British Journal of Psychiatry (1994), **164** (suppl. 23), 9–14

I. The Theory of Schizophrenia

Biological Factors in Schizophrenia
Structural and Functional Aspects

E. K. G. SYVÄLAHTI

A number of factors have been proposed as being linked to schizophrenia: genetic, psychological, endocrinological, metabolic, environmental, virological, and auto-immunological factors, as well as neurotransmitter systems and structural disorders of the brain. All may act as predisposing, triggering, or functionally modulating factors in what is probably a condition composed of several types of disorder with varying aetiology. Neuroanatomical and neuromorphological data have revealed ventricular enlargement and diminished frontal and temporal lobe volume in some patients. These changes are concentrated particularly in the hippocampus/parahippocampal gyrus/amygdala, but are relatively small and span some overlap with healthy subjects. Twin studies suggest that at least some of these changes may result from other than genetic factors. Functional disturbances of the brain have also been connected with frontal and temporal structures in some schizophrenic patients. Of the single neurotransmitter substances, dopamine and serotonin appear to represent some of the central restitutive mechanisms whose function is to maintain mental stability; the understanding of their interplay with other neurotransmitters such as noradrenaline, acetylcholine, GABA, and glutamate, should provide a more integrated view of both normal and disturbed brain function.

As a syndrome, schizophrenia can be approached in several ways, but the most useful data are often acquired through integrating different research methods. Biological, psychodynamic, and psychosocial approaches need not conflict if the scientific theory of each is understood and the methodological restrictions are acknowledged. Figure 1 shows some current approaches to schizophrenia research. Psychosocial, psychodynamic, genetic, pharmacological, and other research systems are included in these approaches.

The way in which schizophrenia was diagnosed previously varied depending on the country and the researcher, but in the 1980s the DSM–III classification came into general use (American Psychiatric Association, 1980) and now a revised version of DSM–III is used. As the reader will know, diagnosis is based on the person's behaviour, symptoms and signs, and on age of onset and duration of the disorder. Diagnoses and clinically distinct subforms of schizophrenia are thus less ambiguous and more objective than previously, but we must not forget that they can still include states of disease which differ from one another in aetiology and in organic and dynamic features. Classification of disease has been based on consensus, and diagnostic limits may change in the future as no specific tests to confirm a case of schizophrenia are available. DSM–IV is now in preparation, as is the newest version of the International Classification of Diseases

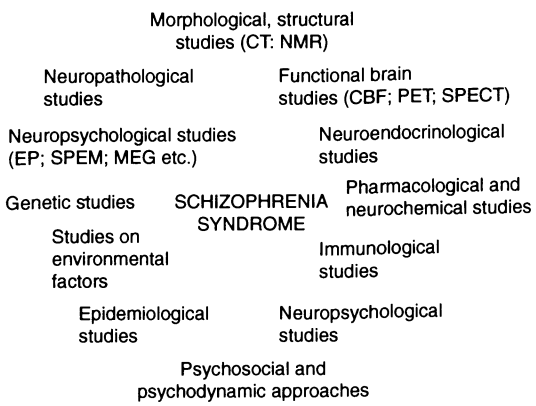

Fig. 1 Different types of investigational approach to schizophrenia.

by the World Health Organization (ICD–10), and these two systems will come into closer agreement, for example, by both using diagnostic criteria based on phenomenological descriptions.

Family, twin and adoption studies have revealed that genetic factors add significantly to the risk of development of schizophrenia; in addition, environmental factors have an undeniable role, though it is difficult to distinguish between the effects of these two groups of factors, due to the complex nature of psychiatric disorders (Dalén & Hays, 1990).

These various genetic, psychological, endocrinological, toxic–metabolic, virus-based, and auto-immunological features, as well as structural changes of the brain and neurotransmitter systems, may act as predisposing, triggering, or functionally-modulating factors.

None of the suggested hypotheses for the aetiology of schizophrenia has so far gained general acceptance, and it has become more and more evident that the condition subsumes several different disorders. This diversity also becomes clear when one studies the structure and function of the brains of schizophrenic patients; the methodological possibilities for this kind of research approach have significantly improved during the last few years. This paper concentrates mainly on structural and functional changes of the brain described in schizophrenics and on central neurotransmitter hypotheses for the disorder.

