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Parkinson's disease dementia

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Dementia affects about 40% of patients with Parkinson's disease; the incidence of dementia in these patients is up to six times that in healthy people. Clinically, the prototype of dementia in PD is a dysexecutive syndrome. Loss of cholinergic, dopaminergic, and noradrenergic innervation has been suggested to be the underlying neurochemical deficits. Nigral pathology alone is probably not sufficient for the development of dementia. Although there is some controversy with regard to the site and type of pathology involved, dementia is likely to be associated with the spread of pathology to other subcortical nuclei, the limbic system and the cerebral cortex. On the basis of more recent studies, the main pathology seems to be Lewy-body-type degeneration with associated cellular and synaptic loss in cortical and limbic structures. Alzheimer's disease-type pathology is commonly associated with dementia but less predictive. Recent evidence from small studies suggests that cholinesterase inhibitors may be effective in the treatment of dementia associated with PD: most studies reported improvement in cognition and no effect of parkinsonism; in all reports, cholinergic drugs were well tolerated and worsening of psychosis and confusion were rarely observed.

Role of dopamine in working memory

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The cognitive processes involved in working memory and the executive functions are closely linked. Most authors currently agree that executive functions include planning, attentional maintenance, mental flexibility and attentional inhibition. Considering that the role of the central administrator, the main module of the working memory model, is to manage new situations, inhibit old non-pertinent schemes, or carry out attentional control, it is clear that it involves the different executive processes mentioned above. Although the working memory model has its origins in the classic concept of short-term memory, it is now situated at the interface between memory and executive functions. The identification of the neuroanatomical support of these processes has been widely explored for many years. The involvement of monoaminergic neurotransmitter systems, and in particular of the dopaminergic system, in these complex cognitive functions has been suggested by numerous studies, both in humans, non-human primates and rodent studies. In particular the mesocortical DA system increases its activity after cannabinoid administration which are known to hamper cognitive functions and working memory in particular. In addition, our preliminary work in opiate-dependent methadone-treated subjects suggest a negative role for opiate receptors which can be overcome by employing buprenorphine.

Investigation of the initial visual processing (N1) in Parkinson disease: a functional and neuroimaging analysis

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Introduction

The evidence that Parkinson's Disease (PD) impairs cognitive functions spurred the present study aimed at exploring the initial phases of visual processing (N1) in a group of parkinsonian subjects compared to a control group. Moreover, the projection of the main electrical field (dipole) of N1 onto the reconstructed brain image allows for a topographic comparison between the groups.

Methods

Ten untreated PD subjects with reduced basal ganglia dopamine transport were investigated. A second group, comparable for age and education was enrolled for control. The experimental design consisted in the administration of the Stroop test and a list of words in order to investigate the composition of the first wave (N1) generated by these tasks. A 64 channel EEG monitored the tasks (STIM, Neuroscan Inc.USA). The dipole sources were projected in a 3D brain reconstruction derived from a volumetric MRI merged with the electrodes position marked by a commercial 3D digitizer.

Results

Our results show that the N1 component in PD subjects differed from controls in both tasks. In particular, the N1 wave presented a double component in PD, whereas in the control group this element was single. Moreover, the duration of N1 was similar in both controls and PD, when referred to the first N1; the onset was, however, delayed in PD (120 msec in controls, 150 in PD). The second N1 in PD was further delayed and the dipole rendering showed a more posterior location of both N1 waves respect to controls.

Discussion

The modification of N1 in PD compared to controls suggests that PD might influence the strategies of the early component of visual processing. These results confirm a dopamine-mediated role of basal-cortical circuits in spatial attention and, given the similar outcome obtained in two different discrimination tasks, hypothesize a basic and precocious impairment of neural activities playing a role in refining spatial attention in PD.

Evaluation of attention processing by means of blink reflex components (R2-R3) analysis in Parkinson disease

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Previous studies have shown that a reduction in basal ganglia dopamine causes an increase in blink reflex (BR) excitability. So, l-dopa and Dopamine agonists reduce BR abnormalities in Parkinson's disease (PD) patients.

The habituation of R2 component in the blink reflex is reduced in PD patients, and the habituation index has adopted as a clinical parameter to define these patients. Analysis of R3 component is a very important method for studying the aspects of maintaining automatic focused attention, while the R2 component was not found to be modulated. Actually a reduced inhibition of the R3 component after warning in PD denovo patients has been shown (Gabrielli et al Int. J. Psychoph. 44, 83, 2002). This reveals a reduced ability to regulate the set preparing for optimal perceptive performance and motor response during a sustained focused attention task This condition is reversed by administration of l-DOPA.

Alteration of inhibition of R3 component in PD patients may be explained by a defect in the nigro-collicular pathway. Attenuation of R3 component inhibition was independent from the degree of motor impairment. Therefore the deficit of R3 inhibition in denovo PD cannot be attributed only to impaired nigro-collicular modulation of polysynaptic response excitability.

In sustained attention conditions, R3 inhibition could be due to alteration of mesocortical dopaminergic system, which regulate delayed inhibitory phenomena. In PD patients such a system degenerates, causing a frontal dopamine deficiency.

We can conclude that altered allocation of attention in cognitive tasks can be viewed as impairment in attentional processing and as a consequence of a basic deficit in the maintenance function.

So, BR analysis can be used as a suitable technique for studying attention disorders and as a tool in the assessment of PD patient performance on attention tasks.

Damage models and markers

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In physiological conditions sleep propensity is regulated by the interaction between an homeostatic process S with a circadian one C. Process C describes sleep *organisation* within the day (maxima at 23-14, minima at 19), while process S depends on the previous sleep-wake behavior.

It is well known that shift-work modifies the workers normal day, in terms of sleep displacement and curtailment. Qualitatively, most shift-workers experiment “sleepiness” during night-time work. The effects depend on the schedule adopted (duration, rotation direction, rotation speed, regularity). Not only night sleep is associated with “sleepiness”: early awakenings ascribable to the morning shifts can induce “fatigue” feelings as well.

Aim of this study is to quantify the effects of schedules on shift-workers sleep-wake cycle, in three categories (nurses, railwaymen, police officers) adopting different fast rotating schedules. The counter-clockwise rotation determines a phase delay of sleep onset time since the very first working shift of the schedule, bringing about a desincronisation with respect to the light-dark cycle. As the schedule proceeds, this phase is propagated to the following days, reaching its maximum level during the night shift. As the schedule proceeds, every day workers are compelled to anticipate awakening time, causing a significant sleep curtailment. Such a sleep deprivation is associated with prolonged wakefulness, determining a significant sleep pressure accumulation, which in particular is evident during the night shift. The schedules adopted by nurses and railwaymen (on 4 shifts only) allow the sleep-wake cycle realignment with the light-dark one during rest-time. This realignment allows workers to reset their sleep pressure to its initial values. The synchronization is temporally limited to rest-time, as the beginning of a new schedule means the beginning of a new desincronisation. Police officers, adopting the longest schedule, will never reach this realignment, and therefore sleep pressure is continuously accumulated with the rotation.

Damage diagnostic and prevention strategies

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Shift-work disrupts the synchrony between the sleep-wake cycle and the other endogenous biological rhythms, bringing about a temporal displacement between subjective activity and the

social synchronizing stimuli determining sleep propensity levels. Both schedule length and typology (speed and direction of the rotation) may influence workers sleep quality and health. Shift-work can contribute in increasing the importance of those pre-existing sleep disorders that bring about excessive sleepiness and/or in determining their long term stantisation.

The consequences of an awakening level reduction are particularly relevant when shift-work condition is sided with tasks requiring high psycho-physical efficiency or with stressing conditions. The effects of both work-related fatigue and excessive sleepiness interact increasing accident risk on work further.

Chronic effects: excessive sleepiness and sleep disorders

1280 Police officers (611 shift-workers S, 669 non shift-workers NS) filled in a questionnaire. Excessive sleepiness was not different between S and NS. S complain more sleep disorders than NS ($p<0.02$). The global sleep disorder was affected on working seniority, sex and BMI in NS, while only shift-work seniority contributes in increasing the global sleep disorder ($p<0.002$) in S.

Our results show that the importance of the global sleep disorder seems to increase with shift-work seniority and could be the consequences of a shift-work-related perturbation of the sleep-wake cycle.

