papers/year) of reports about P300, MMN, bereitschaftspotential, and CNV quoted in Medline in the 1966-1999 period. Keywords about ERPs and neuropsychological concepts (memory, learning, cognition, mind-body, etc.) were compared over time. Keywords on frequent neurological or psychiatric diseases (stroke, dementia, epilepsy, depression, schizophrenia, etc.) and words of common use were referred to in order to normalize the number of ERPs/neuropsychological reports with respect to that of published papers. Reports on ERPs increased in the 1966-1999 time period proportionally to the number of published papers, with trends that did not differ significantly from those of pathologies or common words. An effect of the Decade of the Brain (1990-1999) on the

number of ERPs papers was observed. Normalization by year confirms this observation, with the exception of the bereitschaftspotential.

**Evaluation of Von Restoff paradigm in early Alzheimer's disease**

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Among a series of words, it has been shown that it is easier to recall those words which differ from the others in some characteristic (so called Von Restorff effect). Such a paradigm could be particularly useful in early dementia, such as Alzheimer's disease (AD), but data are not yet available on this issue. In this preliminary study, 8 patients (3 males, 5 females, mean age 74+6 yrs) with early AD (Mini Mental State Examination score ranging between 20 and 28, mean 24.5+-3.1) and 8 age-matched healthy controls (2 males, 6 females, mean age 73.6+-4 yrs) were presented with 25 lists, composed by 10 common words each. Lists were showed by a computer screen. Randomly, in 19 lists a word between the 4th and the 7th was written in double-size characters ("target" words). At the end of each list, subject was invited to write the words just read. The total number of words recalled was significantly ($p<0.001$) lower in AD patients (49+11) than in controls (90+-18). In controls, the target words were more frequently recalled than each of the others in the range between the 4th and 7th (31% vs 23%, $p<0.05$), whereas in AD patients no significant difference was found (14% vs 12%). The lack of Von Restorff effect in AD could suggest a visuoperceptual deficit of the encoding phase of verbal episodic memory, providing attention is maintained; such an interpretation is supported by the finding of the flash VEPs latencies delay in AD.

**Arousal response and heart rate variation to experimental thermal stimulation during sleep in healthy subjects**

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During wakefulness thermal stimuli may provoke an unpleasant pain experience generating a behavioral or motor withdrawal reaction, and a rapid variation of heart rate (HR). During sleep a few data are reported about the effects of thermal stimuli on macro- and microstructure of sleep and HR variability. We studied the polygraphic response to cool (24°C) and heat pain (46-47°) during sleep in 8 normal subjects (mean age 24.4 years). We applied the stimulation (6-12 s in duration) by a Peltier water-cooled thermal device utilized in quantitative sensory testing procedure. We measured EEG arousals, awakenings (AW) or sleep stage shifts (SSS) during St 2NREM, St 3-4 NREM and St REM, and HR variation 6 s before and after stimulation considering sleep stages and microstructure of sleep (Cyclic Alternating Pattern, CAP). We found that heat stimulation evokes a moderate level of cortical arousal during sleep: 48.3% in St 2NREM, 27.9% in St 3-4 NREM and 31.4 % in REM respect to control stimulation. SSS and AW were not influenced by the thermal stimuli. HR increased (7% in ST 2NREM, 5.4% in St 3-4 NREM and 4.3% in St REM) with a significant higher risk (OR 3.3) to provoke arousal with warm stimuli. Moreover the risk is higher (OR 2.5) during a CAP period with respect to a non-CAP period. We conclude that the processing of nociceptive inputs is attenuated but not suppressed across the sleep stages while autonomic nervous system remain active to preserve our body from potentially dangerous stimulation.