Structural changes of the brain in schizophrenia

Neuroanatomical and neuromorphological data on the brains of schizophrenics have been obtained in three principal ways: post-mortem neuropathological studies, computed tomography (CT) studies and, most recently, imaging techniques based on nuclear magnetic resonance (NMR) (see Andreasen (1988) for a review).

Post-mortem neuropathological studies have been carried out on a large scale, but many of the earlier ones were not adequately controlled, and in addition to the general problems of post-mortem studies, they suffered from methodological shortcomings. The latest controlled studies have revealed changes such as neuronal loss and disturbances in neuronal distribution, concentrated in the frontal and temporal lobes and in certain limbic structures such as the hippocampus and amygdala, though these findings require confirmation (Roberts, 1991).

Modern *in vivo* imaging methods such as CT and NMR have mainly been directed to the study of structures related to the temporal lobes. CT studies in schizophrenia began in the mid-1970s and reports regarding enlargement of the cerebral ventricle system, cortical (especially prefrontal) atrophy, and reduced size of the cerebellar vermis have been presented (see Lewis (1990) for a review). Of these three features, changes in the lateral and third ventricle have most consistently been revealed. Such enlargement is thought to take place at the expense of cerebral tissue, and has thus been interpreted as an indirect indicator of functional disorder in adjacent brain substance.

Most NMR studies have confirmed increased ventricular size (particularly frontal and temporal horns) in a proportion of patients. In a recent investigation of monozygotic twins discordant for schizophrenia, enlarged size of the lateral and third ventricles, compared with the healthy twin, was quite convincingly established (Suddath *et al*, 1990). It should be noted, however, that the degree of enlargement of cerebral ventricles is relatively small in most studies (see Mesulam, 1990), and it is seen in only 6–40% of the subjects. In addition, ventricular enlargement is not a finding specific to schizophrenia, since it has been described, for example, in mood disorders. It seems clear, however, that in at least a proportion of schizophrenic patients, relative enlargement of the lateral and/or third ventricle can be established.

NMR studies have significantly improved the anatomical resolution of brain imaging, and have indicated a diminished volume of temporal lobe structures in schizophrenic patients. These changes seem to concentrate in particular structures of the temporal lobe, such as the hippocampus/parahippocampal gyrus/amygdala. In the above-mentioned study of twins (Suddath *et al*, 1990), in addition to ventricular changes, bilateral reduction of the hippocampus and loss of grey matter in the left temporal lobe were found in the affected twin. Also some studies support the hypothesis that cerebral changes in schizophrenic patients may occur specifically in the left hemisphere. As the two hemispheres develop at slightly different rates during differentiation of the central nervous system, it has been suggested that the morbid process of schizophrenia could disturb development of the brain unilaterally, leading to pronounced differences between the two sides in affected individuals (Pilowsky, 1992).

Functional changes in the brain

In addition to structural changes, functional disturbances have been connected with structures of the frontal and temporal lobes in a proportion of schizophrenic patients, though here too, results are sometimes highly contradictory. Regional neuronal activity of the brain has been studied by measuring electrical phenomena related to neuronal activity using electroencephalographic (EEG) techniques, studies of evoked potentials (EP), and more recently magnetoencephalography (MEG). In addition, changes in cerebral blood flow or metabolism related to neuronal activity can be studied using such imaging methods as positron emission tomography (PET), single photon emission computerised tomography (SPECT), and nuclear magnetic resonance (NMR) spectroscopy.

Though a large number of EEG and EP investigations have been done in schizophrenic patients, the findings have shown a substantial amount of divergence. For example, in auditory EP studies, typical changes of the P_{300} component, apparently related to disturbances in cognitive processing, have been described in schizophrenia and in schizophrenic pedigrees (Blackwood *et al*, 1991), but the specificity of these findings is unclear and their significance for schizophrenia undefined. Alterations in smooth pursuit eye movements (SPEM), another interesting neurophysiological parameter, are estimated to be found in over half of those suffering from schizophrenia, and a similar disorder has been detected in 45% of patients' close relatives, compared with only 5% on average in the general population. This finding is seen as a reflection of disorders in controlling attention and central integration (Holzman *et al*, 1973), and may be related more to biological factors predisposing to schizophrenia than to the pathophysiology of the actual disorder.