Car accidents and prevention

Night-work can be dangerous as circadian sleep propensity and prolonged wakefulness contribute towards reducing vigilance levels. As naps are a countermeasure to sleepiness, this study evaluates their role in preventing sleep-related accidents in Italian police drivers. A mathematical model linking number of accidents with S-levels was built. Its generalisation to the theoretical case of drivers omitting naps showed an increase of 48% of accidents. Our data show that napping before evening and night shifts has an efficacy in reducing sleep pressure in shift-workers and accident occurrence.

Psychophysiology: the ontogenetic outline of the neurocognitive potentials. A review.

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This review is a brief analysis of the most significant knowledge acquired in the last 80 years concerning the neuroanatomy and neuro-psychophysiology in humans. The first part traces the history of the important research projects in the field of the classic conditional reflex functions and learning, the so-called "higher nervous activity". In the 25-year period between 1940 and 1965, supported by a general consensus in the scientific and academic worlds and by considerable publicity, the classic "lesional" neurosurgery was transformed into a prevalently "functional" surgery, which attempted, without excessive remorse, to deal with serious pathologies (drug-resistant epilepsies, etc.), including some mental diseases. In the '60s, essentially adopting electrophysiological methods, research began on "event-related" or "neurocognitive" brain activities: CNV; BSP or RP; P300; N400; MMN, etc.. The aims were the attempts to identify and understand the neuroanatomical and neurophysiological substrates involved in cognitive information processing followed by the conception and execution of sensory-motor and behavioural responses evoked by significant sensory stimuli in normal subjects and in pathological situations. In the last years and extraordinarily rapid development of electromagnetic, informatic, functional neuroimaging and multimedial instrumentations have allowed modern psychophysiology to make impressive progress in our knowledge of the morpho-functional organization of the "machine of infinite thought". Very important in this field are also studies of effects of different well identified brain lesions on multiple human cognitive performances. The interpretation of all this findings are in short discussed.

The ontogenesis of consciousness

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Most of present time theories on mind ontogenesis postulate that newborns (Bermúdez 1998; Stern DN 1985, 2004) and even fetuses (Mancia 1989) have "true" perceptual states, i.e they are phenomenally conscious. The consensus about newborn's perceptions is based on experimental evidences which consist of responses to defined patterns of sensory stimuli. This type of inference depends on the pre-experimental idea that newborns behaviour is a reliable mean to infer about their internal states, i.e. it is a reliable substitute of verbal (or explicit) report and, to our knowledge, no systematic discussion of Neural Correlates of Consciousness theories (NCC) applied to developmental conditions has been carried out so far. If the possibility of experiencing a flow of consciousness (the sense of continuity entailed to phenomenal states) depends on the integrated and dynamic functioning of anatomically segregated brain regions (Varela 1997; Tononi 2004), then a theory of mind ontogenesis must account for the development of those functional brain properties which are necessary for consciousness to come about, and shall not rely exclusively on behavioural-type of evidences. Since it is implausible for mind to develop through time in a binary way (from non-conscious to conscious "stages") then it is also implausible that the subjective impression to have (or be identical to) a flow of experiences emerges as an all-or-nothing property: that is to say that the phenomenal property continuity it is likely to arise progressively during development, and this reasonably implies that early phenomenal states (whenever set during development) are characterised by discontinuous windows of presence (Benzoni , 2004).

Unconscious Perception Of Visuo-Spatial Features In Humans: A High-Resolution Eeg Study

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Do visuo-spatial cue stimuli not consciously perceived induce an activation of parieto-occipital cortical areas engaged when the same cue stimuli are consciously perceived? EEG data (128 electrodes) were recorded in 10 subjects. A cue stimulus ("small circle") appeared at the right or left (equal probability) monitor side for a "threshold time" inducing about 50% of correct recognitions. The cue stimulus was followed (2 s) by visual go stimuli ("small circle") located in spatially-congruent or incongruent position with reference to the cue stimuli. The subjects had to click left (right) mouse button if the go stimulus appeared at the left (right) monitor side. After the hand motor response, the subjects had to say "seen" if they had detected the cue stimulus or "not seen" if missed. The reaction time to the go stimuli was shorter during the spatially-congruent than spatially-incongruent "seen" trials, possibly due to covert attention at the cue location. It was also shorter during the spatially-congruent "not seen" than spatially-incongruent "not seen" trials, as an objective effect of the unconscious perception. Visual evoked potentials were mainly generated by a source pattern having similar spatio-temporal features for the "seen" and "not seen" trials. As a unique important difference, a parieto-occipital positive source around +350 ms (P3; Brodmann areas 19 and 7) was significantly stronger in the "seen" than "not seen" trials, as a possible neural correlates of visuo-spatial awareness.

Neuronal Correlates of Cholinergic Enhancement on Cognitive Function: in vivo PET and fMRI Studies in Humans

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The development of non-invasive methodologies for the in vivo functional exploration of the brain, including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), has enabled scientists to investigate the neural mechanisms of cognitive, emotional and behavioral function in physiological and psychopathological conditions in humans. Memory and attention are strictly associated with cholinergic neurotransmission: deterioration of the cholinergic system, as observed in patients with Alzheimer's disease, is followed by a severe impairment of memory and attention and other cognitive function. The main pharmacological strategy employed to slow down the course of dementia in Alzheimer's patients is based on drugs that ameliorate cholinergic system neurotransmission by inhibiting acetylcholine breakdown in the synaptic cleft. To determine the molecular mechanisms of the effects of the cholinergic neurotransmission in the modulation of attention and memory in the human brain, we have conducted a series of PET and fMRI studies to measure regional brain activity during a task of visual working memory (vWM) for faces in young and older healthy individuals. Subjects performed the vWM task under two distinct conditions: while receiving an i.v. infusion of saline solution (placebo condition) or of the acetylcholinesterase inhibitor physostigmine (drug condition). In young individuals, cholinergic enhancement by physostigmine improved WM efficiency and reduced task-related neural activity in right prefrontal cortex (PFC); the degree of behavioral improvement correlated with the magnitude of reduction in PFC activity. In addition, behavioral improvement was correlated with changes in neural activity in many cortical regions involved in WM performance, including visual cortical areas. This suggested that the reduced PFC activity might be an indirect effect due to the enhancement of information processing in visual cortical areas, as subsequently supported also by the results of a separate fMRI study (Furey, Pietrini, Haxby, *Science*, 2000). Elderly individuals showed a recruitment of distinct PFC areas than young subjects during vWM, likely as a consequence of a compensatory cortical functional reorganization. Interestingly, while cholinergic enhancement improved performance similarly in young and older subjects, effects on neural activity were exerted selectively on those task-related PFC regions that were distinctively recruited prior to drug administration by the two age-groups. Thus, the effects of cholinergic modulation are not exerted on structurally-defined PFC regions but rather on functionally-recruited PFC. Altogether, the results of our studies indicate that pharmacological potentiation of the cholinergic neurotransmission improves performance on a visual working memory task by enhancing neuronal processing in task-related cortical areas, such as visual extrastriate cortex, and that this, in turn, reduces the need to recruit those PFC areas that are selectively and distinctively activated in young and older subjects.

Degenerative dementia: does the genotype-phenotype correlation exist?

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Alzheimer's disease research has been the prototype of the genotype-phenotype correlation studies. Three major genes causing the disease were identified: the Amyloid Precursor Protein (APP, Goate et al.1991) and the two presenilines (PS1, Sherrington et al. 1995; PS2, Rogaev et al. 1995).

Although some differences were noted earlier in the clinical picture the main idea was that any given mutated gene corresponded to “its” clinical picture. Nevertheless, the identification of a high number of mutations in these genes leading to different phenotypes (unusual AD features or in some cases apparently different diseases) introduced the doubt about the genotypic-phenotypic correspondence.

The different expression of a disease depends by the combined presence of pathogenic mutations and an unknown number of genetic modifiers and/or innocent polymorphisms. DNA is translated in proteins and the complexities shift from the genomic to proteomic level.

