Depression, mood disorders:
– basic (etiology and investigations)

BRAIN LITHIUM MAGNETIC RESONANCE SPECTROSCOPY SIGNALS CORRELATE WITH SERUM LITHIUM IN PATIENTS ON LONG-TERM BUT NOT ON SHORT-TERM LITHIUM TREATMENT

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In 1988 it was possible for the first time to in vivo measure lithium in human brain using magnetic resonance spectroscopy MRS. A clinical use of lithium is to prevent depressive or manic episodes in affective disorder. The efficacy of this is well established, but it takes six to twelve months of lithium treatment to achieve a decrease in episode frequency. To study whether there is a delay in reaching effective lithium brain concentrations corresponding with the delay in clinical efficacy we compared patients on long-term lithium treatment (› six months) with a group who had been taking lithium for between four and eight weeks. We studied 20 in- and out-patients of the Department of Psychiatry having been on lithium medication for either 4-8 weeks or more than six months . Patients met DSM-III-R criteria for major depression in the course of either recurrent unipolar depressive disorder (DSM-III-R 296.3x) or schizoaffective disorder, depressive type (DSM-III-R 295.70). In each patient it was possible to obtain a satisfactory lithium signal. Accordingly there was a positive correlation of the brain lithium signal after 10 seconds (adjusted to standard solution) with lithium serum levels. There was no correlation of the brain lithium signal after one second with serum lithium. The positive correlation between brain lithium signal (10 s) and serum lithium is due to strong positive correlation in the group of long term patients whereas no correlation is found in the short term group. Distinguishing between diagnostic groups, namely unipolar depressive and schizoaffective, reveals no difference in lithium mean serum concentration and MRS-signal. There is a positive correlation between serum lithium and brain MRS-signal in both groups.

ANHEDONIA AND 5-HT$_2$ RECEPTORS IN DEPRESSION

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5-HT$_2$ receptor changes have been described in depression and long-term antidepressant treatment has been shown to decrease 5-HT$_2$ receptors.
Single Photon Emission Computerized Tomography (SPECT) was used to investigate 5-HT$_2$ receptors in vivo in the brain of depressed patients and normal volunteers, with 2-^{123}I-ketanserin as a ligand.
Our previous findings of a higher uptake of the tracer in the parietal cortex of the patients and of a right greater than left asymmetry in the infero-frontal region of the depressed subjects and not of the controls were confirmed.
A role for 5-HT$_2$ receptors in anhedonia was hypothesized. Indeed, it has been demonstrated that brain serotonin was associated with deficit characteristics in schizophrenia.
Moreover, fenfluramine, which releases 5-HT, and ritanserin, which is a 5-HT$_2$ antagonist, have been shown to have favorable effects on negative symptoms.
A correlational analysis was performed on 2-^{123}I-ketanserin uptake values and Fawcett-Clark Pleasure Scale scores, used a measure of anhedonia.
2-^{123}I-ketanserin uptake values were compared between anhedonic depressive patients and less anhedonic ones.
No relation between anhedonia, or more generally hedonic capacity, and 5-HT$_2$ receptors could be demonstrated.

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EFFECT OF ANTIDEPRESSANT THERAPY ON THE GROWTH HORMONE RESPONSE TO APOMORPHINE

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Several lines of evidence suggest a role for dopamine in the pathophysiology of depression. In 1988, our group reported a blunted response of growth hormone (GH) to apomorphine, a dopaminergic agonist, in endogenous depression. However, antidepressant wash-out period is a major confounding factor in studies of the GH response to apomorphine challenge. Indeed, whereas the influence of tricyclic antidepressants on the GH response to apomorphine is presently unknown, several reports have suggested that tricyclics may impair the GH response to clonidine for periods longer than 3 weeks following their discontinuation. In the present study, we hypothesized that a blunted GH response to apomorphine in depressed patients could be related to the recent administration of antidepressants. Therefore, the GH response to apomorphine (0.5 mg sc) was studied in 11 male DSM-III-R major depressive inpatients who had never received antidepressant therapy compared to 11 normal controls and 11 major depressive inpatients drug free for at least 2 weeks. The three groups differed significantly in the GH peak response : 5.4 ± 4.0 ng/ml in depressed patients who never received antidepressants, 25.5 ± 10.7 ng/ml in normal controls and 5.5 ± 5.1 ng/ml in depressed patients who had not received antidepressants for at least 15 days ($F = 27.8$, $p < 0.00001$). These results suggest that a wash-out period of 2 weeks could be sufficient in studies assessing the GH response to apomorphine.