There have also been numerous PET and SPECT studies on regional cerebral glucose metabolism and blood flow, particularly PET studies of regional cerebral glucose metabolism, using [^{18}F]-labelled deoxydeglucose or [^{11}C]-labelled glucose, and it has been assumed that regional glucose metabolism (as well as blood flow) correlates with regional neuronal activity. However, considering the large number of studies that there have been, suprisingly few distinct findings have emerged from them; this may be related to the complex nature of schizophrenia, the different phases of the disorder, and changes over time. The most consistent finding – though not present in all studies – is the low relative glucose metabolism in frontal regions ('relative hypofrontality') in states of rest, especially in chronic schizophrenic patients. This was originally described in a study of cerebral blood flow using the xenon-113 technique (Ingvar & Franzen, 1974). On the other hand, activation tests which are believed to have a specific effect on frontal cerebral regions do not seem to activate the frontal cortex in schizophrenic patients as much as in healthy subjects.

The finding of relative hypofrontality can be criticised on the grounds of methodology and selection of subjects (chronic patients, exposed to heavy neuroleptic medication), and so its significance is uncertain. In fact, acute patients on no medication may rather exhibit frontal hypermetabolism, although this preliminary finding has not been confirmed. Recent work using phosphorus-31 NMR spectroscopy suggests that schizophrenia may also involve disorder of the frontal lobe cortex; acute patients on no medication exhibited abnormal phospholipid metabolism (Pettegrew *et al*, 1991).

Functional changes have also been described in the temporal lobe in schizophrenic patients: for example, blood flow studies have indicated increased activity of the left temporal lobe, especially in patients who suffer from chronic hallucinations. The MEG technique has recently been used to show that transient auditory hallucinations cause activation comparable to ordinary acoustic stimuli in the auditory cortex; this was in two patients who were on neuroleptics (Tiihonen *et al*, 1992). Contradictory results on activity in different brain regions in functional studies may reflect more the behaviour and inner experiences of a patient at a particular time than the basic disorders themselves.

A number of disorders related, for example, to changes in attention and activity as well as to disturbances of memory and learning, measurable by neuropsychological methods, have been reported in schizophrenic patients (Saykin *et al*, 1991). The most recent observations direct attention to the significance of the temporo-hippocampal region; for example, in selective memory and learning disturbances in schizophrenia.

Neurotransmitter hypotheses

The role of cerebral neurotransmitters in schizophrenia has been the subject of considerable research since the 1960s. It has been suggested that a number of neurotransmitters are related to schizophrenia, including monoamines, peptides, and amino-acids. In each case, the transmitter itself, its metabolites (turnover products) or the enzyme mechanisms participating in its synthesis or metabolism have been measured in blood, cerebrospinal fluid, urine, or post-mortem samples, and the results have then been compared with results from normal controls. In addition, if possible, there have been treatment experiments either with the transmitter itself or a pharmacokinetically compatible derivative. In most cases, however, these treatment experiments in patients have failed.

One of the oldest neurotransmitter theories is the 'dopamine hypothesis' of schizophrenia, which has been extensively criticised over the years, but can still be considered the strongest theory in the pathophysiology of this disorder (see Davis *et al* (1991) for a review). As methods of molecular biology have developed and new dopamine receptors have been discovered, research on the dopamine systems in schizophrenia has become more extensive. New research findings abound. More fundamental aspects of the pathology of schizophrenia may be

revealed by the recently-found D_3 and D_4 receptors (Sokoloff *et al*, 1990; Tol *et al*, 1991), which resemble the D_2 receptors and are located especially in the limbic and cortical structures, and which may be important for emotional reactivity. Other subtypes of dopamine have also been cloned (Sunahara *et al*, 1991; see Sibley & Monsma (1992) for a review). The preliminary report on multiple D_4 receptor variants in the human population (Tol *et al*, 1992) is the first report of a receptor in the catecholamine receptor family that displays polymorphic variation. This may open a new avenue for detecting individual differences in susceptibility to neuropsychiatric disease and in responsiveness to antipsychotic medication.