In degenerative dementias there is a marked overlapping of pathological proteins; in AD tau and amyloid are represented in the affected brains but sometimes also alpha synuclein is seen; alpha synuclein that is the main component of Lewy bodies, the histopathological marker of Parkinson’s disease. Moreover, tau protein resulted to be abnormal not only when map gene is mutated as it occurs in FTDP-17 linked, but also in other rare diseases such as Corticobasal Ganglia degeneration (CBD) and Progressive Supranuclear Palsy (PSP). The above scenario might suggest a common pathogenetic substrate, a common framework for all kind of degenerative diseases (Hardy et al. 2001). In such scenario, genes and proteins interact and cross to each other raising different diseases and phenotypes. In this direction the advancement of the knowledge in one of these degenerative diseases will contribute to the advancement of the knowledge for the others. It is necessary then to entirely disentangle the biochemical pathways before unravelling genotype-phenotype relationships.

Functional Imaging Of Dementia

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Brain imaging is the dominant technology for a quantitative assessment of structural changes associated with development of dementia but since they occur late in the course of the disease, functional imaging modalities have greater potential in identifying dysfunction of neural circuitry that cause cognitive impairment. Both cerebral SPECT and PET demonstrated that patients with Alzheimer disease (AD) have a relative paucity of activity in the temporoparietal regions and the magnitude of this abnormality correlates with the severity of cognitive impairment. Moreover, this abnormal pattern was observed demonstrated also in asymptomatic at-risk populations, with a prognostic value for predicting dementia. Although not used in the routine work-up, functional magnetic resonance imaging (fMRI) offers considerable potential in identification prodromal dementia. fMRI activation patterns have shown in controls two groups of structures involved in working memory, secondary memory, and recall in the prefrontal cortex and the medial temporal lobe. Several recent fMRI investigations have shown diminished intensity and/or extent of activation in the frontal and temporal regions in patients with early AD. These activation discrepancies may depend on either dissimilar task demands or different levels of compensatory reserve. High definition EEG alpha and beta rhythms reactivity during simple motor task have shown that mild AD, in absence of any motor deficit, recruit a larger and bilateral neuronal networks to sustain a finger extension. Recently, transcranial magnetic stimulation was also utilized in AD patients, and demonstrated increased motor cortex excitability together with a shift a frontal and medial in the site of maximal excitability. These findings were hypothesized to be secondary to abnormal intracortical excitatory circuits and suggest a functional reorganization of cerebral cortex which would allows a preservation of motor function during the clinical course. With these premises, the future application of functional imaging will probably include early or preclinical detection of dementia.

Clinical and Genetic-molecular Aspects of Neurodegenerative Dementia in North Sardinia

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Background. In clinical and neuro-pathological terms, dementias are heterogeneous pathologies and every cognitive environment may be involved in the degenerative process. At present clinical symptoms are the only diagnostic indicators, and thus identification of the specific cognitive and behavioural profiles play a crucial role in differentiated diagnosis.

Methods. Degenerative Dementia has been systematically studied in Sardinia since 1998: at present the case study consists of 267 patients, 68 male and 199 female, with an average age at onset of the diseases of 67.9 DS 10.1. In this work particular attention has been paid to the clinical signs of the onset of different kinds of degenerative dementia and to analysing the data for APO-E polymorphism, which is, according to the literature, the major genetic risk factor both because of its type and its precocious onset and later for AD.

Results. The most frequents symptoms of the start of the disease seem to characterise the different types of dementia: mnemonic disturbances dominate during the onset of AD, while depressive-psychotic behavioural disturbances are more marked in the pattern of the onset of Front-Temporal Dementia and Lewy Body Dementia. Linguistic deficits, however, are encountered in all degenerative dementia.

The APO-E polymorphism of 184 Sardinian patients was compared with 582 healthy controls of the same ethnic origin. Statistical analysis probably confirms that the e4 allele is more common in AD patients than in the control group (chi-square=41.3, $p < 0.0001$) even though it does not seem to be associated with Late Onset AD (LOAD).

Conclusions. The results thus seem to confirm the preliminary data from 1998, demonstrating in a larger number of cases that e4 allele plays a significant role in the pathogenesis of these diseases in the Sardinian population.

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The needs of psychophysicologists for data analysis.

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Cognitive potentials are very useful and fascinating because they allow to explore in a non-invasive way the higher order cognitive functions, that determine the development of human behaviour and thoughts. The study of such phenomena is currently limited by several factors, such as the presence of artefacts on the recordings, the low signal-to-noise ratio and the marked inter- and intra-individual variability of the potentials. These troubles are intrinsic to biological systems and above all to the ones involved in cognitive processes: they can be faced by applying mathematical approaches.

Learning is one of the most interesting cognitive processes: it consists in behavioural changes due to increasing experience and to variable environment. Therefore, the main need of psychophysicologists is to monitor the neurophysiological modifications produced by learning and adaptation as time passes. This problem can find a solution in the extraction of the single-trial event-related response: in fact the temporal resolution of traditional averaging is inadequate to these aims. On this matter, several approaches have been proposed, but no really convincing solution has

yet been found, particularly for cognitive potentials that are characterized by low signal-to-noise ratio and high morphological variability.

The extraction of the single event-related response generates a huge amount of data to be analysed: therefore, the peaks and troughs cannot be manually identified and it is necessary to make automatic this measuring. The manual quantification of event-related potentials continues to be the gold standard reference for evaluating the efficacy of automatic methods and it is surely hard to replace with a mathematical model the competency to judge of an experimenter trained by years of clinical practice. Furthermore, the identification of peaks and troughs is often doubtful because the marked variability of cognitive middle- and long-latency components can produce different views even in skilled experimenters: therefore, the employment of mathematical approaches is important not only to reduce the analysis time but also to make univocal and more reliable the analysis results. On this matter, a non-linear alignment method can be applied to reduce the temporal differences between the corresponding peaks and troughs of different signals in order to compare them more easily. Finally, it is helpful to shape the alignment on the frequency content and temporal occurrence of the several event-related components: therefore, the alignment can be applied after a time-frequency decomposition realized by wavelets theory. It can be said that the more complex are the systems under study, the less predictable the signals they produce and therefore the more effective is the clever use of analysis methods and mathematical models.

Computation of templates for reading-related potentials by means of *Wavelet Decomposition* and *Dynamic Time Warping*

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The problem of obtaining a reference signal for RRP during reading tasks is here addressed. The classical procedure based on the calculation of grand-averages on a group of subjects, is strongly affected by the high inter-subject variability that becomes especially relevant when dealing with long-latency waves related to the cognitive functions. A Dynamic Time Warping procedure is applied to pairs of signals after a time-scale decomposition through wavelet transform.

The RRP used for this analysis were recorded from 16 normal children of mean age 9.6 ± 0.08 yrs. The subjects underwent three different tasks: symbol presentation, letter presentation and letter recognition.

The RRP related to each subject is decomposed in seven details and one approximation, filtering the signal through a high-pass and a low-pass filter. The analysis results in a set of wavelet coefficients, which indicate how close the signal is to a particular basis function in different time intervals and in different frequency scales. Short-latency waves are characterized by high frequencies, while long-latency waves are characterized by low frequencies and are then separated into different wavelet details, at different scales. As the decomposition level increases the number of wavelet coefficients decreases and the procedure can be iterated until the last meaningful signal.

The meaningful peaks are located in a limited window, whose dimension increases at the coarser scales. Therefore each signal is windowed before the alignment, obtaining 18 samples, 9 pre-stimulus and 9 post-stimulus. The details and the last approximation are then aligned according to a binary tree on the whole set of 16 normal subjects and a signal template is obtained that represents the examined population. Five characteristic peaks were identified on the templates: N₁, around 150 ms, related to attention; P₂, around 300 ms, traditionally linked to cognitive processes; N₃ and N₄, between 400 and 500 Hz, likely related to association graphema-phonema during reading and P₆₀₀ probably related to feed-back processes. The multi-scale decomposition of the signal permits to optimize the time warping procedure to the different temporal dynamics of the analyzed components and then to reconstruct a more reliable template. The proposed method provides a tool

for the evaluation of RRP during cognitive tasks and for a better comparison among subjects and between groups.

