Eleven healthy subjects (10 men, 1 woman; 23–34 years) and nine neuroleptic naive schizophrenic patients (8 men, 1 woman; 21–28 years) (DSM-IV) were recruited according to previously formulated criteria [2]. MRI was performed to exclude brain pathology. Two PET experiments were performed in each subject. In each experiment 200–300 MBq of the ^{11}C-labelled selective D_1-receptor antagonist SCH 23390 was injected IV as a bolus. In the first a high (321–2061 Ci/mmol) and in the second a low specific radioactivity (2.3–4.3 Ci/mmol) was injected. Radioactivity was measured for 33–63 min using the Scanditronix PC2048-15B PET-system. Anatomical delineations for regions of interest (ROI's) for the caudate nucleus and putamen were made on all MRI sections where these structures appeared. For the cerebellum ROI's were drawn on the 2 middle sections. The ROI's were transferred to the corresponding PET sections. The total radioactivity in each structure was measured for each sequential scan, corrected for decay and plotted as a function of time. For the quantitative analysis the cerebellum was used as reference region to estimate the free radioligand concentration in the brain. Specific [^{11}C]SCH 23390 binding was defined as the difference of radioactivity concentration in the caudate/putamen and that in the cerebellum. An equilibrium analysis was performed to determine B_{max} (density) and K_d (affinity) values for [^{11}C]SCH 23390 binding in the caudate and putamen [2].

There was no difference between the group means of the B_{max} and K_d values in the caudate and putamen (Fig). There was a significantly greater variability both in the B_{max} and K_d values of the putamen in the patient group (Fig.). There was also a significantly greater variability in the K_d values of the caudate in the patients ($p < 0.01$). The Bound/Free ratio (binding potential) in the putamen tended to be lower in the patient group ($p = 0.1$) (Fig.).

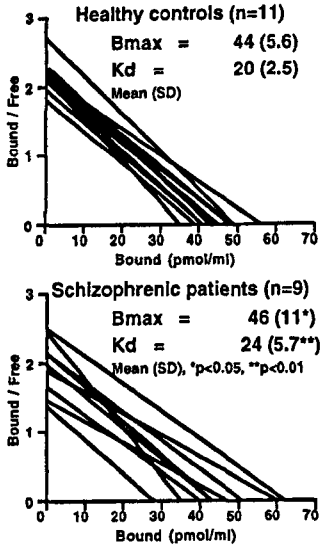

Fig. Scatchard plot of [^{11}C]SCH 23390 binding in the putamen measured by PET

The larger variability of [^{11}C]SCH 23390 binding may reflect a disturbed D_1-dopamine receptor activity in some schizophrenic patients.

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5HT2 RECEPTOR MEASUREMENT IN SCHIZOPHRENIA BY PET

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An involvement of the serotoninergic system has been hypothesized in schizophrenia: some post-mortem studies reported abnormalities of the 5-HT2 receptor numbers in the prefrontal cortex of schizophrenic patients. Furthermore, many antipsychotic drugs (APD) have a high affinity for these receptors and it has been proposed that this ability might be involved in some of their therapeutic effects. We used positron emission tomography and 18-F Setoperone, a high affinity radioligand of cortical 5-HT2 receptors, in order to study: 1/ the in vivo frontal cortex 5-HT2 receptor density in a group of untreated schizophrenic patients and 2/ the effect of conventional dosages of various antipsychotic drugs on the binding of 18-F setoperone to these receptors.

Preliminary analysis in a group of 14 untreated schizophrenics did not demonstrate change in the frontal cortex 18-F setoperone specific binding. However, when compared with the untreated group, patients receiving chronic treatments by clozapine (CZP) but also by chlorpromazine (CPZ) had a marked reduction of the specific binding of 18-F setoperone in the frontal cortex. In the CPZ group, this reduction correlated with oral and plasma dosages of the drug, and total saturation of the cortical 5-HT2 receptors was reached for oral doses equal or superior to 800 mg/d. In the CZP group, usual therapeutic doses induced at least 80% occupancy of these receptors and saturation was reached at 500 mg/day. Patients treated by amisulpride, a specific dopaminergic receptors antagonist, did not differ from untreated patients. In the basal ganglia, interaction with the 18F Setoperone binding was less marked with CZP than with CPZ.

These results suggest that both CZP and a typical neuroleptic such as CPZ produce at therapeutic dosages a significant effect on the cortical serotoninergic system in schizophrenic patients. This effect appears to be neither specific to atypical APD nor common to all neuroleptics.

THE IMPACT OF IN VIVO RECEPTOR PET MEASUREMENT ON NEUROPHARMACOLOGY

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Positron emission tomography (PET) is a direct, quantitative approach to explore relationships among central neuroreceptor occupancy, psychotropic drug blood levels and clinical effects. In the development of new drugs PET may be used to define dose-response relationships and to explore mechanisms of atypical effects. We have used the radioligands [^{11}C]raclopride and [^{11}C]NMSP to study antipsychotic drug binding to central D_2- and 5-HT_2 receptors in man. Clinical treatment with classical neuroleptics induces a uniformly high (70–90%) D_2 receptor occupancy. The risk of extrapyramidal side-effects was significantly increased in patients with D_2 receptor occupancy above 80%, whereas patients with low (below 50%) occupancy were less likely to receive antipsychotic effect. Receptor occupancy was high already at low drug plasma concentrations. Schizophrenic patients in remission treated with haloperidol decanoate had only an intermittently high (> 70%) occupancy during a 4-week injection interval. A continuously high D_2 receptor occupancy may thus not be required to prevent schizophrenic relapses. Our observations point to the need to re-evaluate dose-response char-

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acteristics of the conventional neuroleptics, in particular, at doses considerably lower than previously examined.