Another transmitter theory which has been widely studied is the serotonin hypothesis (see Meltzer (1991) for a review). For schizophrenia, this was first proposed in the early 1950s, based mostly on the hallucinatory and antiserotonergic effects of lysergic acid diethylamide (LSD), but later it became apparent that LSD also had stimulating effects on the serotonergic system. Drugs that have effects solely on the serotonergic system have so far not proved efficacious in schizophrenia, although isolated successful treatment experiments have been reported. Clozapine is the prototype of a compound that has lesser effects on D_2 receptors than classical neuroleptics like haloperidol, but unlike them it exerts pronounced effects on serotonin (5HT-1c/5HT-2) receptors (Hietala *et al*, 1992). Clinically, clozapine is effective in some schizophrenic patients who are resistant to other drugs, and it may have a therapeutic action on negative symptoms (see Deutch *et al*, 1991). There have also been case reports of striking therapeutic effects with some of the new selective serotonin-reuptake-blocking drugs such as fluoxetine and citalopram in schizophrenic patients (Kallioniemi & Syvälahti, 1992). Here, a certain amount of dopamine blockade may also be necessary, together with the modulatory serotonin effects.

One of the latest neurotransmitter candidates in schizophrenia is glutamine acid – an excitatory transmitter – which has been proposed as participating in the pathophysiology of schizophrenia on the basis of post-mortem studies (Harrison *et al*, 1991). These studies imply that at least a proportion of patients suffer from relative malfunction of the glutamate system in certain limbic regions, particularly in the hippocampus, though the effect of previous neuroleptic treatment cannot yet be excluded.

On the basis of these anatomical and functional findings relating to different transmitters, hypothetical models have been developed to explain the disordered biological mechanisms and the effects of drugs. For example, one hypothesis aims to explain schizophrenia as a phenomenon connected with overactivation of the cortex; the functioning of the thalamus as an important relay station and filter for information passing on to the cortex would then be disturbed (Carlsson, 1988). Transmitters regulating relevant feedback functions include GABA, glutamic acid, and dopamine, so that strengthening of the thalamic filtering action would be induced by controlling the functional activity of dopamine neurones.

The dopamine hypothesis

The dopaminergic system regulates not only motor activity but also a number of cognitive and emotional functions, which are transmitted through specific dopamine receptors. These receptors are principally divided into the D_1 and D_2 categories, although functional receptor subtypes already number at least six (Sibley & Monsma, 1992). The dopamine hypothesis assumes that disturbed function of central dopamine systems, particularly in mesolimbic and mesocortical pathways, is connected with schizophrenia (Fig. 2). In its most simplified form it

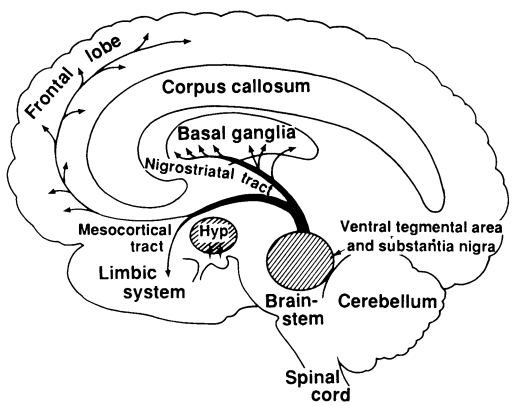

Fig. 2 The mesolimbic and mesolimbic–cortical dopamine pathways originate primarily from the A10 dopamine neurone group (ventral tegmental area). The mesolimbic tract mainly innervates the nucleus accumbens and olfactory tubercle, and is considered to be involved in arousal, locomotor activity, and motivational and affective states. The mesolimbic–cortical pathway innervates septum, hippocampus, amygdala and many cortical regions (such as the prefrontal and cingulate cortices), and is important in higher cortical functions. It has been suggested that blockade of, in particular, limbic and prefrontal dopamine D_2 receptors may be the mode of action for the therapeutic effects of antipsychotic compounds. The major part of the nigrostriatal dopamine pathway originates from the A9 dopamine neurone group (substantia nigra) and projects primarily to the striatum (nucleus caudatus, putamen and globus pallidus). The striatum is thought to be critically involved in the regulation of movement and may also subserve some cognitive processes. The nigrostriatal tract is believed to be associated with the production of extrapyramidal side-effects by antipsychotic drugs. (The drawing is adapted from Andreasen (1988), with permission.)

assumes that an overactive dopamine system is the cause of schizophrenia, but it has been substantially modified over the years.

