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ABSTRACTS

EEG-SPECT Correlation in Dementia

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EEG and SPECT are powerful markers of disease severity in Alzheimer's disease (AD), although their role in less common forms of dementia, such as frontotemporal dementia (FTD), is less known. The most significant (r= -0.52) correlation between planar Xe-133 rCBF and qEEG was found between relative power of the 2-6 Hz. band and parieto-temporal rCBF in the right hemisphere in 42 AD patients with different severity of disease. In another series of AD patients with similar features undergoing Tc-99m HMPAO SPECT, correlation (r= -0.49) was found in both hemispheres between parietal perfusion and both 2-6 Hz and 8-12 Hz relative power, whereas hippocampal perfusion correlated (r= -0.40) with the right 2-6 Hz. relative power only. In FTD, significant (r=0.57) correlation was found between rCBF-SPECT and qEEG mean frequency in the right frontal region. After the introduction of Acetylcholinesterase inhibitors (AchEIs), both qEEG (6-12/2-6 Hz ratio) and rCBF (analysed by Statistical Parametric Mapping= SPM) have been shown to deteriorate less in treated than in untreated patients. EEG was especially preserved in a right frontal region, whereas no significant rCBF change was observed in AchEI-treated patients in spite of rCBF reduction in left temporo-occipital areas in untreated ones. By merging qEEG and rCBF data together in SPM analysis of covariance, specific regions of significant correlation have been identified.

Coherence Analysis in Dementia

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Coherence analysis of the electroencephalogram (EEG) can be used to quantify the correlation between two EEG channels as a function of the frequency. Coherence is a normalized spectral index and is independent from the power of each signal at the investigated frequency. The synchronicity of a particular frequency, shared by two signals in the analyzed time window, is reflected by a high coherence value. High coherence values between two EEG signals can be interpreted as indicating high degree of functional connections between the respective cortical areas. Some biasing factors can be taken into account when analyzing coherence such as signal dependence on the reference and volume conduction effects. Laplacian transformation of raw EEG data is suggested to avoid misinterpretations. Coherence analysis has been applied in the study of several types of dementia. In Alzheimer's disease, decreased alpha coherence has been found in the temporal regions, probably related to alterations in cortico-cortical connections, while a delta coherence increase could be related to the lack of influence of subcortical cholinergic structures on cortical electrical activity. In patients affected by multiple sclerosis, cognitive impairment has been shown to be mostly dependent upon dysfunction of cortico-cortical connections related to demyelination and/or axonal loss within the white matter immediately underlying the cortex.

The Incremental Diagnostic Value of Structural Imaging and its Cognitive Correlates

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In the context of cognitive disturbances, structural imaging can be used to: 1) enhance diagnostic accuracy in clinical settings, and 2) study the pathophysiology of cognitive disturbances in research settings. In the former case, the variable that critically affects the incremental diagnostic value of structural imaging is whether the dementing syndrome is or is not full-blown. The more severe the cognitive deficit, the easier to detect specific neuropsychological patterns that per se direct the diagnosis without resorting to imaging. Similarly, more profound disability, more severe are behavioral disturbances, and more marked neurological signs can more strongly direct the diagnosis prior to imaging. On the contrary, the closer to normality are cognition, disability, behavior, and neurological exam, the greater is the potential incremental diagnostic value of structural imaging. This is the case of mild cognitive impairment, a very early stage of Alzheimer's disease. In these patients, medial temporal atrophy has been found with image analysis tools of different complexity (linear measures, volumetrics, voxel-based morphometry). To date, it is not clear which of these is the most efficient tool, but it is sensible to hypothesize that the low biological severity of mild cognitive impairment will make technologically more advanced techniques the tools of choice. In the case of the study of the pathophysiology of cognitive disturbances, one of the most intriguing issues is the role of apoE as a predisposing genetic factor to developing Alzheimer's disease. It is increasingly clear that apoE alleles (e2, e3 and e4) have a biological effect during brain development and are associated with different brain structure. Cognitively intact elderly people carriers of the e4 allele feature smaller medial temporal structures (hippocampus, amygdala, entorhinal cortex) but larger frontal lobes on volumetric analysis. Such structural pattern might be responsible of greater susceptibility of these individuals to diseases affecting the medial temporal lobe such as Alzheimer's disease, but greater resistance to damage of the frontal lobes. This might be the biological basis of clinical observations indicating that AD patients carrying the e4 allele have greater memory impairment but better frontal tests, while non-carriers show an opposite neuropsychological profile. The use of the more advanced computerized image analysis tools (voxel-based morphometry, tensor-based morphometry, and high dimensional brain mapping) will contribute to further clarify the issue.