It has been proposed that the "atypical" properties of clozapine is explained by its simultaneous interaction with 5-HT_2 and D_2 receptors. We have demonstrated very high (85–90%) 5-HT_2 receptor occupancy and low (20–67%) D_2 receptor occupancy in patients treated with low to moderate doses of clozapine. This finding supports the position of the 5-HT_2 receptor as potential mediator of atypical effects. The putative atypical antipsychotics risperidone and olanzapine induced high occupancy of both D_2- and 5-HT_2 receptors at clinically relevant doses. Further clinical characterization of such new compounds will thus provide valuable leads to the clarification of atypical antipsychotic action.

IN VIVO RECEPTOR SPET STUDIES OF ANTIPSYCHOTIC DRUG ACTION

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Nuclear medicine techniques (positron emission (PET)- and single photon emission tomography (SPET)) now permit examination of brain receptors in living subjects. As these receptors are targeted by antipsychotic drugs, hypotheses concerning drug action may now be tested in vivo. In particular, schizophrenic nonresponders and responders to classic antipsychotic drugs show similar levels of D2 blockade by the drugs. The atypical antipsychotic drug clozapine has beneficial effects without high striatal D2 receptor blockade. We will report data showing the novel atypical drug, olanzapine occupies striatal D2 receptors to the same low extent as clozapine. However, another new atypical antipsychotic drug, sertindole, like risperidone, shows high levels of striatal D2 blockade but few extrapyramidal side effects. These data will be discussed in the light of recent theories as to the neuropharmacology of schizophrenia.

S78. New perspectives in psychiatric epidemiology

Chairmen: H Hafner, J Angst

EPIDEMIOLOGY OF SEXUAL PROBLEMS AND DYSFUNCTIONS IN THE COMMUNITY

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Representative community studies of sexual dysfunctions are almost non-existent. Two studies have been conducted on middle aged women [1,2], but no studies of males have been launched as yet.

In the Zurich cohort study 591 males and females were interviewed five times during a 15 year period, from ages 20–35. At age 35, 69% of the subjects were still in the study. Sexual dysfunctions were assessed in one section of a broad semi-structured interview carried out by clinical psychologists. The prevalence rates obtained were cumulatively gathered over the five interviews and weighted back to the normal population.

Emotional sexual problems were found in 21% (males 12.6, females 29.2), low sexual desire in 29% (males 23%, females 35.1%) and functional problems in 17% of cases (males 10.5%, females 23.3%). Sexual dysfunctions were found to be associated with depression, anxiety disorders and insomnia, but no association with other functional somatic syndromes was recorded. Females differed from controls in their elevated scores of neuroticism and autonomous lability as found by Osborne et al. [2]. Moreover, females were characterised by low self-esteem and mastery and by increased avoidance coping strategies. Subjects with children developed sexual problems more frequently and these were usually caused by difficulties in partnerships and core family.

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CEREBRAL VENTRICLE DIMENSIONS AS RISK FACTORS FOR SCHIZOPHRENIA AND AFFECTIVE PSYCHOSIS: AN EPIDEMIOLOGICAL APPROACH TO ANALYSIS

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The literature on neuroimaging in psychosis contains many references to, so called, "enlargement" of some structures, the dimensions of which vary continuously throughout the population with considerable overlap between affected and unaffected groups. Is this concept of enlargement valid?

A case-control study was undertaken of volumetric computerized tomographic scan measures in 216 consecutive admissions for functional psychosis and 67 healthy community controls. Odds ratio analysis demonstrated significants linear trends in the association between increasing lateral and third ventricle volumes, and both RDC schizophrenia ($N = 121$) and schizo-affective disorder ($N = 41$); cases were consistently associated with larger volumes than controls. There was an association between larger third, but not lateral, ventricle size in affective psychoses ($N = 54$). These associations were statistically independent of intracranial volume, sex, social class and ethnicity, factors which were significantly associated with ventricular measures in the controls and presumably, in the general population. There was no evidence of a threshold corresponding to the notion of normal *versus* enlarged ventricles.

GENETIC EPIDEMIOLOGY OF FUNCTIONAL PSYCHOSES

W. Maier.

The presentation will focus on schizophrenia and bipolar affective disorder.

During the last decades a broad variety of studies explored the patterns and the determinants of the familial aggregation of the major psychiatric disorders. As most other common diseases all functional psychoses are aggregating in families.

The diagnostic specifity of the familial patterns of aggregation is low. Particularly with affective disorders occurring more frequently than expected by chance in families of probands with schizophrenia. The various subtypes of both disorders are not breeding true in families with the single exception of bipolar affective/schizoaffective disorders.

Family, twin and adoption studies clearly demonstrated that both disorders are of multifactorial origin. Although the specific nature of causes is widely unknown it is evident that genetic as well as environmental factors (familial as well as individual) are contributing as it has also been shown for other common diseases.