A well-known hypothesis by Crow represents a modification of the dopamine hypothesis (Crow, 1987). In this model there are two types of schizophrenia: type I and type II. The pathological process in type I is overactivity of the dopaminergic system, and its symptoms are mostly positive (thinking disorders, hallucinations and delusions, etc.). Type II is based on cellular loss, particularly in structures of the temporal lobe; the functioning of the dopaminergic system is normal and the symptoms mainly negative (social withdrawal, general passivity, poor emotional life etc.). The response to neuroleptic treatment is also expected to differ in these two types, so that in type I it will be mostly good, and in type II principally poor. However, these two types of disease are not regarded as separate entities, but rather two contributing factors in the process of schizophrenia, which might overlap.

Unlike other neurotransmitter hypotheses, the dopamine hypothesis is supported by several kinds of clinical evidence. A fundamental basis for it is the strong positive correlation between the D_2 dopamine receptor binding activity of antipsychotic compounds and the dose used clinically ('dopamine hypothesis of neuroleptic action'). This has been confirmed by evidence from several research groups, including recent PET studies which show that all clinically effective antipsychotic drugs occupy a substantial proportion of D_2 receptors in the brain. Eleven chemically different 'classical' neuroleptics in normal doses cause a 70–80% D_2 receptor occupancy in the striatum of patients (Sedvall, 1990). Another important clinical issue is the occurrence of psychotic symptoms in persons taking drugs that increase dopaminergic activity: for example, amphetamine may trigger a psychosis similar to paranoid schizophrenia. Additionally, the hypothesis is supported by post-mortem studies, some of which have found increased D_2 receptors in the basal ganglia and certain limbic regions of patients' brains (Seeman *et al*, 1987).

The dopamine hypothesis can also be criticised, though. For example, D_2 receptor blockade caused by neuroleptics is an acute effect, but the therapeutic response can be observed only days or weeks later. Also, post-mortem studies which support an excess of D_2 receptors in the schizophrenic brain can also be criticised for the accuracy of the diagnoses. The long-lasting biochemical consequences of D_2 receptor blockade caused by neuroleptics are particularly problematic. It is now possible to examine dopamine activity in the early stages of schizophrenia by the PET technique *in vivo* and in such a way that it is quite certain that patients have never received neuroleptics before the study. In addition, PET findings can be related to the patient's clinical condition and diagnosis. The first American PET study concerning schizophrenia and dopamine D_2 receptors was published in 1986. It showed that in schizophrenic patients who had never been exposed to neuroleptic drugs, the number of D_2 receptors in the striatum was two or even three times the number found in control material (Wong *et al*, 1986). Later, in a study of 21 schizophrenic patients not exposed to neuroleptic drugs, results were rather less convincing, but the schizophrenic group still had twice as many D_2 receptors in the striatum as controls. However, this finding has not been confirmed in corresponding studies carried out in Sweden, France, and Finland. In these, schizophrenic patients did not differ significantly from the control group when averages of D_2 receptors in the striatum and affinity were compared (Farde *et al*, 1990; Martinot *et al*, 1991). In the Finnish study, there were a few patients for whom the number of D_2 receptors in the striatum was almost twice the average for the control group (Hietala *et al*, 1991).

Several explanations have been proposed for these contradictory results; for example, there were considerable differences in patient selection (the American study used older patients than the others) and the methods used to measure the amount of receptors (e.g. radioligand). In any case, studies in new schizophrenic patients suggest that an increased number of D_2 receptors in striatal regions of the brain is not a general phenomenon in schizophrenia. However, there may still be a subgroup of patients who actually have an excess of D_2 receptors, and thus suffer from overactivity of the dopaminergic system. Thus, the results conform well with the clinically complex nature of schizophrenia. Due to restrictions in the resolution of the PET technique, it has only been possible so far to study structures such as the striatum, which are large and contain a considerable number of dopamine receptors. Even within the striatum, there are variations in structure and neural connections between the different parts (Gerfen *et al*, 1990). Since the function of limbic and cortical dopamine pathways is not analogous with striatal activity, it has been proposed that schizophrenia may involve decreased dopaminergic activity in the prefrontal cortical area and (possibly compensatorily) simultaneous overactivity in subcortical or limbic areas. This could also partly explain the varying occurrence of the 'negative' and 'positive' symptoms of schizophrenia.

