

type of schizoaffective disorder or a non-residual schizophrenia with prominent depressive symptoms have been investigated. The combination of amitriptyline and haloperidol was superior to risperidone in major depression with psychotic features but not in the depressive type of schizoaffective disorder, where both treatment groups showed comparable reductions of BPRS and BRMS scores. Thus, the nosological distinction by categorical diagnoses could be corroborated by pharmacological means.

In another clinical trial, the efficacy of the selective D<sub>2</sub>-like antagonist amisulpride was investigated versus the D<sub>2</sub>-/D<sub>1</sub>-like/5-HT<sub>2</sub> receptor antagonist flupentixol in schizophrenia with predominant positive symptomatology, and improvement of co-occurring negative and depressive symptoms was evaluated in 132 patients. Both drugs improved negative symptoms as measured by the SANS but this effect was more marked in the amisulpride group. With regard to depressive symptoms, amisulpride produced a greater BRMS decrease than flupentixol, but this difference did not reach statistical significance. However, it has to be taken into account that amisulpride caused less extrapyramidal side effects than flupentixol.

The distinction between negative and depressive symptomatology provokes methodological problems with regard to syndromal overlap, appropriate assessment scales and their sensitivity to change. A pharmacological dissection between negative and depressive symptomatology by the response to selective psychotropic agents may contribute to a more powerful and workable functional definition. Certainly, not only positive symptoms improve under neuroleptic treatment. Specific neuroleptics with different receptor affinity profiles and antidepressive/antipsychotic combinations may be effective treatments for psychotic syndromes with both depressive and negative symptoms, and their differential effect sizes have to be clarified by further clinical trials.

#### BRAIN CHANGE OVER TIME IN SCHIZOPHRENIA — RELATIONSHIP TO NEGATIVE SYMPTOMS AND OUTCOME

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Brain structural deviations (ventricular enlargement, cortical volume reduction, and other anomalies) are present in patients with chronic schizophrenia. The origin of these observations, however, remains controversial. While some structural differences may have resulted from faulty brain growth prenatally or during the early years of life, others may be part of an actively progressing brain process from childhood through adulthood, and continuing after the onset of psychotic symptoms. Although, it is difficult to study a large population of schizophrenic patients before they are identified with definite illness, we have been conducting a prospective follow-up study of 1st episode schizophrenia, as close to the illness onset as possible. A total of 50 patients and 20 controls have been followed over an approximate 5 year period. A battery of clinical diagnostic and cognitive evaluations have been performed, as well as MRI scans of the brain on an annual basis. Ventricular size enlarges over time to a small degree in both patients and controls. Hemispheric cortical volume, on the other hand, decreases over time and significantly more so in patients than controls. No clinical correlates, however, were found to cortical change. Further analyses of regional brain change and specific cognitive change are in progress in order to determine the significance of these findings.

#### BRAIN IMAGING OF DOPAMINERGIC VARIABLES IN NEGATIVE SCHIZOPHRENIA, AND DURING NEUROLEPTIC TREATMENT

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It has been hypothesized that negative symptoms may be related to a deficient dopaminergic transmission, and respond poorly to classical neuroleptics.

At the presynaptic level, we studied the dopaminergic function with PET and 18F-FluoroDOPA, using the Patlak method in 6 non-neuroleptized schizophrenics and controls. The variance of the 18F-Dopa uptake constant K<sub>i</sub> was significantly increased in patients: the 18F-Dopa uptake constant K<sub>i</sub> was markedly increased in some, but not all, schizophrenics, and decreased in catatonia.

In order to investigate the links between primary negative symptoms and dopamine D<sub>2</sub> (postsynaptic) receptors, we selected young, drug-free negative schizophrenics. The measure of the striatal D<sub>2</sub> receptors assessed by PET negatively correlated to the scores of a dimension of psychomotor poverty, involving core negative symptoms as alogia and blunting of affects [1]. The therapeutic effects of low doses of a benzamide specific for D<sub>2</sub>/D<sub>3</sub> receptors (amisulpride), were assessed in these patients: it improved some negative symptoms in a double blind therapeutic trial [2].

The relationships between the in vivo D<sub>2</sub> receptor occupancy by neuroleptics and their dosages were investigated in an extended sample of patients. The levels of D<sub>2</sub> occupancy associated with the dosages recommended for therapeutic effects on positive, or on negative symptoms differed, but there was no evidence of a difference in D<sub>2</sub> occupancy in responders or non-responder patients [3]. In order to look for the optimal therapeutic dose range for amisulpride in responder patients, the in vivo D<sub>2</sub> occupancy intervals were studied in a group of schizophrenics before, then while receiving this compound. A range of 70–80% occupancy of the striatal D<sub>2</sub> receptors, suggested as an optimal interval for therapeutic action on positive psychotic symptoms, was obtained with an amisulpride dosage ranging between 630 and 910 mg a day, while an occupancy of 85%, suggested to be associated with pronounced extrapyramidal side-effects, was reached with 1100 mg a day [4].

[1] Br J Psychiat 1994 164, 27–34.

[2] Am J Psychiat 1995 152, 130–133.

[3] Psychiat, Psychobiol 1990 5, 231–240.

[4] Psychopharmacol 1996 (in press).

#### PSYCHOPHARMACOLOGY OF POSITIVE AND NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: BEHAVIOURAL MODELS AND PHARMACOLOGICAL PROFILES

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The so-called typical antipsychotic agents are active in treating positive symptoms of schizophrenia but are much less effective against negative symptoms. Atypical antipsychotics have reduced liabilities to produce extrapyramidal side effects and, in some cases, also reduce negative symptoms. Clinical efficacy against negative symptoms has been reported for clozapine, risperidone and amisulpride and close scrutiny of the behavioural and neurochemical profiles of these drugs may provide an understanding of potential commonalities in their mechanisms of action. All three drugs have affinity for dopamine D<sub>2</sub>/D<sub>3</sub> receptors but their overall neurochemical profiles show major