Motor Cortex Functionality in Alzheimer's Disease: A Transcranial Magnetic Stimulation Study

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The aim of the present investigation was to test motor function by examining specific parameters of motor cortex physiology via TMS in initial forms of AD patients.Sixteen patients were recruited. They all satisfied the NINCDS-ADRDA for possible or probable AD diagnosis. No clinically evident motor disturbances were found on a routine, complete neurological evaluation. An age matched control group was formed by 13 healthy volunteers. In order to map the motor cortex output to the superior limb, Motor Evoked Potentials were recorded from Extensor Digitorum Communis (ECD) and Abductor Digiti Minimi (ADM) following the transcranial magnetic stimulation of the scalp, during two conditions: full relaxation (muscular and mental) and active contraction of the target muscle. Excitability threshold was evaluated via international guidelines (Rossini et al 1994, 1999) and increased by 10%. Main result was increased motor cortex excitability in AD patients, expressed as lower intensity to elicit MEPs and increased area and volume of the map in both hemispheres, together with a frontal shift of the motor maps for hand and

forearm muscles. Subclinical motor reorganization is already evident in early disease stages in patients with a mild to moderate form of AD.

The Role of the Cerebellum in Cognition. Lessons from Patient and Animal Studies

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Emerging evidence suggests that the computational properties of the cerebellum extend beyond the domain of motor control and may be important in cognitive functions such as learning, planning, judging time, emotional control, attention, perception and some aspects of language. In the last decade we addressed this topic by characterizing cognitive abilities in cerebellar patients. Procedural learning was evaluated by means of Nissen and Bullemer's serial reaction time task. Cerebellar patients were clearly more impaired in recognizing the sequences than in performing it. Visuo-spatial abilities were analysed using tests of increasing complexity. A defined impairment in bi- o tri-dimensional folding of objects was observed. The observation of agrammatism in right cerebellar patients allowed us to hypothesized a specific locus for the cerebellar contribution to language. Working memory data in patients with cerebellar damage allowed us to include the cerebellum within the structures involved in short term memory function. The above mentioned data indicate that many cognitive functions are affected by damage of the cerebellar circuits and challenge the classical theories of cerebellar function. At present the general picture of the cerebellar involvement in cognition is far from being complete and new evidence are still widening the areas of competence of the cerebellum.

Cognitive Theories and the Study of the Relationships between Function and Structure

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For a long time, the study of the relationships between cognitive processes and the brain has largely relied on analyses of the correlations between clinically defined neuropsychological syndromes (aphasias, amnesias, neglect, etc.) and lesions to brain structures. This popular approach, however, was irremediably flawed by the lack of adequate analyses of the functional deficits observed in brain-damaged individuals. This state of affairs has changed dramatically over the past two decades, largely owing to investigations in cognitive neuropsychology, which have produced detailed hypotheses on the organization of cognitive and linguistic processes. Added to the availability of more sophisticated and less invasive procedures, such as PET, fMRI, MEG, TMS, which allow to correlate cognitive processes and brain structures with increasing temporal and spatial definition, current functional models provide us with the theoretical tools needed for a fresh look at the relationships between cognition and the brain, in both normal and cognitively impaired subjects. Current investigations that exploit these theoretical and technical developments are beginning to shed light on the neural networks representing cognitive functions in the brain. Recent applications of this approach will be reviewed, with special reference to language and aphasia.

Verb-Noun Dissociations in Aphasia

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The aim of the present study is to estimate the rate of dissociated impairments for nouns and verbs on a sample of aphasic patients, and to investigate the mechanisms underlying such phenomena.
A confrontation naming task for verbs and nouns was administered to 58 aphasic patients. The major lexical (e.g. word frequency) and semantic variables (e.g. imageability) were considered for each noun and verb used in the task. The data were analyzed twice: (i) as a group study comparison of major aphasic subgroups and (ii) as a multiple single case study. The results confirm the existence of dissociated naming impairments of verbs and nouns. Selective impairment of verbs is more frequent than that of nouns. In some cases, the dissociated pattern of naming impairment disappeared when the effect of the concomitant variables was removed, but in approximately one third of the cases the noun- or verb-superiority was preserved. The results lend support to the hypothesis of an independent mental organization of nouns and verbs, but a substantial effect of imageability and word frequency suggests an interaction of the naming impairment with underlying lexical and semantic aspects.

A Psychophysiological Investigation of Syntactic Processes in Patients

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We set out to explore language comprehension processes with event-related brain potentials (ERPs) in comparison to behaviroal measures in aphasic and non-aphasic patients. This was done to find out if there is a lesion-specific failure or modulation of ERP components in specific patient groups. Thus, brain structures which might be engaged in the generation of language-specific components could be identified. In experiment 1 we compared syntactic processing in patients with cortical and subcortical lesions. Based on data from healthy subjects that shows an early negativity followed by a P600 after syntactic violations, we expected that these components might be modulated as a function of lesion site. The data suggest that the left frontal, cortex, but not subcortical areas support the activation of the early negativity. The late positivity was only attenuated in the patient group with subcortical lesions. In Experiment 2 we explored a second group of patients, namely Parkinson (PD) patients with the same paradigm as there is a conflict in the literature as to whether PD results in syntactic deficits or not. Our results show that comparable to patients with subcortical lesions PD patients show an early negativity, but a strongly modulated P600 after syntactic violations. The results will be discussed in the context of the functional role of the basal ganglia during syntactic language processing.