Looking to the future, a new level of understanding of the role of dopamine – as well as several other neurochemical systems – in brain and in schizophrenic disturbances can be reached with the sophisticated new research methods. There is hope that the novel discoveries on normal and abnormal brain structure and function can be gradually integrated with each other and with the other neurobiological achievements in schizophrenia research. These discoveries, and the increasing understanding of genetic, environmental, psychosocial and psychodynamic factors, improve the prospects for creating an integrative view on the aetiology, pathogenesis and treatment of schizophrenia.

References

AMERICAN PSYCHIATRIC ASSOCIATION (1980) *Diagnostic and Statistical Manual of Mental Disorders* (3rd edn). Washington, DC: APA.

ANDREASEN, N. (1988) Brain imaging: applications in psychiatry. *Science*, **239**, 1381–1388.

BLACKWOOD, D. H. R., ST CLAIR, D. M., MUIR, W. J., *et al* (1991) Auditory P300 and eye tracking dysfunction in schizophrenic pedigrees. *Archives of General Psychiatry*, **48**, 899–909.

CARLSSON, A. (1988) The current status of the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology*, **1**, 179–186.

CROW, T. (1987) Two syndromes of schizophrenia as one pole of continuum of psychosis: a concept of the nature of the pathogen and its genomic locus. In *Handbook of Schizophrenia, Vol. 2: Neurochemistry and Neuropharmacology of Schizophrenia* (eds F. A. Henn & L. E. DeLisi), pp. 17–48. Amsterdam: Elsevier.

DALÉN, P. & HAYS, P. (1990) Aetiological heterogeneity of schizophrenia: the problem and the evidence. *British Journal of Psychiatry*, **157**, 119–122.

DAVIS, K. L., KAHN, R. S., KO, G., *et al* (1991) Dopamine in schizophrenia: a review and reconceptualization. *American Journal of Psychiatry*, **148**, 1474–1486.

DEUTCH, A. Y., MOGHADDAM, B. & INNIS, R. B. (1991) Mechanisms of action of atypical antipsychotic drugs: implications for novel therapeutic strategies for schizophrenia. *Schizophrenia Research*, **4**, 121–156.

FARDE, L., WIESEL, F.-A., STONE-ELANDER, S., *et al* (1990) D2 dopamine receptors in neuroleptic-naive schizophrenic patients: a positron emission tomography study with [^{11}C]-raclopride. *Archives of General Psychiatry*, **47**, 213–219.

GERFEN, C. R., ENGBER, T. M., MAHAN, L. C., *et al* (1990) D_1 and D_2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science*, **250**, 1429–1432.

HARRISON, P. J., MCLAUGHLIN, D. & KERWIN, R.W. (1991) Decreased hippocampal expression of a glutamate receptor gene in schizophrenia. *Lancet*, **337**, 450–452.

HIETALA, J., SYVÄLAHTI, E., VUORIO, K., *et al* (1991) Striatal dopamine D2 receptor density in neuroleptic-naive schizophrenics studied with positron emission tomography. In *Biological Psychiatry*, Vol. 2 (eds G. Racagni, N. Brunello & T. Fukuda), pp. 386–387. Amsterdam: Elsevier.

———, KOULU, M., KUOPPAMÄKI, M., *et al* (1992) Chronic clozapine treatment down-regulates serotonin 5HT-1c receptors in rat brain. *Progress in Neuropsychopharmacology and Biological Psychiatry*, **16**, 727–732.

HOLZMAN, P. S., PROCTOR, L. R. & HUGHES, D. W. (1973) Eye tracking patterns in schizophrenia. *Science*, **181**, 179–181.