Single sweep analysis of reading-related potentials

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The neurophysiological signals recorded during the execution of cognitive tasks likely change by learning and adaptation. Considering psychophysiological studies, the quantification and characterization of such modifications would be very useful to better understand the changes occurring in the processing strategies of the nervous system as time passes in different conditions. This work proposes a method for the extraction of the single event-related response: this method has been specifically applied to reading-related potentials recorded during visual presentation and reading aloud of Italian alphabetic letters. This approach is based on autoregressive models with exogenous input (ARX): each recording is modelled as the sum of raw EEG and single event-related potential. EEG is obtained as the outcome of an AR model fed by a white noise. The single potential derives from filtering the traditional average with an autoregressive moving average model (ARMA). The identification of the model parameters is obtained by minimizing the prediction error with the least squared method. The choice of model orders is one of the most critical steps of the analysis and several possible solutions have been explored. At the beginning we tried to apply models with the same complexity to all the recordings. This approach is efficient and computationally worthwhile, but its efficacy is limited to the potentials characterized by a simple morphology and with an amplitude quite higher than the background signal. Reading-related cognitive potentials have a poor signal-to-noise ratio, involve middle-and long-latency components and are affected by a marked morphological variability. Therefore, it is necessary to consider different model orders for each recording in order to produce reasonable results. The effects of different rules for choosing model orders were compared using both simulated and real data, in order to identify an optimum criterion. Finally, the method performances as a function of the signal-to noise-ratio were evaluated to clearly investigate the potentialities and the limits of single sweep extraction by means of ARX.

Individual Differences In Emotional Information Processing: Psychophysiological Aspects

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In recent years, there has been increased interest in neurophysiological mechanisms underlying the interaction between cognition and emotion. In particular, a growing body of psychophysiological research has concerned with the question of how attention is influenced with emotion. In the present report will be reviewed results from two experiments, inspired by Jeffrey A. Gray's temperamental model (Gray, 1982; Gray & McNaughton, 2000), demonstrating that attentional, affective, and physiological components are part of a complex neurophysiological self-regulated system that serves to integrate these functions. In the first study, we examined P3 peak of the event-related potentials (ERPs) and heart rate (HR) responses in anxious and impulsive subjects who performed on a visual oddball task with emotional target words. Frontal and temporal P3 amplitudes, HR slowing, and emotional ratings were more pronounced in anxious subjects when they processed unpleasant target words. In contrast to predictions, the processing of pleasant words did not discriminate between impulsive subjects and controls. Anxious subjects also displayed higher emotional ratings and more pronounced HR decelerations to unpleasant targets. Impulsive subjects,

compared to controls, showed smaller P3 peaks for negative valenced words mainly over parietal and occipital cortical regions and longer P3 latencies across all recording sites. The expected amplification of the response to negative emotion in anxious subjects was confirmed, but the corresponding prediction for impulsiveness and positive emotion was not supported by Gray's theory. In the second study, we examined the MMN while subjects were reading, or watching emotionally negative, positive, and neutral pictures. Participants were assigned to either a 'low' or 'high' group in Sensitivity to Punishment (SP- or SP+) and in Sensitivity to Reward (SR- or SR+), according to their scores on the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ; Torrubia et al., 2001). The MMN (at Fz and Cz sites), was stronger in SP+ subjects when they looked at negative pictures as compared to positive and neutral ones, but this effect was stronger in SP+/SR- participants. SR- participants displayed an enhanced MMN peak in the presence of negative slides compared to positive, reading, and neutral slides. The present results are discussed in the light of a recent hypothesis ('joint subsystem hypothesis') that Corr (2002) derived from Gray's theory. This hypothesis assumes that both the behavioral inhibition system (BIS) and the behavioral activation system (BAS) have the potential to influence both punishment-mediated and reward-mediated behaviors.

Emotional correlates of trait-anger

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The investigation of violent and aggressive behaviors is almost exclusively confined to psychopathology, or to sociopaths, ADHD and traumatized patients. A limitation in this line of research is collapsing together patients with very different characteristics, on the basis of the deficit in impulse control they share. Aggressive-impulsive individuals in the above mentioned nosographic categories often show paradoxical reduction in autonomic activation. On the other hand, emotional subjective report can vary markedly, from affective apathy to enhanced anger or frustration. Autonomic hyporeactivity seems to be related to right hemisphere dysfunctioning (Raine et al., 2001; Angrilli et al., 1999) and changes in the usual pattern of the event-related potentials (ERPs) (Houston & Stanford, 2001). Overall, empirical findings converge on two elements: impulsive-aggressive individuals show a) abnormal information processing, leading to inadequate understanding and regulation of their emotional states and activation levels; b) low peripheral activation, particularly during unpleasant situations.

In the present study 40 students have been selected based on their scores in trait anger on the STAXI-1 (Spielberger, 1991). Twenty subjects have been thus selected for each of two groups, high vs. low trait anger, scoring above the 75^o and below the 25^o of sample distribution, respectively. Participants viewed 72 standardized emotional pictures selected from the International Affective Picture System (Center for the Study of Emotion and Attention, 1999). The following physiological measures have been measured: heart rate (HR), skin conductance response (SCR), and ERPs. High anger individuals showed reduced SCRs associated with enhanced N100, but reduced Low positive complex in the ERPs. In line with the literature on impulsive subjects, also high trait-anger individuals show dysfunctional emotional information processing associated with low arousal levels.

Emotional information processing in blood phobia

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Blood phobics (BP) show an autonomic response pattern characterized by initial increase in heart rate (HR) and blood pressure followed by an abrupt drop in both measures (Öst et al., 1984). This response pattern can lead to vasovagal syncope (Graham et al., 1961) and is possibly related to physiological and psychological conflict between action and inhibition (Engel, 1978).

Surprisingly, the investigation of the electrocortical activity during the processing of fear-relevant stimuli in BP has received little attention.

The present study investigated the emotional processing of phobic stimuli in BP by means of event-related potentials (ERPs). Twenty-three BP and 26 controls, all females, were shown seventy-two pictures taken from the International Affective Picture System (IAPS, Center for the Study of Emotion and Attention, 1999), depicting unpleasant (mutilations and threat), pleasant (erotic couples and sport/adventure) and neutral (household objects and neutral people) contents. The ERPs to picture onset were recorded. Moreover, the magnitude of the startle blink elicited during picture viewing was assessed in order to probe the motivational organization of the phobic response. Skin conductance response (SCR) and HR were recorded as autonomic measures of the fear response pattern. Viewing time (VT) and subjective ratings of pleasantness, arousal and dominance were also collected.

In both controls and BP, mutilations engaged a larger amount of attentional resources than threat, as indicated by larger ERPs positivity, larger SCR, and reduced potentiation of startle blink amplitude. Relative to controls, BP showed significantly reduced cardiac deceleration and shorter VT to mutilations. Also, they rated mutilations as more unpleasant and arousing and reported lower dominance. In BP, enhanced processing of blood-related stimuli as compared with other unpleasant contents is accompanied by a defense response, as evidenced by reduced HR slowing, possibly indicating concurrent and conflicting activation of opposite action tendencies.

Diagnostic Difficulties On “Trasversal” Diseases

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The author underlines the problem of clinical difficulties on diagnostic approach to out patients with a psychiatric and neurological disease in comorbidity.

The author, besides, underlines the practical difficulty both on psycho-neuro-pharmacologic and relational aspects.

Countertransferral troubles related to the management of patients with “trasversal” diseases between psychiatry and neurology are illustrated.

Further, particularly importance is attributed to the doctor professional background and a good equipe work.

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Cognitive dysfunction in Multiple Sclerosis

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For several decades, clinicians have rarely performed accurate assessments of neuropsychological deficits in multiple sclerosis (MS) patients. Only during the past 20 years have they become aware of the prevalence of MS-related cognitive impairment and its profound functional impact. Approaches to clinical management are in their infancy, however. The first unresolved issue is assessment of cognitive function. Routine neurological examination and mental-state assessment

will not detect cognitive dysfunction in the majority of MS patients, hence the need for sensitive, cost-effective and reliable screening procedures that can be applied in everyday clinical practice.

Cognitive dysfunction, as with other symptoms of MS, is highly variable - estimates of its frequency range from 43% to 72%. Severe dementia is observed in 20–30% of cognitively impaired MS patients. The domains of cognitive function most commonly impaired are episodic memory, attention/concentration, processing speed, and verbal fluency. Domains often compromised are executive functions such as concept formation, abstract reasoning, planning, monitoring and visual perception. Language, semantic memory and attention span are less frequently involved.