Specific Brain Responses in the Acquisition of Natural Language Grammatical Rules

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Some types of simple and logically possible syntactic rule never occur in human language grammars, leading to a distinction between grammatical and non-grammatical syntactic rules. The comparison of the neuroanatomical correlates underlying the acquisition of grammatical and non-grammatical rules can be conclusive as to the existence of neural processes specifically dedicated to language acquisition in a given developmental stage. We report novel data from an fMRI experiment, where we investigated the acquisition of grammatical and non-grammatical rules in the

specified sense in 14 healthy adults. Within a bilateral fronto-parietal network that was activated by both rule types, selective differences were found. In particular, grammatical rules compared to non-grammatical rules specifically activated a left hemispheric network including Broca's area. These findings, which provide a first evidence for the neural mechanisms underlying language acquisition in adults, will be discussed with reference to the processing of positional syntactic representations and to current research on the functional neuroanatomical rearrangements underlying automatic language processing and language proficiency in multilinguals.

Event-Related Potentials in Language Comprehension Investigation

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Linguistic event-related potential (ERP) studies are conducted to detect language production, comprehension and dysfunction. One of the major ERP advantages is their high temporal resolution which allows to obtain on-line informations about distinct aspects of language comprehension. There are various linguistic paradigms eliciting different potentials (e. g., N400, P600) linked to complex neural network activation underlying specific language processing mechanisms. Despite the high sensibility of the ERP method, the single components are less specific. Furthermore, the administration of more than one paradigm could be time-spending and may require multiple recording sessions. The aim of this study is to improve ERP specificity using non-linguistic and linguistic tasks in one recording session and creating a brief electrophysiological method of language comprehension investigation. Auditory oddball P300 as preliminary assessment of cognitive status, sintactic P600 and semantic N400 as investigation of language comprehension were recorded in 40 healthy volunteers. The first linguistic paradigm examines postlexical syntactic integration aspects by a number agreement violation paradigm. The second task assessed semantic memory by means of a semantic integration paradigm. The mean total session time (electrode placement, subject's instruction, EEG recording) was less than 2 hours. Subjects showed the expected central positive wave (P300) elicited by auditory target stimuli, a late symmetric positive effect (P600) for syntactically incorrect sentences, and a broad negative deflection (N400) for semantically incongruent words. This method could be useful to study aspects of language comprehension and to evaluate possible language impairment in various pathological conditions.

Beta and Gamma EEG Bands during Sleep

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The aim of this study was to analyze the relationships between two newly introduced measures, correlated with the high-frequency EEG bands Beta and Gamma, and the Delta and Sigma bands at REM sleep onset and end, in order to understand their eventual role in the sleep modulation mechanism. Moreover, also some aspects of topographic scalp distribution of these new parameters were analyzed. Ten healthy females aged 18-20 years participated to this study. Polysomnography (EOG, EMG of the submentalis muscle, EEG from at least 3 derivations: F3 and/or F4, C3 and/or C4, and O1 and/or O2, all referred to the contralateral mastoid) was performed in all of them. The power of the bands ranging 0.75-4.50 Hz (Delta), 4.75-7.75 (Theta), 8.00-12.25 (Alpha), 12.50-15.00 (Sigma), 15.25-24.75 (Beta), 25.00-34.75 (Gamma 1), and 35.00-44.75 (Gamma 2) was calculated for the whole period of analysis(7 h). We also computed two additional time series: the ratio between Beta and Gamma2 (Beta ratio), and between Gamma1 and Gamma2 (Gamma ratio). For each subject, we extracted from C4 3 epochs of 30 minutes corresponding to the 15 min preceding and the 15 minutes following the onset of the first 3 REM episodes. Data were then averaged in order to obtain group mean values and standard deviation. The same process was

applied to the 30-minute epochs around REM sleep end. The course of the Delta band around REM sleep onset was found to be characterized by a first phase of slow decline lasting from the beginning of our window up to a few seconds before REM onset; this phase was followed by a sudden, short decrease centered around REM onset, lasting for approximately 1.5–2 min. At the end of this phase, the Delta band reached its lowest values and remained stable up to the end of the time window. The Sigma band showed a similar course with stable values before and after REM sleep onset. The Beta and Gamma ratios also showed a 3-phase course; the first phase, in this case, was characterized by stable low values, from the beginning of our window up to approximately 5 min before REM onset. The following second phase was characterized by an increase which reached its maximum shortly after REM sleep onset (approximately 1 min). In the last phase, both Beta and Gamma ratios showed stable high values, up to the end of our time window. At REM sleep end, the Delta band only showed a very small gradual increase, the Sigma band presented a more evident gradual increase; on the contrary, both Beta and Gamma ratios showed a small gradual decrease. The results of this first study show a different time synchronization of the changes in the Delta band and in Beta and Gamma ratios, at around REM sleep onset, and seem to suggest that the oscillations of these parameters might be modulated by mechanisms more complex than a simple reciprocity. All these considerations point to the fact that REM sleep can be considered as a complex phenomenon and the analysis of high-frequency EEG bands and of our Beta and Gamma ratios represent an additional important element to include in the study of this sleep stage. The analysis of the scalp topographic distribution of these measures indicated that during nonREM slow-wave sleep, the Delta band shows the highest values over the central and frontsal regions, followed by those observed over the occipital lead. During sleep stage 2, the Sigma band shows the highest values over the central regions, followed by those observed over the occipital areas and, last, those from the frontal lead. During REM sleep, the Beta ratio showsits highest values over the central field which are significantly higher that those obtained from both the frontal and the occipital regions. Gamma ratio shows a statistically nonsignificant tendency to present a similar topographic distribution pattern. Beta and Gamma ratios show regional differences being highest over the central areas, during REM sleep; on the contrary, during nonREM sleep the Delta band shows its highest values over the frontal-central areas and the Sigma band over the central and occipital regions. REM sleep can be considered as a complex phenomenon with a differential involvement of multiple cortical and subcortical structures. Thus, again, the analysis of high-frequency EEG bands and of our Beta and Gamma ratios represent an additional important element to include in the study of sleep.