CATECHOLAMINERGIC FUNCTION AND P300 AMPLITUDE IN MAJOR DEPRESSIVE DISORDER

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Neurobiology of P300 is still a way of controversies. Many human and animal psychopharmacological studies have shown the implication of norepinephrin, dopamine, acetylcholine and serotonin for the generation and modulation of P300 amplitude. Neuroendocrine strategy may provide an indirect index of central transmission. In particular, the growth hormone (GH) response to clonidine (a postsynaptic $\alpha 2$ adrenergic agonist), and to apomorphine (a dopaminergic agonist) are two well studied neuroendocrine tests impaired in depression. In this study, we investigated the relationship between P300 amplitude and catecholaminergic functions as assessed by the clonidine and the apomorphine tests in 15 major depressive patients. The results showed a significant positive correlation between apomorphine test and P300 amplitude ($r = 0.59$, $p = 0.03$), but no relationship was found between the clonidine test and P300 amplitude ($r = 0.09$, $p > 0.05$). This study support that dopamine could be a neurobiological modulator of P300 amplitude.

MOOD DISORDER IN STROKE PATIENTS. IMPORTANCE OF LOCATION OF LESION

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Objective: This study tries to confirm previous reports about post-stroke depression. More specifically, it tries to document the relationship between the incidence and severity of post-stroke depression and lesion location visualized on CT-scan. Methods: Sample: A hundred and thirty patients in the fourth week of the evolution of an unilateral CVA fulfilled inclusion and exclusion criteria. Assessment: Schedule for Affective Disorders and Schizophrenia (SADS) and Research Diagnostic Criteria (RDC), standard measures of severity of depression: Hamilton Rating Depression Scale (HRDS), Montgomery & Asberg Depression Rating Scale (MADRS) and Beck Depression Inventory (BDI). Patients'CT scan were evaluated by one of us who was blinded to the clinical finding, two sorts of the lesion location were considered (Robinson's criteria): a) right/left *hemisphere*, b) *anterior/posterior* . Results: 1) 34 (26%) fulfilled the RDC criteria for major depression, 14 (11%) for minor depression, 8 (6%) for other psychiatric disorders and 74 (57%) had no psychiatric disorders. 2) The prevalence of depression post-stroke (37%) more frequent in anterior lesion ($p=0.009$) and left hemispheric (N.S.) tends to confirm previous reports. Conclusions: These results suggest a close relationship between mood and lesion location after stroke.

ELECTRODERMAL FINDINGS, SYMPTOM STRESS AND PERSONALITY TRAITS IN ANXIETY PATIENTS.

