patients with schizophrenia, patients s/p unilateral anterior temporal lobectomy, patients s/p surgical excision of focal frontal tumors, and healthy controls. Results reveal that initial acquisition functions correlate as expected with illness severity parameters, but after titration on initial accuracy levels, delay effects are similar across groups. These findings suggest that after controlling for basic perceptual and response classification processes, differential frontal and mesiotemporal lesion effects are difficult to discern. The results support the hypothesis that both patients with schizophrenia and those with focal frontal or mesiotemporal lesions may show deficits reflecting integrated frontolimbic system dyscontrol, and severity of impairment in basic classification operations may mark this dysfunction.

SHAPE PERCEPTION IN SCHIZOPHRENIA: EEG ANALYSIS OF A CORTICAL ACTIVATION TASK

Bernd Gallhofer. *Centre for Psychiatry, Justus-Liebig University, Am Steg 22, D-35385 Giessen Germany*

Altered lateralization of brain function is currently under intensive discussion as a possible factor in the pathogenesis of schizophrenia. Numerous studies have demonstrated lateralized EEG patterns under activation. Right parietal cortical regions are well known to be pivotal for shape perception in normals.

We developed a shape perception task in which slowly changing elementary geometric forms (circle, triangle, rhombus) were displayed on a computer screen. Subjects were asked to press a reaction button when changing shapes were perceived as symmetric. Topographic cEEG and reaction times were measured during the task.

15 unmedicated sub-chronic (total duration of illness less than 2 years) patients with schizophrenia (ICD-10 F20.0, F20.3) were compared to 15 matched normal controls. Patients with major depression (ICD-10 F31.4, F32.2) were recruited as an additional control group.

EEG Analysis showed distinct patterns of lateralization in the examined groups. Implications are discussed in view of the ongoing debate on the pathogenesis of schizophrenia.

TOWARDS AN UNDERSTANDING OF THE COGNITIVE BASIS OF DELUSION FORMATION IN SCHIZOPHRENIA USING VISUAL SCAN PATHS

M.L. Phillips, A.S. David. *Department of Psychological Medicine, Institute of Psychiatry, London. SE5 8AZ*

Cognitive explanations for delusion formation have emphasised the role of distorted appreciation of complex stimuli. The study investigated information processing in deluded subjects (DS) using a novel, physiological marker of visual attention, the visual scan path — a map tracing the direction and duration of gaze when an individual views a stimulus. The aim was to demonstrate the presence of a specific deficit in processing meaningful stimuli (eg. human faces) in DS by relating this to abnormal viewing strategies. Visual scan paths were measured in DS ($n = 7$), non-deluded schizophrenics ($n = 7$) (≥ 3 and < 3 on SAPS, respectively) and age-matched normal controls ($n = 10$). Neuroleptic medication, SANS score and illness duration did not differ significantly between patient groups. The eye-tracking unit employed a pupil-diameter determination technique via infrared illumination. A fixation was defined as consecutive gaze positions within one degree for 200 milliseconds or more. DS employed abnormal strategies for viewing single faces and face pairs in a recognition task, staring at fewer points and fixating non-feature areas to a significantly greater extent than control groups ($p < 0.05$). Testing on a second occasion with DS demonstrating improvement in delusion ratings revealed a less-marked difference in viewing strategies across all three groups. The results indicate the presence of abnormal information processing in DS: reliance on less-salient visual information for decision-making in the recognition task, which diminishes with resolution of delusions. This suggests a state-dependent processing abnormality in DS, and can be linked with theories of abnormal reasoning underlying delusion formation.

THE HISTORICAL BACKGROUND AND COGNITIVE NEUROSCIENCE OF PERCEPTUAL PROCESSES IN PSYCHOSIS

M. Spitzer. *Experimental Psychopathology Section, Department of Psychiatry, University of Heidelberg, Voss-Str. 2, D-69115 Heidelberg, Germany*

In the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), hallucinations are defined as "a sensory perception that has the compelling sense of reality of a true perception but that occurs without external stimulation to the relevant sensory organ." (p. 767).