Cerebellar Cognitive Affective Syndrome: A Nine-Month Follow-Up Case Report

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Clinical, neuroimaging and neuropsychological investigations have assessed the important role of the cerebellum in cognitive function modulation and have led to the definition of a particular clinical entity in patients with cerebellar lesions, named the 'cerebellar cognitive affective syndrome'. The syndrome is characterized by impairment on executive function, memory, spatial cognition, and language. We report a 68-year old man with acute onset of poor and transitory motor features, but predominant mental and behavioral disorders such as disinhibition, perseverance, dysprosodia, disorientation, memory and attention deficits. Brain MRI revealed extended bilateral ischemic lesions of the cerebellar cortex, without any abnormalities like cortical atrophy, vascular and/or degenerative alterations of cerebral hemispheres and brainstem. Neuropsychological assessment disclosed deficits of attention, executive function, long-term verbal and visuo-spatial memory. Auditory oddball event-related potentials showed a P300 with abnormal wave morphology and amplitude reduction. After nine months patient's behavior and spatial confusion seemed to be improved and psychometric tests indicated a slight recovery of cognitive functioning. The presence of "pure" cerebellar cognitive affective syndrome in absence of motor function involvement,

strengthens the hypothesis of cerebellar cognitive function modulation. Our nine month follow-up observation may shed light on the discussion about recover modalities from acute cerebellar lesions.

Age-Related Functional Changes of Dorsolateral Prefrontal Cortex (DLPFC) in Visuospatial Long-Term Episodic Memory: A rTMS Study

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Background and objectives: by means of rTMS-induced interference, it has been demonstrated (Rossi et al. 2001) that in healthy young subjects there is a certain degree of functional asimmetry for visuospatial long-term memory: the right DLPFC seems crucial for the correct functioning of retrieval, while the left DLPFC would be hierarchically prevalent onto the right for encoding operations.
Methods: 30 healthy subjects, divided in three classes of age (< 40, 50/65 e >65) were investigated along 6 experimental blocks, each one including an encoding phase (= Enc) of complex figures (8 internals and 8 externals) and a retrieval phase (= Ret) –one hour later- in which 8 internals tests and 8 distractors were again presented. Trains of rTMS (500 ms, 20 Hz, 10% below motor threshold) were delivered on F3 or F4 (corresponding to DLPFCs) at images presentation. After a "go" signal appearing on the picture, subjects were asked to press one of the two buttons. The 6 randomized blocks were: R-Enc: right rTMS in Enc, no stimulation in Ret; L-Enc: left rTMS sin in Enc, no stimulation in Ret; sham rTMS (left in Enc and right in Ret); R-Ret: no stimulation in Enc and right rTMS in Ret; L-Ret: no stimulation in Enc and left rTMS in Ret; absence of stimulation (= baseline).
Risults and conclusions: the error rate linearly increased with age, independently by the presence of rTMS. The left/right functional asimmetry detected in young subjects progressively decreased for the 50/65 years class and was no longer present in subjects over 65 years. This suggests that, during physiological ageing, alternative strategies of memorization and recall of visuospatial information are probably taking place.

Impairment of Abstract Reasoning in Mild Alzheimer's Disease: The Use of Weigl's Sorting Test

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Loss of executive functions is found early in fronto-temporal dementia, but is commonly thought to be a late feature in Alzheimer's disease (AD). To test the hypothesis that abstract reasoning may be already impaired in the mildest stages of AD, we studied 27 consecutive patients (75.6±6.7 years, 19 women and 8 men, educational level: 6.9±3.3 years) with mild AD (as defined by a MMSE score ≥ 20) by the Weigl's sorting test, which assesses abstract reasoning in a simple way. Attention and verbal fluency were tested as well. Twenty-nine healthy subjects of comparable age (72.3±6.2 years), sex distribution (22 women and 7 men), and educational level (9±3.9 years) served as controls. Seven patients scored less than the mean value –3 SDs of control group. MMSE score did not significantly differ between the subgroup of AD patients with impairment of abstract reasoning and the remaining patients. In the whole group of 27 AD patients, only a slight correlation ($r = 0.34$, $p<0.05$) was found between MMSE and Weigl's scores. A subgroup of AD patients shows

impairment of abstract reasoning already in the early phase of the disease. Such an impairment is mostly not clinically evident, and is only slightly related to the degree of cognitive impairment.

Prognostic Value of Short-Latency Somatosensory Evoked Potentials in Comas: A Study in 131 Patients.