Cognitive dysfunction can have a dramatic impact on several aspects of quality of life, and independently on degree of physical disability. Cognitive impairment significantly affects the ability to maintain employment, and cognitively impaired patients require greater assistance with daily living activities and are less likely to socialize than cognitively intact MS patients. The capacity of a patient to benefit from inpatient rehabilitation can also be limited by cognitive impairment.

Few authors have studied the natural history of cognitive dysfunction in MS patients. In a 3-year follow-up study, incipient cognitive decline seemed to be widespread and progressive, while in another study, the percentage of patients with cognitive impairment increased from 26% to 56% over a 10-year follow-up period, and the profile of cognitive deficits tended to expand.

The frequency of cognitive dysfunction in MS, and its severity and impact on everyday functioning, leads to increasing consensus that NP assessment should accompany the neurological examination and become a factor in therapeutic decision-making.

Multiple Sclerosis and psychophysiology of fatigue

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Fatigue is a common symptom in MS, being referred by about one third of the patients. For many of them it is the most disabling symptom, with negative consequences on the working activity and daily life. There are no objective measures of fatigue which is essentially assessed based on subjective complaints. Even if fatigue may be influenced by motor disturbances and depression it is largely independent from both. Also peripheral mechanisms, like muscular disuse and deconditioning, joint abnormalities, metabolic changes of muscular fibres, have very little role in MS fatigue. All the available data indicate that fatigue is a “central” phenomenon, due to multiple causes. Neurophysiological studies revealed an impairment of volitional drive to the descending motor pathways and functional imaging studies found a selective involvement of frontal cortex and basal ganglia. Therefore, a dysfunction of the circuits involving thalamus, basal ganglia and frontal cortex, affected by the MS lesions and/or disturbed in their function by the products of inflammation could be the substrate of fatigue in patients with no evident motor impairment.

Multiple Sclerosis: cortical or subcortical dementia?

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Cognitive function is impaired in about 50% of MS patients. The pattern of mental dysfunction is considered as typical of subcortical dementia, explained by the disconnection of large proportions of cortical associative areas. Both advanced analysis of the electroencephalogram (EEG) and Event-

Related Potentials (ERPs) may provide information on the pattern of cognitive impairment in MS. Spectral analysis of the EEG revealed abnormalities in 40-79% of MS patients, mainly increased of slow frequency and decrease of alpha band, which are related to cognitive dysfunctions. However, the sensitivity of these EEG parameters is unsatisfactory to allow a clinical utilization of the techniques. EEG coherence, a measure of functional cortico-cortical connectivity, has been reported to be correlated with white matter involvement and to be reduced in MS patients with cognitive impairment. P300, an indicator of information processing speed, which is electively affected in MS, has been found delayed in MS patients. This increase is correlated with cognitive impairment and with the degree of white matter involvement. Again, this test allows the separation of groups of MS patients with and without cognitive involvement, but not to classify single patients. ERPs to more sophisticated tasks than the traditional oddball paradigm may increase their diagnostic value. Simple and complex reaction times provide a parametric measure of speed of sensory-motor and cognitive processing, and revealed abnormalities in MS patients related to neuropsychological impairment. Finally, functional MRI provided evidence of cortical reorganization in the sensorimotor system even in patients at the initial stages of the disease, with scarce evidence of brain tissue damage.

Quality of life in MS patients

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Assessing and improving quality of life (QoL) is crucial in managing patients with chronic disorders. When assessing QoL some fundamental domains are measured, such as the subjective perception of one's health status, disease severity, familial, social and occupational entourage, the cognitive and the psychic status.

In multiple sclerosis (MS) widely validated scales are used to evaluate QoL. Nevertheless, the reductionistic essence of such scales prevents from an accurate assessment of QoL, which is in fact influenced by multiple factors whose evaluation is complex and difficult. The following are the most frequently encountered issues: (1) the use of self reporting scales may bias veraciousness and (2) may not allow a correct comprehension of the battery items in cognitively impaired patients; (3) in patients with depression, MS versus depression-related symptoms, eg., fatigue, weakness, are often indistinguishable such scales; (4) factors such as territory and health care sources, comorbidity, care givers' contribute and the possibility to obtain support are often overlooked despite their significant influence on QoL.

A correct evaluation of QoL must take into account (1) the possibility to verify items comprehension and response veraciousness, (2) the possibility to distinguish between MS-related versus more psychiatric symptoms, (3) an increase in the number of assessment scales focussed on more variables. Although, administering more detailed scales requires a longer time for administration, the analysis of all variables on QoL is so informative, that it is evidently in contrast with the reductionistic scales currently available.

Clinical experience suggests that a patient is willing to provide information about his/her life only when he is given the possibility to share and analyse these issues with a trusting and skilled care provider. Therefore, it is crucial that the patient be given an appropriate feedback on the data collected, and – provided consent - the possibility to involve the patient's general practitioner, family, the territory volunteering associations and other health care providers so as to establish measures finalised at improving the QoL.

Pitfalls and limitations are mostly represented by the great efforts and time that such assesment approach requires so as to yield to a proper evaluation. However, we believe that QoL must not barely represent a topic for research, but rather the ultimate goal to achieve for its significant psycho-physical impact on the disease.

The Transcranial Magnetic Stimulation As A New Research Tool In Psychophysiology Of Sleep

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Due to a low time resolution and to the specific procedures for data acquisition, the brain imaging measures cannot be extensively used in sleep research. Transcranial magnetic stimulation (TMS) is now an established technique in neurosciences allowing the non-invasive assessment of motor cortical excitability, but its systematic application to sleep has been limited by the fact that delivering a single suprathreshold magnetic stimulus awakens subjects, or lightens their sleep. Furthermore, the acquisition of multiple responses to magnetic pulses to record motor evoked potentials (MEPs), reflecting brain excitability, seems incompatible with the intrinsic peculiarities of sleep. Since several findings support the feasibility of the assessment upon awakening from different sleep stages to compare their pre-awakening cortical physiology, we have used TMS in three different protocols: 1. Motor thresholds (MTs) to assess corticospinal excitability upon REM and NREM awakenings; 2. Cortico-cortical paired pulses to assess intracortical facilitation and inhibition upon REM and SWS awakenings; 3. Inter-hemispheric paired pulses to assess callosal inhibition upon REM and NREM sleep awakenings.

The main findings are:

- (a) an increase of MTs upon REM sleep awakenings reflecting the brainstem inhibitory effect on spinal motoneurons [Bertini et al., *J Sleep Res* 13:31-6, 2004];
- (b) a heightened cortical facilitation upon awakening from REM sleep than to SWS and wakefulness [De Gennaro et al. *Eur J Neurosci* 19:3099-104, 2004];
- (c) a drop of callosal inhibition upon awakening from REM sleep [Bertini et al. *Sleep* 27:875-82, 2004].

The coherent pattern of empirical results encourages the psychophysiological study of the corticospinal organization in different sleep stages by means of the TMS protocols upon awakenings from different sleep stages, legitimating the introduction of this technique as a new tool for sleep research.

A Human Visual System Model For No-Reference Digital Video Quality Estimation

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Objectives: Digital video broadcasting, video-telephony and video-streaming services should achieve satisfactory visual quality in almost all operating conditions. In-service quality monitoring is essential in order to improve perceptual quality according to Human Visual System (HVS). While MPEG-1,2,4 and H.26x digital compression standards are based on Discrete Cosine Transform (DCT), novel standards (JPEG 2000, H.264) use different encoding methods. Blockiness distortion affects DCT-block-based coding systems. Wavelets-based encoders bring blurring/ringing distortion impairments. Several distortion effects in video-streaming/playback systems are included within *moving artifacts* distortion. Quality measurement becomes very difficult because it must include several distortion artifacts and their effect on human perceived quality. Subjective measures estimate visual quality by subjective tests. Objective methods estimate distortion level using spatial/frequency-domain operations. No-reference measurements, directly derived from received video sequences, are difficult to implement and often present low accuracy levels. Thus, methods based on HVS models should be implemented in order to increase accuracy.

Methods: The proposed method consists in a pre-processing step, on received video, that takes into account HVS Luminance Masking, based on Weber-Fechner-Stevens's laws and Contrast Sensitivity Function (CSF), approximated by a frequency-domain model. A temporal masking

model is also included. Video distortion level is then computed using blind blockiness and blurring metrics that have been modified in order to implement the HVS temporal integration effect. A novel no-reference *moving artifacts* measure is also used. Finally, a single quality index is obtained using pooling algorithms (block, temporal-window, frame, and sequence levels).