This definition dates back to Karl Jaspers, who not only established the clear-cut distinction between perception and imagery, presumably on "phenomenological" grounds, but also likened hallucinations to perception. This view has remained standard in clinical psychiatry up to the present although it was questioned whenever hallucinations were scrutinized in detail. In fact, the concept was explicitly stated to be of little use for clinical work (cf. Schröder 1915) as well as in research into the effects of hallucinogens (cf. Beringer 1927), sensory deprivation (cf. Shurley 1962, Vernon 1963), and electrical cortical stimulation (cf. Penfield & Perot 1963). Recent findings in the field of cognitive neuroscience, as summarized by Kosslyn (1994), further question the validity of the perception-imagery distinction and any concept based on it.

It is concluded that the history of the concept as well as recent findings from research into visual and imagery processes justify a conceptual change. Hallucinations should not be defined as "true sensory perceptions", but rather as experiences that are more or less perception-like. It is argued that although this definition appears to be less precise than the current definition, it in fact leaves more room for clinical description and does not force the clinician to making an arbitrary distinction.

VISUAL SCANNING STRATEGIES AND COGNITIVE DYSFUNCTIONS IN A VISUOMOTOR TRACKING TASK IN THE COURSE OF SCHIZOPHRENIA

W. Wölwer, M. Streit, W. Gaebel. *Dept. of Psychiatry, University of Düsseldorf, 40605 Düsseldorf, FRG*

In the search for neurobiological determinants of cognitive dysfunctions in schizophrenics, objective and differentiated behavioral indicators of these dysfunctions are needed. In normals the analysis of visual scan path has proved to be a useful tool to study cognitive processes for years. Appropriate task conditions presupposed, scan path analysis may also help in a differentiation of cognitive dysfunctions in schizophrenia. Using eye movement recordings during the performance of the trail-making test (TMT) we have recently shown that acute schizophrenics have difficulties in parallel processing of visuomotor search and manumotor tracking, resulting in poorer TMT performance. Since these — timestable — dysfunctions occurred especially under test conditions requiring the subjects to alternate between two response categories (TMT-B) but not under conditions using only one response category (TMT-A), the present study should clarify the contribution of (1) pure manumotor tracking abilities and of (2) the ability to shift response categories to the TMT performance deficit. Therefore, the original TMT-A/-B and experimental variations of the task (1) without the necessity of concurrent visuomotor

search to manumotor tracking or (2a) with an external support of the category shift and (2b) a task which assesses the ability to switch response categories without concurrent visuomotor search and manumotor tracking were applied to 22 remitted schizophrenics (S), 15 remitted major depressives (D) (DSM-III-R) and 25 normal controls (N).

Our former results from acute S showing deviations in visual scanning strategies associated with a TMT-B performance deficit — but unrelated to neuroleptic medication — could be replicated in remitted S, too. Moreover, results of the TMT variations reveal that the performance in TMT-A relies mainly on manumotor tracking abilities, whereas TMT-B performance is mainly determined by the ability to shift response categories, which seem to be especially impaired in schizophrenics. This points to a reduced cognitive flexibility in schizophrenics, most probably related to prefrontal lobe dysfunctions. Using the research approach outlined in the present study research on this relationship probably will be facilitated in future.

S63. The natural history of psychotropic drugs

Chairmen: M Lader, J Angst

MOCLOBEMIDE: A PARADIGM OF RESEARCH IN CLINICAL PSYCHOPHARMACOLOGY

Jules Angst [1], Roman Amrein [2], Max Stagbl [2]. [1] *Psychiatric University Hospital Zurich, P.O. Box 68, CH-8029 Zurich, Switzerland;* [2] *F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, CH-4002 Basel, Switzerland*

The pre-clinical development of moclobemide is an example of broad research combined with serendipity. Moclobemide was first hypothesized as being an anti-lipemic or antibiotic, but the screenings were negative. The search for its antidepressant qualities, based on anticholinergic tests, proved also negative and moclobemide was then suspected of being an antipsychotic before its specific and reversible MAO-A inhibition qualities were detected. After the establishment of its lack of relevant interference with tyramine pressure response, clinical trials were launched in 1977.