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The aim of this study was to define the patterns of median nerve somatosensory evoked potentials (mnSSEPs) abnormalities in comatose patients, in relation to the etiology of coma. We examined 131 patients (mean age: 50,6±16,6 years; range 14-85) comatose after cardiac and respiratory failure (n=49), ischemic or hemorragic stroke syndrome (n=45), traumatic brain injury (n=22), complications of neurosurgery (n=12) and encephalitis (n=3), hospitalised in ICUs, with a Glasgow Coma Scale score less than 8 at the time of the recording of SSEPs. Bilateral mnSSEPs were recorded according to the International Federation of Clinical Neurophysiology guidelines (1999). One month after the onset of coma all patients were classified in three categories: awaken, not awaken and dead. Out of 44 patients who recovered consciousness, 9 (20,5%) had bilateral reduction of N20 component amplitude and none had bilateral absence of response; of the 40 subjects who did not survive, 17 (42,5%) had bilateral amplitude loss and 5 (12,5%) bilateral absence of N20. Among the 47 patients who were in persistent coma at 1 month, 6 (13%) had bilateral absence of N20 and 15 (32%) dramatic bilateral amplitude reduction. We plotted the amplitude values versus the outcome and chose as cut-off criterion the one below which none of the patients had recovered. In the group of post-anoxic coma 21 subjects out of 49 (42,8%) had an N20 amplitude < 0,6 μV and none of them recovered; in the sample of comatose patients after a stroke syndrome N20 was < 0,6 μV in 21/45 (46,7%) of which 11 did not recovered; in the post-traumatic group N20 was < 0,6 μV in 7/23 (30,4%) of which 3 did not recovered. The central conduction time (CCT) did not relate to the outcome in any group.

Evoked Potential Correlates of Pre-Attentive Visual Perception

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Objectives: To report the results of three experiments, performed on normal subjects with texture stimuli, that were able to identify evoked potential correlates of different aspects of pre-attentive visual perception.
Methods: In all experiments uniform texture stimuli alternated with textures which included segregated patches defined by orientation gradients (vertical / horizontal) of local elements (line segments). In the first experiment checkerboard squares were segregated and the segregation maintained also in the following stimulus, but with reversed orientation of local elements, in order to identify components related to edge detection and to surface 'filling-in'. In the second experiment a more complex figure-ground related segmentation was presented which was intended to identify components related to amodal completion. In the third experiment horizontal or vertical stripes were segregated, which were constituted of horizontal or vertical line elements, in order to identify possible effects related to anisotropy at the local or at the global level.
Results: In all experiments the 'basic' waveform that was obtained with all stimulus types, irrespective of the presence or absence of segregated elements was a N75-P100-N150 sequence with latencies only slightly varying across the tree experiments. The presence of segregation was

related (in all experiments) to an enhancement of negativity in the P100-N150 latency range, which was identified in the difference traces as a negative 'segregation component'. The first experiment was able to show that edge-detection effects were related to an earlier subcomponent the segregation component (in the P100 latency range), whereas surface 'filling-in' effects were related to a later subcomponent (in the N150 latency range). The second experiment showed that the figure-ground related effect was also related to a later subcomponent of the segregation component, which was in the same latency range as the 'filling-in' related component. The third experiment showed that orientation-related effects were able to modulate the N75 component, but exclusively in the condition of collinearity between global and local elements. An anisotropy of this modulation was found, as horizontal collinearity was associated with greater positivity in the N75 latency range, whereas vertical collinearity was associated with greater negativity.
Conclusions: The three experiments show that different aspects of preattentive visual perception modulate texture visual evoked potentials with effects that are specific in latency and in polarity.

Chromatic Pattern-Reversal Electroretinograms (Chpergs) are Spared in Multiple System Atrophy Disease

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Several studies support the hypothesis that dopaminergic deficiency at retinal level might underlie some visual changes of either achromatic or chromatic vision in Parkinson's disease (PD). Evoked potentials changes are not reported as characteristic feature of the disease in multiple system atrophy (MSA); moreover impairment of the luminance and colour-opponent pathway at retinal level has never been investigated. In previous works we noted that both VEPs and PERG to blue-yellow (B-Y) chromatic stimuli were more vulnerable than those to red-green (R-G) and Black-white stimuli in PD (Sartucci et al., Invest. Ophthalmol. & Visual Sci. 1999, 40, (4), S822; Sartucci et al., CLINPH. 2000, 111 (1), S65). Aim of this study was to investigate the relative involvement at retinal level of pathways to R-G, B-Y equiluminant and achromatic luminance Yellow-Black (Y-Bk) stimuli in patients with MSA. We enrolled 5 MSA patients (3 man and 2 females; mean age 56 ± 5.4 yrs; range 50 - 63) not undergoing any pharmacological treatment, as well as 12 "de novo" idiopathic PD patients, and a group of age-matched controls. PERGs were recorded monocularly in response to equiluminant R-G, B-Y and Y-Bk horizontal gratings of 0.3 c/deg and 90% contrast, reversed at 1Hz, displayed on a TV monitor at a viewing distance of 24 cm (59.2*59 deg field). In MSA patients the mean N1 latency and N1-P1 PERG amplitude resulted normal both for chromatic- and luminance stimuli, whereas in patients with PD they were dramatically delayed in latency and reduced in amplitude compared with controls. Present data indicate that chromatic and luminance PERGs are not altered in MSA as in "de novo" PD or other disease. Overall, our findings on ChPERGs suggest that the two diseases may be separate and underlie different pathogenetic mechanisms. Further, chromatic PERG can contribute to the differential diagnosis of the Parkinsonian syndromes.

