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_2-like antagonist amisulpride was investigated versus the D_2-/D_1-like/5-HT_2 receptor antagonist flupentixol in schizophrenia with predominant positive symptomatology, and improvement of co-occuring 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

L.E. DeLisi, M. Sakuma, D. Polina, R. Grimson. *Department of Psychiatry, HSC, T-10, SUNY Stony Brook, Stony Brook, NY 11794, USA*

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

J.L. Martinot, M.L. Paillère-Martinot, M.H. Dao-Castellana, D. Levy, M.F. Poirier, Y. Lecrubier, J.F. Allilaire, A. Manus, A. Feline. [1] *INSERM U 334, GiPsy, SHFJ-CEA, 91406 Orsay; Psychiatric departments from the hospitals: Bicêtre, A. Chenevier, Ste Anne (SHU), La Salpêtrière, France*

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 Ki was significantly increased in patients: the 18F-Dopa uptake constant Ki 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 D2 (postsynaptic) receptors, we selected young, drug-free negative schizophrenics. The measure of the striatal D2 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 D2/D3 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 D2 receptor occupancy by neuroleptics and their dosages were investigated in an extended sample of patients. The levels of D2 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 D2 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 D2 occupancy intervals were studied in a group of schizophrenics before, then while receiving this compound. A range of 70–80% occupancy of the striatal D2 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

D.J. Sanger, R. Depoortere, Gh. Perrault, B. Scatton. *CNS Research Department, Synthelabo Recherche, 31 Ave P.V. Couturier, 92220 Bagneux, France*

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_2/D_3 receptors but their overall neurochemical profiles show major

differences. Amisulpride is a selective antagonist at D_2/D_3 receptors with preferential activity at presynaptic autoreceptors. In marked contrast, clozapine and risperidone show higher affinity for $5HT_2$ and α than for D_2/D_3 receptors. Many traditional models used for drug screening involve the antagonism of effects induced by dopamine agonists and may be more relevant to positive symptoms (or even motor side effects) than to negative symptoms. However, a number of recent studies have attempted to develop alternative behavioural procedures modelling different psychotic symptoms. In such studies, amisulpride has been found to exert pro-hedonic activity and clozapine has been reported to reduce spontaneous or drug-induced social withdrawal. Further pharmacological analysis of these models may eventually provide more sensitive procedures and allow the discovery of more effective antipsychotic drugs.

NEURAL NETWORKS, NEUROPLASTICITY, AND NEUROMODULATION: A FRAMEWORK FOR UNDERSTANDING FORMAL THOUGHT DISORDER AND DELUSIONS

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

From a neurocomputational perspective, the cortex can be viewed as a computational surface that creates and maintains dynamic maps of representations of important sensorimotor and higher level aspects of the environment and the organism. Most importantly, representations of information in the cortex and in these maps have been demonstrated to dynamically change according to salience and frequency of the input. This feature is referred to as neuroplasticity. The fact that general operational characteristics of computational maps in the cortex can be fine-tuned according to specific processing needs is referred to as neuromodulation. Within this framework of cortical maps and their computational models, the following hypotheses regarding formal thought disorder as well as acute and chronic delusions are discussed:

(1) Formal thought disorder is caused by dysfunctional lexical access which can be modeled in terms of low signal-to-noise ratio within network information processing. Evidence for the crucial role of dopamine modulating signal-to-noise is presented and a model of schizophrenic thought disorder is developed, which allows a parsimonious explanation of a number of otherwise inexplicable or unrelated clinical phenomena and experimental results. (2) Acute delusions may represent a state of too high signal-to-noise, as suggested by some experimental studies and clinical features. (3) In chronic delusions, cortical representations become deformed as the result of long-term dysfunctional activation of the network.

In conclusion, the neurocomputational approach to schizophrenic symptoms provides new insights into psychopathological phenomena. The approach is detailed enough to allow empirical testing and has therapeutic implications.

S8. Craving reduction in alcoholism

Chairmen: H Sass, K Mann

ADDICTIONS AND DEPRESSIVE DISORDERS

J. Adès, M. Lejoyeux. *Service of Psychiatry, Hospital Louis Mourier, 92700 Colombes, France*

The frequent co-occurrence between addictions and depressive disorders is well established, even if many questions are unsolved concerning the nature of this interrelation. Three situations can be emphasized: Some addictive disorders, especially alcoholism, opiate and cocaine addictions are secondary to depressive disorders, and can be explained through the "self treatment" hypothesis of depression mood by psychoactive substances. The principal data are here discussed, for alcoholism and heroine addictions: the frequency of primary depressive disorders is well established in opiate addiction, better than for alcoholism.

- In most cases, depressive disorders are secondary to addictive disorders: this is especially the case for alcoholism, as well as about 80% of depressive disorders appear after the onset of alcohol abuse and wean with proctacted withdrawal. In those cases, depression could be due to the pharmacological and psychological effects of alcoholic intoxication, as many pharmacological data demonstrate the negative effects on mood of alcoholic during use.

The third hypothesis will be discussed involving an accidental co-occurrence of depressive disorders and addictions, considering the high prevalence of those troubles in the general population.

RESULTS OF A CONTROLLED MULTICENTER STUDY WITH RITANSERIN AND THE EFFECTIVENESS OF OTHER SEROTONERGIC AGENTS IN ALCOHOLISM

J. Boening, G.A. Wiesbeck. *Department of Psychiatry, University of Wuerzburg, Fuechsleinstr. 15, 97080 Wuerzburg, Germany*

There is considerable evidence from both human and animal studies that serotonergic mechanisms play an important role in the modulation of alcohol intake and dependence (LeMarquand et al 1994). Yet, only a few serotonergic substances have been tested in clinical trials with a satisfying methodological design (Boening 1996). *Fluvoxamine,* a specific serotonin reuptake inhibitor, showed no efficacy in a controlled European multicenter study with 530 alcohol dependents who were treated for six months (Chick, unpbl.). *Fluoxetine* also failed to be superior to placebo in a 12-week trial with 101 alcohol dependent patients (Kranzler et al 1995). In animal studies the $5\text{-}HT_2$ receptor antagonist *ritanserin* was able to significantly reduce both the preference for and the intake of alcohol and cocaine. In an early phase II trial positive effects of *ritanserin* were shown in humans as well (Monti and Alterwain 1991). Therefore, it was hypothesized that *ritanserin* is more effective than placebo in preventing relapse in detoxified alcohol dependents. In a controlled double-blind European multicenter study 493 chronic alcoholics were treated with three doses (2.5/5/10 mg) *ritanserin* versus placebo over a period of six months.

Ritanserin was well tolerated. The most frequent adverse experiences were headache and insomnia. A small increase in weight in the ritanserin-treated patients and a small QTc prolongation in the ritanserin 10 mg group were observed. There was no significant difference between *ritanserin* (2.5/5/10 mg daily) and placebo in the number of relapses, the time to relapse, the craving for alcohol, and the drinking habits after relapse. So far, no serotonergic substance has shown its effectiveness in relapse prevention in clinical trials with demanding methodological designs. Maybe that only subgroups of alcoholics (Cloninger Type II, high impulsivity, etc.) can be considered for the relapse prevention with serotonergic substances.

OPIATE RECEPTORS: ROLE IN ADDICTION AND RELAPSE IN ALCOHOL DEPENDENCE

J.D. Chick. *Royal Edinburgh Hospital, Edinburgh EH10 5HF, Scotland*

The endogenous opiate transmitters, endorphins, are released as one of many acute actions of ethanol on the limbic system. Research in

https://doi.org/10.1016/0924-9338(96)88422-7 Published online by Cambridge University Press