In a first stage, multiple, small open and double-blind studies were carried out. Two decisive large multicentre double-blind studies were later performed in Latin America and Austria. Further trials have confirmed the broad antidepressant activity of RIMAs, which is not confined to any one subtype of depression and which show good tolerability and low toxicity. Since moclobemide has been available on the market, extensive meta-analyses of a large data set provided a series of methodological results: factor structure of the HAM-D, optimal criteria of efficacy, predictors of response, onset of action for antidepressants and placebo.

THE HISTORY OF TACRINE IN THE TREATMENT OF ALZHEIMER'S DISEASE

S.A. Eagger. *Senior Lecturer in Psychiatry of the Elderly, Imperial College School of Medicine at St Mary's, Academic Unit of Psychiatry, St Charles' Hospital, Exmoor Street, London W10*

Since Tacrine, a cholinesterase inhibitor was first reported to enhance cognitive function in patients with Alzheimer's Disease by Summers et al in 1986, it has indeed been a controversial drug. The history of its use in this context, the numerous trials and issues raised will be covered by this presentation.

It has become the first licensed treatment for Alzheimers Disease primarily approved by the FDA in the United States, some European countries and Australia.

THE RISE AND FALL OF THE BENZODIAZEPINES

M.H. Lader. *Institute of Psychiatry, De Crespigny Park, London, SE5 8AF*

The first of the benzodiazepine group of drugs, chlordiazepoxide, was introduced after 1960 to most countries of the world. It was followed by a large number of similar compounds which were used as anxiolytics, hypnotics, anticonvulsants, muscle relaxants and as pre-operative sedation. The major advantage of these compounds was their safety in overdose and an apparently low predisposition to inducing dependence and abuse. Although early studies suggested some dependence potential, this did not seem to materialize in practice. Because of this, early concerns about the benzodiazepines soon subsided and they became amongst the most successful drugs ever introduced. Inevitably, their usage increased and their indications widened into non-medical conditions such as worry and misery. The number of chronic users escalated and concerns began to be expressed about the extent and usage — the *"Benzodiazepine Bonanza"* and the *"Opium of the Masses"*. It was even suggested that these tranquilisers were prescribed by male doctors to help disadvantaged females acclimatize to their social and economic problems.

A series of studies showed that dependence could occur at normal dose ie without escalation. It became apparent that a substantial proportion of long-term users encountered clinical problems on attempting to withdraw. A concerted campaign was conducted by many doctors and by the media in order to warn users of the potential dangers. At the same time it became increasingly aware that the benzodiazepines were major drugs of abuse being taken either adjunctively to other drugs of abuse or as the primary agent. The mode of administration could be orally by sniffing, but increasingly by intravenous injection. The last resulted in extensive vascular trauma. Finally, it became clear that these drugs produced toxic effects, especially in the elderly.

Regulatory authorities throughout the world brought inwarnings about the benzodiazepines and attempted to limit their use both as tranquilisers and as hypnotics. The benzodiazepines were scheduled as potential drugs of abuse and this is becoming more rigorous.

CLOZAPINE — THE FALL AND RISE OF AN ANTIPSYCHOTIC

Dieter Naber. *Psychiatrische und Nervenklinik, Universitäts-Krankenhaus-Eppendorf, Universität Hamburg, Martinistrasse 52, 20246 Hamburg*

Clozapine is an atypical neuroleptic drug, not only because of its clinical profile, but also due to a peculiar history. It was investigated in Central Europe, the first open trial with 19 chronic schizophrenic patients did not show neuroleptic efficacy, a second one with pain patients was also unsuccessful. The company was close to "bury" the drug, when, in 1962, Gross and Langner found impressive improvements in 54% of chronic schizophrenic patients treated with 400 mg/day. Technical difficulties in the synthesis of clozapine resulted in the delay of further clinical trials, but more important was the surprising finding that clozapine had no extrapyramidal effects, despite antipsychotic efficacy. At that time, there was a "psychopharmacological dogma" that motor effects were necessary for a "real"

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