Event-Related Desynchronization (ERD): Laterality Effects in the Sensory and Motor Systems

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Event Related Desynchronization (ERD) - power decrease - of mu and beta EEG bands is observed over the sensorimotor areas during movement preparation and execution as well as somatosensory

stimulation, followed by beta power increase - Event Related Synchronization (ERS). The aim of our study was to investigate laterality effects to movement and sensory stimulation. Mu and beta ERD/ERS were evaluated in 14 right-handed normal subjects during self-paced movement and after median nerve stimulation (7 subjects). Mu and beta ERD to movement preparation of the right and left thumb started over the contralateral sensorimotor areas (C3 or C4) and became bilateral closer to movement execution. Ipsilateral pre-movement ERD (-300/-50 msec) was higher for left compared to right movement for both bands ($p<0.04$). Beta ERS occurred 200-400 msec after movement termination, with contralateral predominance (ipsilateral vs contralateral: $p<0.03$). Ipsilateral ERS was higher for left than for right sided movement ($p<0.05$). Mu ERD after median nerve stimulation had contralateral predominance for stimulation of both sides (ipsilateral vs contralateral: $p<0.05$) and beta ERD only for right ($p<0,04$). No significant difference was observed in ipsilateral ERD between left and right stimulation. Beta ERS to somatosensory stimulation had contralateral predominance for both stimulation sides (ipsilateral vs contralateral: $p<0.03$). Ipsilateral post-stimulus beta ERS was higher for left than for right sided stimulation ($p= 0.03$). Our findings of more bilateral ERD/ERS to left hand movement compared to right in right handed subjects are consistent with previous literature (Stancak et al 1996; Leocani et al. 2001). Our finding of a more bilateral ERS to left compared to right median nerve stimulation in right handed subjects suggest that laterality effects are also present in the sensory system.

Visuo-Spatial Imagery ad Eye Movements

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Although eye movements may provide an opportunity to describe the evolution of visuo-spatial cognitive processes, so far the attempts to uncover mental activities from the oculomotor behavior proved particularly difficult. We present evidence that spontaneous eye movements represent a reliable correlate of mental rotation and motion imagery. In the mental rotation task, subjects had to add an instructed angle to a certain point on a target circle in the clockwise direction. Supposedly, a mental rotation strategy is employed to solve this task. In the motion imagery task, subjects had to explicitly imagine a dot rotating along portions of a target circle. Bi-dimensional eye movements were recorded throughout the response time with the scleral coil technique or infrared oculometry. Response times were also recorded. The pattern of saccades reflected faithfully the expected mental process, often literally designing the evolution of the covert rotation, both in unconstrained (mental rotation) and guided (motion imagery) conditions. We contend that this eye movements-based approach do represents a way to precisely measure the spatio-temporal evolution of visuo-spatial mental processes. As such, it may be fruitfully associated to techniques like ERPs, MEG, PET, fMRI or TMS to compare brain activity with the ongoing mental activity.

Effects onCortico-Cortical Interconnections Involved in CNV Activity Generation Induced by Localized Cortical Lesions and Ablations in Humans

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This didactic lecture synthesize on our various 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 acoustic stimuli, in both pathological situations and normal control subjects. In this field

great interest was aroused in the early '70s by the rare, fortunately unrepeatable, opportunity of examining, also with repeated recordings, the CNV patterns in various psychiatric patients treated with psychosurgical Freeman-Watts bilateral prefrontal "radical" lobotomy or bimedial bifrontal cingulotomy. In the same period investigations into CNV activity recorded in patients submitted to a complete callosotomy ('split brain') were also begun and were continued into the '80s-'90s also with regard to other types of ERP (N400 etc.). All these data furnished unique information about the sub-second dynamics of unilateral or bihemispheric cortico-cortical and cortico-subcortical interconnections in humans. In recent years, with a classic method of ERP analysis based on sequential scalp-topographic bidimensional neuroelectric colour mapping, 21/19 electrodes connected to 3 different references, and binaural/monaural clicks as warning signals (S1), we have repeatedly examined the CNV activity of 11 selected patients submitted to a complete ablation of the damaged cortical areas, with uni- or bilateral lesions restricted to the prefrontal or associative parieto-temporal areas. We have always used the standard CNV paradigm (S1-S2-motor response) which evokes a complex of neurocognitive potentials, including the P300 from S1, which are well-known since they are certainly among the most studied ERPs in the various ages and races of normal subjects, psychiatric patients and subjects with different brain diseases. The most important results have been: 1) In normal subjects the MRI and the latency differences of some CNV component measurements along the bidirectional pathways functionally interconnecting ipsilateral distant associative cortical areas (e.g. the arcuate-superior longitudinal complex bundle) were accounted for by the transcortical conduction time, which varies in our scalp recordings from 1 cm/0.74-1.28 ms (~9.8 m/s). 2) Constantly, no true auditory S1-elicited N1a, b, c, P2, N2, P3 components or CNV slow waves (O- and P-wave) were recordable over the whole of the ablated cortical areas. 3) The post-S1 ERP/CNV complexes on the intact hemisphere were found to be within the normal limits. 4) Effects of severe disruption on the S1 ERP/CNV complexes evocable on the site and on remote ipsilateral apparently normal anatomo-functionally interconnected brain regions were observed in 5 patients, 4 of whom had extensive frontocortical ablations. In 2 of the latter the distant disruptive action on the CNV components over the neuro-radiologically normal ipsilateral two-way connected post-rolandic sensory and association areas was seen to be partially reversible, showing aspects of a probable slowly-evolving diaschisis-like effect. Similar deactivation of some ERP components was observed in reverse on the ipsilateral dorsolateral frontocortical region in the fifth patient with large parieto-temporal cortex ablation. These data require confirmation and, when this phenomenon is observable, it must be appropriately monitored with different methods of functional neuroimaging. This will serve not only for medical and neuro-psychophysiological diagnosis purposes, but particularly for a correct and really useful planning of neurorehabilitation activities in selected cases.