Results: Video sequences coded with different standard at several compression ratios have been used. A non-linear regression method has been derived, in order to obtain the greatest linear and rank-order correlation factors between human observer ratings and the proposed index. Validation tests have been developed to assess index performance and computational complexity.

Conclusions: Results show that, using HVS models, high correlation factors can be achieved between subjective and objective evaluations.

Quality Assessment Of Compressed Medical Images Based On Human Visual System

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Objectives: Several medical devices, *e.g.* X-ray scanners, CT, MR, PET, Ultrasound, DIC, confocal microscopes, make extensive use of numerical data for diagnosis, storage and transmission. The problems related to these tasks are mainly concerned with data size, which may vary from few MBs to several hundreds of MBs. Then, image compression plays an essential role in minimizing and organizing data into scalable streams. Since lossless compression is generally unable to achieve high compression rates, lossy compression may be compulsory in transmission-critical applications. However, lossy coding is often unacceptable, since it inevitably introduces artifacts that might undermine the significance of medical data. Under certain conditions, recent coding algorithms provide *near-lossless* quality and may be fit for medical imaging. However, in order to assess their validity, a specific quality metric is required. It is very important to properly rate compressed medical images according to human perceived quality and clinical analysis capabilities. Thus, methods based on HVS models should be implemented.

Methods: Blockiness, Blurring and Ringing are the most frequent distortion effects introduced by lossy compression encoders. The proposed method consists in a pre-processing phase, applied to original and compressed images, including an effective HVS model. It includes the Luminance Masking effect, based on Weber-Fechner-Stevens's laws and the Contrast Sensitivity Function (CSF), approximated by a frequency-domain model. Blockiness, Blurring and Ringing measures are obtained from the pre-processed data. Finally, a global quality index is computed using a pooling algorithm.

Results: Medical images coded with different techniques at several compression ratios have been used. A non-linear regression method has been derived, in order to obtain the greatest linear and rank-order correlation factors between human observer ratings (in terms of diagnostic accuracy) and the proposed HVS-based index. Validation tests have been developed to assess index performance and computational complexity.

Conclusions: The proposed HVS-based quality metric allows for a proper evaluation of compressed medical images and results show that it is representative of medical images perceived quality.

Decrease of inter-hemispheric functional connectivity between auditory cortices during dichotic listening: an EEG coherence study

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During dichotic listening (DL) of complex tone pairs having near fundamental frequencies (competing tones), subjects mainly perceive tones presented to left ear. This effect might be due to a different pattern of activity in the auditory areas of the two hemispheres. As a logical consequence, we hypothesized that functional connectivity between these areas decreases during DL of competing than non-competing tones. To this aim, a randomized series of dichotic and monotic tone pairs was presented to 15 healthy right-handed subjects during electroencephalographic (EEG) recordings. Stimuli were composed by complex tones having near (261 and 293 Hz, competing tones) or distant (261 and 391 Hz, non-competing tones) fundamental frequencies. Inter-hemispheric functional connectivity was evaluated by the analysis of spectral coherence of EEG data recorded over right and left auditory cortices. Frequency bands of interest for the spectral analysis were delta (1-3 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-30 Hz), and gamma (31-42 Hz). Results showed that inter-hemispherical EEG coherence did not differ between monotic competing and non-competing stimuli. In contrast, inter-hemispherical EEG coherence was significantly lower during DL of competing than non-competing tone pairs. This was true at all bands of interest. These results confirm the working hypothesis that inter-hemispheric functional connectivity between the two auditory areas is reduced during DL of competing complex tones.

The ALTEA project and the ALTEA-mice experiment at GSI: preliminary data and project perspectives

Sannita WG and the ALTEA team

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The ALTEA-MICE project investigates the effects of heavy ions on the visual system of normal and mutant mice with retinal defects in order to define reliable experimental conditions for space research and develop animal models for the study of physiological consequences in man of space travels. Remotely controlled mouse set-up, applied electrophysiological recording methods, remote particle monitoring, and experimental procedures were developed and tested. The project has proved feasible under laboratory-controlled conditions comparable to those of astronauts in space. Experiments are performed at the Brookhaven National Laboratories and the Gesellschaft für Schwerionenforschung. Electrophysiological changes exceeding the limits of spontaneous variability under anaesthesia and time-related to pulsed ¹²C have been identified in the absence of evident retinal damage. The mechanisms of these effects can be only postulated and the relevance of high-energy particle effects on the CNS as a potential (functional) risk in space requires further investigation.

Dynamic noise and visual stimuli with cognitive content: a neuromagnetic experiment of stochastic resonance in human vision.

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Meaningful words embedded in dynamic noise and presented visually to human volunteers in a “threshold stochastic resonance” [threshold-SR model] stimulus paradigm evoke cortical brain responses. The source equivalents identified by neuromagnetic methods (306-channel MEG system, Elekta Neuromag) indicate sequential activation of the primary and associative visual cortex and of cortical areas involved in language processing. The topography of identified dipoles was common to all subjects, with the dipole latency/amplitude measures fitting the contrast-to-

noise function of the word+noise threshold-SR stimuli regardless of activated cortical sites. This observation suggests that the "threshold-SR" stimulus function can be transferred across activated brain structures dedicated to visual and language processing, with the conceivable involvement of basic neuronal mechanisms.

Psychological And Psychophysiological Aspects Of Pain: Clinical Study In Normal-Weight And Overweight Patients With Neuropathic And Osteoarticular Pain.

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Objectives: Aim of this study was to compare psychological characteristics and differences in thermal threshold (thermal sensitivity and thermal pain) in patients affected by neuropathic pain (NP) and chronic osteoarticular pain (COP), obese and normal-weight.

Materials and Methods: 49 subjects (mean age 45.8 years), 19 of them complaining pain (5 NP, 8 COP obese, 6 COP normal-weight subjects and 30 controls (20 obese and 10 normal-weight), underwent to a battery of psychometrical tests (MMPI-2, CBA-2.0, McGill Pain Questionnaire and SF-36) and an informatised analysis of thermal sensation and thermal pain thresholds (MEDOC T.S.A.).

Results: COP obese subjects showed worse psychological characteristics compared with NP subjects, COP normal-weight subjects and obese subjects without symptoms of pain. In particular COP obese patients showed statistically significant ($P<0.05$) higher (pathological) scores in FAM (familiar diseases) and WRK (working problems) Scales of MMPI-2 compared with NP subjects. COP obese subjects also showed statistically significant ($P<0.01$) higher threshold values in perception of warm sensation on lower limbs compared with controls, and a trend toward higher warm and cold thresholds (both sensitivity and pain) at both face and limbs compared with NP subjects. Differences found in distribution of correlational scores between psychometrical results and thermal thresholds values furthermore distinguish our groups of patients.

Conclusions: Our study showed that evaluation of pain can be influenced by a great number of variables related to and specific of the main and the possible concomitant pathology and can condition different aspects of patients' quality of life. A psycho-physiological variable like thermal sensory and thermal pain threshold can assume characteristics of complex perception, because its relationship to some psychological aspects. Furthermore, our data confirm the psychological impact of pain and the physical impairment due to pain itself on affective aspects, especially for those with a pre-existing psycho-pathology.

EEG spectral analysis in normal aging and Mild Alzheimer's Disease

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Quantitative analysis of electroencephalographic (EEG) rhythms provides more information than visual inspection. This type of analysis includes the estimation of the power density of the EEG frequency bands selected. Moreover the EEG evaluation in the elderly subjects provides interesting suggestions about the widespread problem of the successful aging.

Compared to healthy subjects, Alzheimer's disease (AD) patients remark specific changes in the EEG patterns, which are the increasing of the delta power (0.5-4 Hz) and theta power (4-8 Hz), and the decreasing of the alpha power (8-13 Hz) (Giaquinto S et al 1986; Moretti DV et al 2004).

One of the most important outcomes of the quantitative analysis EEG is the identification of different sub-bands through the range of traditional frequency bands, which subserve different cognitive functions (Klimesch W et al 1999).