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42 patients with known anxiety disorder classified according to the DSM-3-R criteria for Panic Disorder (PD), Generalized Anxiety Disorder (GAD) and Anxiety Disorder Not Otherwise Specified (ADNOS) were registered for Basic Skin Resistance (BSR), Unspecific Galvanic Skin Response(UGSR), and during auditive stimulation habituating and Specific Galvanic Skin Response (SGSR). The patient groups were compared to a control group of 12. The measurements were repeated after a week under approximately standardized circumstances. The psychophysiological variables were related to the patients personality profiles and anxiety states - found by Millon Clinical Multiaxial Inventory (MCMI) and Spielbergers State-Trait Anxiety Inventory (STAI).
Kruskal-Wallis ANOVA (K-W) was applied to all groups and secondly including only the patient groups. Were significant differences were found Mann-Whitney U-test (M-W) was used on combinations of groups. When appropriate Fisher Exact Probability Test and Spearman Rank Order (S-R) correlations were used. All differences were significant at a two-tailed Alpha level .05 or lower.
Independent of medication the PD patients habituate significantly poorer than controls. GAD patients habituate also poorer than controls allthough not significantly. Measured by BSR ADNOS patients have significantly less physiological arousal than both PD patients and GAD patients. PD patients and GAD patients differ significantly in UGSR as an expression of autonomous diverging reactions to acoustic stress. On neither personality traits nor symptom stress scales the patient groups differ significantly. Therefore, one can say that the uniformity in traits of personality and subjectively registered symptoms correspond to a certain psychophysiological variability.

THE DOPAMINE HYPOTHESIS OF SLEEP DEPRIVATION

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Limbic hyperperfusion and hypermetabolism have been found in patients with major depression responding to total sleep deprivation (TSD) before TSD, but not in nonresponders (1;2). We compared TSD responders and nonresponders with regard to differences in cerebral perfusion and activation of the dopamine system. To assess perfusion rates, 40 patients with major depression, melancholic type (DSM-III-R) and 10 controls were studied with HMPAO SPECT before and after TSD. 14 patients with melancholic depression and 8 controls were investigated with IBZM SPECT before and after TSD to assess D2 receptor blockade. Additionally, the prolactin responses to sulpiride before and after TSD were compared (3). TSD responders had significantly higher limbic perfusion (cingulate gyrus, prefrontal cortex) before TSD than TSD nonresponders and controls. Hyperperfusion was normalized after TSD. Responders had a significantly reduced D2 receptor blockade and a significantly greater prolactin response to sulpiride after TSD than nonresponders, a finding which argues for a greater dopamine release in TSD responders as a correlate of therapeutic action. It is concluded that TSD may act by downregulation of limbic hypermetabolism and upregulation of dopamine release in a subset of depressed patients.

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FREE FORMS OF CATECHOLAMINES AND THEIR ACID METABOLITES IN URINE OF PSYCHOPATHIC PATIENTS WITH DEPRESSIVE SYNDROMES

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Now the interest to the pathogenesis of the psychopathic is brought about not only by the prevalence of this pathology in all developed countries itself, but by the social role of aggressive and autoaggressive behavior, alcohol and narcotic abuse, depressive disorders which often accompany this pathology. The study of the neurochemistry basis of psychopathies and accompaining them depression syndromes is able to improve the elaboration of treatment and rehabilitation approaches of this disorder. The content of free forms of dopamine (DA), norepinephrine (NA), dihydroxyphenilalanine (DOPA), dihydroxyphenilacetic acid (DOPAC), homovanylic acid (HVA) and vanyllylmandelic acid (VMA) was measured by high pressure liquid chromatography with electrochemical detection methods in diurnal urine of 70 psychopathic patients. Eighteen of them had anxiously- depressive syndrome, sixteen patients had asteno-depressive syndrome and 16-hysterically-depressive. Control group included 30 healthy subjects of the same ages.

The results make us to suppose that:

1) versus controls all psychopaths have disturbances of catecholamine system directed to increasing of free forms catecholamine anabolism, combined with marked increasing of activity of monoamine oxidase desamination.

2) all depressive statements investigated in this study are characterized by the common catecholamine system disturbance - the decreased activity of the norepinephrine link.

3) in various group of patients with depressive disorders, there are observed different statements of dopamine system, which possibly determinate some specific clinical features of this depressive statements.

LOCUS OF CONTROL IN ANXIETY DISORDERS : AN ELECTRODERMAL AND EVENT RELATED POTENTIALS STUDY

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This presentation reports on the results of a study concerning the relation of locus of control (LC) to electrodermal (EDA) and event related potentials (ERP) in patients with anxiety disorders.