Topographic Analysis of Brain Electrical Activity in Psychiatry

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The development of topographical and tomographical techniques for imaging brain electrical activity and sources has opened new important perspectives in the study of neural mechanisms underlying mental states. In the presentation, two recent sets of findings obtained by our group will be presented to illustrate main research issues facing the application of topographic electrophysiological techniques in Psychiatry. In the first study, the brain electrical microstates (BEMs) were investigated in subjects with panic disorder during a target detection task. The results indicated a hyperactivation of the circuits involved in early visuospatial analysis, and a reduced activation of those involved in the integration of stimulus features with subjective states. In the second study, BEMs and LORETA technique for source imaging were applied to investigate the auditory P300 topography in subjects with deficit and nondeficit schizophrenia. An abnormality of

the left hemisphere circuits involved in P300 generation was observed only in subjects with nondeficit schizophrenia. Both sets of findings demonstrated that collapsing data across time frames and patient groups can be highly misleading and underlie the importance of the high temporal resolution of electrophysiological techniques in Psychiatry.

Neurophysiological Evaluation of Executive Function in Obsessive-Compulsive Disorder

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Converging evidence suggests view of frontal lobe involvement in Obsessive Compulsive Disorder (OCD). Movement slowness is a frequent feature of OCD. Abnormal cerebral bood flow over prefrontal areas and basal ganglia, which are also involved in motor control, has also been reported. Event-related desynchronization of mu and beta EEG rhythms is considered a correlate of motor activation during motor preparation and execution, followed by cortical idling or inhibition indicated by event-related synchronization. Delayed onset of mu event-related desynchronization with movement preparation and less postmovement beta synchronization has been found in untreated OCD patients compared to normal subjects. Delayed event-related desynchronization in OCD is consistent with involvement of structures related to motor programming, such as basal ganglia. Lower levels of postmovement beta synchronization suggest impairment of the inhibitory system in OCD, consistently with findings reported using transcranial magnetic stimulation. These findings may extend the concept of reduced inhibition in this disease and raise the question of whether this finding reflects the inability of OCD patients to refrain from performing impelling actions. Impaired inhibitory mechanisms in OCD have also been suggested by event-related potential findings. Moreover, reduced motor cortical inhibition in OCD patients has been found with transcranial magnetic stimulation.

Functional Magnetic Resonance Imaging of Working Memory in Schizophrenia

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Functional Magnetic Resonance (fMRI) is an imaging technique with high spatial and temporal resolution that allows investigation of *in vivo* information about the functionality of discrete neuronal groups during their activity utilizing the magnetic properties of oxy- and deoxy-hemoglobin. fMRI permits the study of normal and pathological brain during performance of various neuropsychological functions. Several research groups have investigated prefrontal cognitive abilities (including working memory) in schizophrenia using functional imaging. Even if with some contradictions, large part of these studies have reported relative decrease of prefrontal cortex activity during working memory, defined as hypofrontality. However, hypofrontality is still one of the most debated aspects of the patophysiology of schizophrenia because the results can be influenced by pharmacotherapy, performance and chronicity. The first fMRI studies in patients with schizophrenia seemed to confirm hypofrontality. However, more recent studies during a range of working memory loads showed that patients are hypofrontal at some segments of this range, while they are hyperfrontal at others. These studies seem to suggest that the alterations of prefrontal functionality are not only due to reduction of neuronal activity, but they probably are the result of complex interactions among various neuronal systems.