INGVAR, D. H. & FRANZEN, G. (1974) Abnormalities of cerebral blood distribution in patients with chronic schizophrenia. *Acta Psychiatrica Scandinavica*, **50**, 425–462.

KALLIONIEMI, H. & SYVÄLAHTI, E. (1992) Citalopram, a specific inhibitor of serotonin re-uptake in treatment of psychotic and borderline patients. *Nordisk Journal of Psychiatry*, **46**, 181–187.

LEWIS, S. (1990). Computerised tomography in schizophrenia 15 years on. *British Journal of Psychiatry*, **157**, 16–24.

MARTINOT, J.-L., PAILLERE-MARTINOT, M. L., LOC'H, C., *et al* (1991) The estimated density of striatal D2 receptors in schizophrenia: a study with positron emission tomography and 76Br-bromolisuride. *British Journal of Psychiatry*, **158**, 346–350.

MELTZER, H. Y. (1991) The significance of serotonin in neuropsychiatric disorders. *Journal of Clinical Psychiatry*, **52** (suppl. 12), 70–72.

MESULAM, M. M. (1990) Schizophrenia and the brain. *New England Journal of Medicine*, **322**, 842–845.

PETTEGREW, J. W., KSHAWAN, M. S., PANCHALINGAM, K., *et al* (1991) Alterations in brain high-energy phosphate and membrane phospholipid metabolism in first-episode, drug-naive schizophrenics. *Archives of General Psychiatry*, **48**, 563–568.

PILOWSKY, L. S. (1992) Understanding schizophrenia; structural and functional abnormalities of the brain are present in the condition. *British Medical Journal*, **305**, 327–328.

ROBERTS, G. W. (1991) Schizophrenia: a neuropathological perspective. *British Journal of Psychiatry*, **158**, 8–17.

SAYKIN, A. J., GUR, R. C., GUR, R. E., *et al* (1991) Neuropsychological function in schizophrenia: selective impairment in memory and learning. *Archives of General Psychiatry*, **48**, 618–624.

SEDVALL, G. (1990) PET imaging of dopamine receptors in human basal ganglia: relevance to mental illness. *Trends in Neurological Sciences*, **7**, 302–308.

SEEMAN, P., BZOWEJ, N. H., GUAN, H.-C., *et al* (1987) Human brain D1 and D2 dopamine receptors in schizophrenia, Alzheimer's, Parkinson's and Huntington's diseases. *Neuropsychopharmacology*, **1**, 5–15.

SIBLEY, D. R. & MONSMA, F. J. Jr (1992) Molecular biology of dopamine receptors. *Trends in Pharmacological Science*, **13**, 61–69.

SOKOLOFF, P., GIROS, B., MARTRES, M.-P., *et al* (1990) Molecular cloning and characterization of a novel dopamine receptor (D_3) as a target for neuroleptics. *Nature*, **347**, 146–151.

SUDDATH, R. L., CHRISTISON, G. W. & TORREY, E. F. (1990) Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *New England Journal of Medicine*, **322**, 789–794.

SUNAHARA, R. K., GUAN, H.-C., O'DOWD, B. F., *et al* (1991) Cloning of the gene for a human dopamine D_5 receptor with higher affinity for dopamine than D_1. *Nature*, **350**, 614–619.

TIIHONEN, J., HARI, R., NAUKKARINEN, H., *et al* (1992) Modified activity of the human auditory cortex during auditory hallucinations. *American Journal of Psychiatry*, **149**, 255–257.

TOL, H. H. M. VAN, BUNZOW, J. R., GUAN, H.-C., *et al* (1991) Cloning of the gene for a human dopamine D_4 receptor with high affinity for the antipsychotic clozapine. *Nature*, **350**, 610–614.

———, WU, C. M., GUAN, H.-C., *et al* (1992) Multiple dopamine D4 receptor variants in the human population. *Nature*, **358**, 149–152.

WONG, D. F., WAGNER, H. N., TUNE, L. E., *et al* (1986) Positron emission tomography reveals elevated D2 dopamine receptors in drug-naive schizophrenics. *Science*, **234**, 1558–1563.

E. K. G. Syvälahti, MD, *Psychiatrist, (Acting) Professor, Department of Pharmacology, Turku University, Turku, Finland*