Using a LC scale as a screening instrument and adopting the ± 1 SD criterion, two groups were identified among 183 patients meeting the DSM III-R criteria for generalized anxiety (n=58), OCD (n=48), panic (n=40) and phobic (n=37) disorders: a group with "internal" (n=37) and a group with "external" (n=42) LC traits.

Both groups were undertaken on separate occasions psychophysiological assessments of (a) EDA (skin conductance level, response latency, amplitude, recovery time and habituation to a series of identical tones and a dishabituating (novel) tone) taken from patients' both hands and (b) ERP (latencies and amplitudes of N100, P200, N200, P300 and N400 waveforms) during a programmed presentation of the Stroop Coloured Words Test, while randomized warning tones were administered to R-ear, L-ear or binaurally. Recordings were taken from the Cz, C3-T5/2 and C4-T6/2 sites.

Regarding EDA, "external" LC patients were significantly superior to "internals" in almost all measures taken (skin conductance level = $P<0.02$, mean amplitude = $P<0.01$, amplitude to "novel" stimulus = $P<0.05$, recovery time= $P<0.05$, spontaneous activity = $P<0.05$ and trial-to-habituation = $P<0.01$). With respect to ERP's, "external" LC patients demonstrated significant prolongation of N200 latency in almost all testing conditions (P range from <0.05 to <0.01).

The findings of this study indicate that "external" LC patients exhibit higher levels of electrodermal arousal leading to prolongation of habituation, coupled with similar habituation difficulties as far as CNS processes are concerned. It is concluded that the biological basis of LC traits is suppotred by the results of this study. The implications to the treatment of anxious patients are discussed.

ANXIETY, DEPRESSION AND LOW MONOAMINE OXIDASE ACTIVITY ARE ASSOCIATED WITH HEART DISEASE PRONENESS IN DANISH MEN AND WOMEN

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A series of three studies were carried out on possible relations between psychological and biological traits that have often been associated with coronary heart disease. The first study examined personality traits that may predispose an individual to develop a coronary heart disease. Four hundred males and four hundred females were randomly selected from the Danish population. They received the Jenkins Activity Survey (JAS) on two occasions, once in 1988 and again in 1992. The JAS provided a measure of coronary-prone behavior (CPB) in terms of the degree of time urgency and ambitiousness (Factor A), speed and impatience (Factor S), hard-driving and competitiveness (Factor H) and job involvement (Factor J) shown by the subjects. The scores obtained for all four factors tended to be lower in 1992 than in 1988, indicating that CPB has tended to decline during the past four years in the Danish adult population.

The second study investigated possible relations between negative emotions (i.e. anxiety and depression) and CPB in angina patients. The Bech Rating Scale (BRS) of mood disorders and the Jenkins Activity Survey (JAS) were administered to a consecutive sample of angina patients, to a consecutive sample of noncardiac patients, and to a random sample of adults from the general population. Anxiety and depression were both more frequent and more severe in angina patients than in noncardiac patients or in the general population. No consistent changes in anxiety, depression or CPB were observed in angina patients during more than seven years of illness, except for an initial decline in job involvment. Clinical features of angina patients, such as the use of nitroglycerin and the presence of ECG abnormalities, failed to be reliably related to the severity of anxiety and depression. The findings indicate that anxiety and depression tend to be both severe and long-lasting in patients with angina pectoris, in support of the notion that negative emotions may play a central role in the course of the illness.

The third study examined whether CPB is associated with the activity of monoamine oxidase, an enzyme responsible for the degradation of catecholamines in the bloodstream. Forty healthy male nonsmokers completed the Jenkins Activity Survey (JAS) and had a blood sample drawn while at work. High scores on JAS scales were associated with low MAO activity in blood platelets. The findings support the notion that low activity of MAO may contribute to sympathetic hyperreactivity in coronary-prone individuals.