The EEG has been recorded in 5 elderly healthy subjects (65-74 years) and 1 Mild AD patient (52 years).

The aim of this study is to describe and evaluate minutely the EEG variation in different resting condition.

Subjects have been undergone for 5 minutes of EEG recording at rest with eyes closed (REC) and with eyes open (REO). This process has been carried out twice spending 20 minutes of EEG recordings.

According to the 10/20 system with linked-earlobes reference, the EEG data have been acquired (0.3-70 Hz bandpass) on a computer-based system (Micromed BQ3200 ACQ/DV) from 8 electrode locations. All data have been digitized in continuous recording mode (256 Hz sampling rate). Frequency analysis has been performed using a Fast Fourier Transform (FFT) algorithm on a computer-based system (Micromed BQ3200REV/DV). The EEG variable chosen is the Relative Power in contiguous 1 Hz bandwidths in the range 0.5-13.5 Hz for 4 EEG channels (C3, C4, O1, O2).

It has been analysed through EEG Power Spectra, the difference between REO and REC.

The introduction of frequency bands with step of 1 Hz could provide much more information about the EEG power bands and it could better characterize the psychophysiological condition of subject at the moment of the recording.

Language Disturbances In Subjects With Agenesis Of The Corpus Callosum

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There has been an increasing interest on the connections between higher cognitive functions and corpus callosum. Among the others, language abilities have been studied in relation to acquired damage to the corpus callosum, such as in closed head trauma or chirurgical sections of the callosum, and to its congenital absence (ACC).

We wanted to explore how language functions develop in individuals with Agenesis of Corpus Callosum (ACC), either complete or partial. A thorough clinical assessment of the language abilities (repetition, comprehension and production), at all the main linguistic levels (phonology, semantic and syntax) was run by means of standardised tests.

The sample has been selected from a clinical population of more than 50 patients referring to a Northern Italian Hospital (I.R.C.C.S. Medea), and it is formed by 8 individuals with normal PIQ and no other CNS associated malformations, ranging from 4 to 24 years of age, 4 of them with partial ACC, mainly in its posterior parts, and 4 with complete ACC. Each subject's performance was matched to controls of the same age and handedness and with no language impairment or academic difficulties. Results show that more than half the sample has some Language Impairments. A patient whose language performance is currently within normal range, was, in fact, administered repeated language rehabilitation sessions while younger. Difficulties in lexical access are also showed by two patients out of 8. Interhemispheric transfer abilities were assessed too, as there is still much discussion about how defective those abilities are in ACC. Results show that callosal tactile transfer appear to be suboptimal and atypical in comparison to controls. Differences in performances in the uncrossed and crossed task are well known in normal population, children

doing 7% and adults doing just 2% worse in the crossed task. However, the subjects with ACC performed worse than controls in the uncrossed task, and were below controls in the crossed task especially when the right hand was stimulated. This result lends support to the Dennis' hypothesis (1976) that topographic representation of hands be also impaired in ACC (in the within hand performance of the same tactile test). The present study is the first that systematically assesses language at all the main linguistic levels and in all the abilities at the same time. Present results pinpoint that linguistic abilities are more likely to be affected when Corpus Callosum is absent since birth. Furthermore, it is suggested that neurological plasticity may bring to suboptimal reorganisation of cognitive functions.

Electrophysiological patterns of cognitive dysfunctions in Multiple Sclerosis (MS), Parkinson's disease (PD) and Amyotrophic Lateral Sclerosis (ALS)

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Background: MS, PD and ALS commonly share a severe motor impairment that may interfere in both daily and professional activities of patients. Also cognitive impairment is reported in such diseases but physical disability often does not allow the neuropsychological (NP) assessment. Cognitive functions can be investigated by means of the electrophysiological method as the Event related potentials (ERPs) even in very disabled patients.

Objectives: a) to analyze cognitive dysfunctions in MS, PD and ALS patients; b) to identify the specific electrophysiological pattern for each disease by using *electrophysiological markers* (latency, amplitude and topography); c) to compare the peculiar pattern of specific disease.

Methods: ERPs elicited by visual and auditory oddball paradigm (VisP300 and AudP300 respectively) and NP evaluation.

Results: ERPs were recorded by all patients in contrast to the NP testing that was partially performed by MS and ALS patient group. Electrophysiological markers revealed abnormal VisP300 and AudP300 latency and/or amplitude in 75% of MS patients, prolonged VisP300 and AudP300 latency in 58,4% of PD patients and in 75% of ALS patients. NP testing demonstrated severe deficit of memory and Deterioration index (DI) but mild impairment of attention in MS group. PD patients showed slight linguistic deficits and ALS patients displayed severe executive dysfunctions, attention and constructional apraxia deficits. As for MS patients, significant correlations were found between increased latency of VisN200, VisP300 and AudP300 and DI. About ALS patients, increased VisN200, VisP300 and AudP300 latencies significantly correlated with scores of executive functions tests.

Conclusions: In MS, ERP abnormalities were consistent with attention and memory deficits. In PD neurophysiological results revealed a subclinical impairment of attention. In ALS, the electrophysiological markers accounted for executive dysfunctions and working memory impairment. The electrophysiological patterns characterizing cognitive dysfunctions in MS, PD and ALS indicate a subcortical dysfunction. In MS, the interruption between cortical and subcortical structures and between intra-cortical connections (because of demyelinating process and also axonal degeneration) generates the *subcortical disconnection dementia*. In PD, the subcortical dementia is due to the dopaminergic mesocortical pathways degeneration that interconnect the tegmental ventral area with frontal and limbic cortex. In ALS, the neural loss in primary motor areas determines the interruption of neural pathways between frontal areas and thalamic and limbic structures as recently demonstrated by functional *neuroimaging* data (PET, fMRI).

In conclusion, the P300 may be helpful in evaluating cognitive impairment of MS, PD and ALS patients because it is objective and independent by physical status.

Age-Related Changes Of Cortical Activation To Voluntary Movement: Evidence From Erd/Ers

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Introduction: Voluntary movement may be investigated using the analysis of Event-Related Desynchronization (ERD) of the electroencephalogram (EEG). ERD or power reduction of the mu and beta sensorimotor rhythms contralateral to voluntary movement is considered a sign of cortical activation during motor planning and execution, whereas the sensorimotor beta synchronization (ERS) after movement termination is considered a sign of cortical idling or inhibition.

Objective: The aim of this study was to study age-related changes of cortical activation using event-related desynchronization/synchronization (ERD/ERS) to self-paced movement.

Patients and Methods: Thirty-three healthy volunteers participated in the study; they were subdivided in two groups according to age: 14 'older' subjects (mean age 59 ± 9 yrs, 6 females, 8 males) and 18 'younger' subjects (mean age 23 ± 3 yrs; 5 males, 13 females). Mu and beta ERD/ERS (percent decrease/increase with respect to the resting period) to self-paced movement was obtained from 29 scalp electrodes.

Results: Compared with the younger subjects, the older group showed significant decrease of mu ERD over the contralateral sensorimotor region during motor execution, while mu ERD was increased over the ipsilateral sensorimotor and premotor and bilateral parietal regions, during both preparation and execution of movement. Similarly, the older subjects had significantly increased beta ERD in the posterior and middle frontal regions during motor preparation and over both parietal regions during preparation and execution. Post-movement beta ERS was diffusely reduced in the older group compared with the younger group.

Conclusions: Our findings, in older subjects, of reduced activation (ERD) over the contralateral sensorimotor region, together with increased activation of cortical areas non directly involved in the production of movement (ipsilateral sensorimotor, premotor, middle frontal and parietal), consistent with functional neuroimaging data, may represent a correlate of compensatory mechanisms occurring with age.

Psychophysiological Findings Of Linguistic Function In Parkinson's Disease

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Background: Only in the last decade deficits of language comprehension in non-demented patients with Parkinson's disease (PD) have been observed. These alterations could concern verbal fluency, the semantic domain and the cognitive-linguistic flexibility. The event-related potentials (ERPs) represent an electrophysiological tool for studying the global cognitive state (P300) and linguistic functions of semantic and syntactic postlexical integration (N400 and P600, respectively).

Objective: to evaluate language comprehension in patients with PD by means of ERP recording.