Spontaneous and Activity-Dependent Modulation of Human Motor Cortex Excitability to Transcranial Magnetic Stimulation: Normative Data in Healthy Subjects and Possible Applications in Neuropsychiatric Diseases

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Motor activity can influence the excitability of sensorimotor cortex and such influence is quantitatively and qualitatively related to motor performance. Opposition movements of the thumb performed at 2hz rate for one minute produce a 55% decrease of Motor Evoked Potentials (MEPs) amplitude of 20-40 minutes duration. MEPs amplitude recovery is not influenced by a second bout of 2hz movements performed during the phase of maximal MEPs depression. On the contrary, opposition movements of 1hz rate can transiently reverse MEPs previously depressed by two bouts of 2hz movements. Interestingly, the same 1hz movements produce no changes of MEPs when performed starting from resting conditions. Activity-dependent MEPs depression is also an adapting phenomenon since repetitive performance of the same 2hz opposition does not longer produce a MEPs decrement while such a decrement is restored by different (rotatory) motor tasks. MEPs amplitude modulation is also a spontaneous phenomenon. When series of MEPs derived from resting subjects are submitted to spectral analysis by means of FFT and ARMA, periodicities at 0.003-0.005 and 0.01-0.02 hz have been found. After normalisation of sampling rate, a tendency for a 0.0008 hz periodicity might also be suggested. These data are discussed in relation to possible applications in Neuropsychiatry.

Repetitive Transcranial Magnetic Stimulation (rTMS): A Novel Therapeutic Approach for Major, Drug-Resistant Depression

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Recent studies suggest the genuine potential for rTMS as a psychiatric therapy. This technique has generated positive views about its likely efficacy and usefulness in the treatment of depression. However data are limited and further research is necessary to confirm and extend these findings, particularly in seeking optimal treatment parameters like frequency and duration. Our objective was to cast light on the mechanisms underlying the rTMS-treatment in depression and to verify its clinical applicability. We applied slow as well as high, frequency stimulation in a group of drug-resistant patients, who met criteria for major depressive disorder, schizoaffective disorder and bipolar disorder (ICD9). The Results show that in 61% of the cases active treatment is better than sham treatment. In 5% of the cases treatments are equivalent. In 34% of the cases sham treatment is better than active treatment. Although the results of this study are encouraging, the efficacy of rTMS in the treatment of mood disorders still requests further work on the determination of optimal treatment parameters that may lead to a more complete and enduring response. These preliminary results suggest that rTMS is a promising non-invasive tool for treatment-resistant patients with depression.

Brain and Language: Convergence and Divergence Between Lesion Studies and Neuroimaging

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Most of our knowledge about the cerebral organization of language has been derived from clinical investigations in aphasic patients, conducted using the different methodologies of anatomo-clinical correlation. These findings are the basis of the widely accepted concept of "language areas" in the left hemispheric perisylvian cortex. In recent years, this research field has been considerably enriched by the contributions of psychophysiological and neuroimaging studies in normal subjects, investigated while engaged in linguistic task. The integration of these evidences with the "classical" neuropsychological knowledge has resulted not only in convergence, but also in some discrepant, or unexpected findings. This has led to the revision of some concepts, for example about the function of Broca's area, the neural basis of aphasia recovery, the cerebral correlates of bilingualism and the physiopathology of developmental dyslexia, and to the formulation of innovative, testable predictions about the relationship between brain and language.

Spontaneous Eye Blinking in Consciousness Disturbances

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According to a recent theory consciousness should be maintained and continually renewed by a serial mechanism that allows to confront and integrate the self with the external world by means of an oscillation of attentive focus between these two poles. This attentional shifting should be underlined by the spontaneous eye blinking which correspond to the storage of informations concerning the preceding temporal span. The working memory should make continuous a process that is really discontinuous in origin. Spontaneous blinking rate (BR) results from the balance of substantially two opposite systems, the dopaminergic (excitatory) and the cholinergic (inhibitory) one, and is modulated by cognitive aspects mainly related to information-processing and memory. According to these assumptions the BR analysis in poor or not at all collaborating patients with awareness disturbances and unaffected wakefulness could allow us to infer some informations about cognitive networks activities. From the findings collected in 8 pts a fixed almost automatic BR correspond to the severity of consciousness involvement, whereas a recovery of BR modulation coincides with the first stages of cognitive improving.

ERPs, Thalamo-Cortical Transactions and Consciousness

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The thalamus has been proposed as a neural structure regulating long-latency Event-Related Potentials and behavior (Yingling and Skinner, 1977). More recently, thalamocortical transactions have been shown to represent a substrate for consciousness (Llinas and Ribary, 1998) and evidence has been provided that “non specific” (mostly intralaminar) thalamic nuclei play a pivotal role in this network. Aim of the present study is to review neurophysiological data illustrating the involvement of thalamic nuclei in the regulation of attention, arousal and, ultimately, consciousness. In addition, results are reported of the electro-clinical investigations conducted on a patient with a bilateral paramedian thalamic stroke (“top of the basilar” syndrome) presenting with a condition of akinetic mutism, a global disorder of consciousness. The patient had bilaterally normal

somatosensory evoked potentials, whereas EEG was dominated by a 7 c/sec background activity. Polysomnography revealed lack of a normal structure of sleep, with only stage 1 and 2 NREM sleep, and absence of deeper NREM stages and REM sleep as well. Both the macro and the microstructure of sleep were severely impaired. Mismatch Negativity (MMN) and N1 and P2 components of ERPs were preserved, but P300 could not be recorded. These observations support the role of the paramedian thalamus in mediating regulation of sleep, generating P300 and subserving full consciousness.

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