Methods: Oddball auditory P300 and linguistic N400 and P600 were recorded in 8 patients (2 females) with possible PD (mean age 64.2 ± 7.1 years; mean education level 8.9 ± 4.9 years; mean disease duration 28.8 ± 26.9 months; mean UPDRS score 9.5 ± 4.4). Neuropsychological tests evaluated global cognitive status, memory, executive function and language.

Results: Normal P300 was elicited in all patients, N400 resulted abnormal in 5 patients (62.5%), P600 was altered in all patients (100%). Psychometric tests confirmed the impairment of language comprehension in all patients.

Conclusions: ERPs represents a useful electrophysiological tool to detect language function in PD. The major impairment of the P600 wave could confirm the hypothesis of basal nuclei involvement in syntactic postlexical integration.

Psychophysiology In A Case Of Restless Legs Syndrome

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Restless legs syndrome (RLS) is a sleep behaviour disorder characterized by disagreeable sensations in the legs and motor restlessness occurring during lying or resting, but being stopped by movement. Some author proposed the involvement of central dopaminergic systems, particularly the nigrostriatal system and the mesocorticolimbic system, in the pathophysiology of RLS. Neuroimaging studies and the beneficial effect of levodopa and dopaminergic drugs in RLS fit this possibility. We studied a 48-year-old woman who developed a definite RLS two days after the complete recovery from a transitory, slight motor deficit to the left body side. She experienced also difficulties in reading and comprehension. The brain MRI showed a small ischemic infarction in the territory of the lateral lenticulostriate arteries to the right involving the caudate, the external capsule and the claustrum. Laboratory data were normal and electromyographic investigation excluded peripheral neuropathies. Treatment with pramipexole 0,25mg daily improved immediately the sleep disorder but not the semantic difficulties. Event-related potentials showed a good global cognitive status (P300) and alterations in semantic and syntactic postlexical integration (N400 and P600, respectively). Psychometric evaluation confirmed lexical dysfunction. Recently, an involvement of the nucleus caudatus in linguistic comprehension has been hypothesized. This case could shed new light on the understanding of the physiological role of basal nuclei in language comprehension.

Speech and language disorders in the primary degenerative dementias: case study

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Language disorders can be related to subjects affected by a degenerative cortical process which at the beginning involves selectively the main language areas. Aphasias are those neuropsychological deficits which reveal the functioning of “normal” language starting from its pathology. The study of primary progressive aphasia (PPA) allows us due to its slowly progression to analyse the different components of speech and language and to correlate them to their anatomical seats.

The PPA is a focal dementia characterized by a gradual and isolated disintegration of all linguistic functions and is diagnosed when the language impairment is the **only** progressive dysfunction for at least the first 2 years of the disease (MESULAM, M.M et. al. (2003), The Core and Halo of Primary Progressive Aphasia and Semantic Dementia, *Ann. Neurol.*; 54: S11-S14).

Case 1: C.M. 79-years old, female, right-handed and 5 years of school attendance - her clinical picture of non fluent dysphasia of Broca’s type with dysprosody, articulation difficulty, linguistic barriers, agrammatism and integrity of the other cognitive functions confirms the suspect of PPA. The CT imaging reveals atrophy of the left hemisphere and of the left temporo-insular region.

Case 2: C.A. 73-years old, male, right-handed, 7 years of school attendance came to our observation due to slowly and worsening language disorder in June 1999. In 2002 C.A. was affected by mutism and by a serious impairment of all other cognitive spheres - this suggests a frontotemporal dementia which began with a non fluent PPA. The CT imaging reveals signs of cerebral and cerebellar cortico-subcortical atrophy with an involvement of the insula and the left frontal and temporal lobes.

Case 3: T.F. 67-years old, male, right-handed and 5 years of school attendance. We noticed a non fluent, dysprosodic and agrammatical speech with signs of phonetic disintegration and frequent anomia, and a total loss of all writing capacities with a beginning loss of memory – this suggests a PPA in evolution towards a non-Alzheimer’s type dementia. The CT imaging reveals signs of cortical atrophy involving the prefrontal and insular region on both sides, but more emphasized on the left.

The analysis of the neurolinguistic disorders of our subjects reveals how the degenerative process has selectively involved the main language areas, disintegrating the phonetic-phonological and the syntactic-grammatical level. All three subjects are affected by PPA, and the brain images confirm the involvement of the left hemisphere, in particular of the frontal and temporal lobe and of the omolateral insular region.

Motor deficit in virtual environment: a study in Parkinson’s disease.

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Objective: Aim of this study was to assess the behaviour of patients with Parkinson’s disease (PD), selected with different severity of motor symptoms.

Materials and Methods: We tested 15 control subjects (mean age 61,8 yrs) and 23 PD patients (mean age 65,3 yrs). Cognitive abilities of patients was evaluated by a neuropsychological assessment battery including MMSE, Corsi’s Span, Raven’s CPM, Frontal Assessment Battery. VR environments reproduces usual daily living situations, where subjects can move around and interact with the objects.

Results: A KW’s Anova and Mann-Whitney “U” Test was used to compare the 2 groups: Control Subjects and Patients. Control’s performances in VR generally was better than patients, in term of times of execution in exploration and pointing. Control’s precision was better too: objects avoiding and ability of pointing. A positive correlation was founded between the involvement of frontal abilities (evaluated by neuropsychological tests) and both more advanced stage in Hoehn & Yahr scale and partial scores subitems and total score of UPDRS ($p < 0,01$).

Discussion: Compared with controls, our findings show a marked difference in time score and in accuracy of execution: PD patients are slower than controls and their performance is generally worse. Patients subdivided on the basis of their disabilities (according UPDRS and H & Y) show differences in cognitive tests that involves frontal abilities: patients more impaired reveals worse frontal sight, but no differences was founded about their VR’s performance compared to those less impaired.

Conclusions: We tested the adaptation of parkinsonian patients in a virtual environment that reproduces usual daily living situations . Our findings show that , even if PD patients show worst performances than controls in VR, this difference is not dependent by severity of motor disability. Probably, VR could facilitate PD patients supporting their planning strategies by means of creation of useful mental images.

Mismatch Negativity In Drug-Resistent Epileptic Patients Implanted With Vagus Nerve Stimulator.

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Background and Objective: Management of seizure's activity by traditional pharmacological approaches is, in most cases, successful. However, it is also known that some patients (up to 30%, according to some studies) do not respond to conventional treatment and are considered drug resistant. For this group, when resective epilepsy surgery is not indicated, Vagal Nerve Stimulation (VNS) should be taken into account. VNS consists of intermittent stimulation of the left vagus nerve in the neck, which is achieved by implanted electrodes connected to a subcutaneous generator inserted below the left clavicle.

As far as concerns the effect of VNS on cognitive functions, previous studies proved that patients treated with VNS did not show any cognitive impairment; furthermore in some instances, enhancement in specific memory tasks have been reported. Several clinical studies, however, demonstrated significant improvement in Quality of Life of patients treated with VNS.

Aim of our study was to investigate the short term memory of patients treated with VNS through Mismatch Negativity (MMN), a specific auditory event-related potential (ERP) indexing automatic comparison of meaning stimuli to an existing memory trace.

Materials and Methods: We selected 4 drug-resistant patients among those referring to the ambulatory for epilepsy of our department which were candidate to VNS implantation. MMN was elicited using a deviant acoustic stimuli paradigm. Brain electric activity was recorded from the scalp of each subject by a 32 electrode cap using a Synamps[®] Amplifier device (Neuroscan EEG System, Neuroscan[®] Inc.). For each subject, MMN was elicited and recorded just before and after VNS implantation, and then at every current intensity adjustment.

Results and Conclusions: For each recording, latency and amplitude of MMN curve were measured. Independent component analysis was also performed to remove muscular and ocular artefacts and to increase signal-to-noise ratio. Statistical analysis was performed using a Student's t-test. MMN latencies and amplitudes were normal in 3 out of 4 patients before VNS implantation: in these subjects no significant changes in latency or amplitude were detected in MMN recorded after VNS implantation or after every current intensity increase, suggesting that short term memory investigated through Mismatch Negativity is either slightly or not impaired by VNS. In one case, MMN latency and amplitude were abnormal in basal conditions: after VNS implantation and after every current intensity increment a significant reduction in latency and an increase in amplitude were detected, suggesting a potential positive effect of VNS on pre-attentive processes investigated by MMN.