

Peter F. Liddle

## Inner connections within domain of dementia praecox: role of supervisory mental processes in schizophrenia

Received: 10 October 1994 / Accepted: 6 February 1995

**Abstract** Kraepelin's conclusion that there were underlying common features justifying the amalgamation of catatonia, hebephrenia and paranoia hallucinatoria to form a single illness is confirmed by factor analytic studies delineating the various dimensions of schizophrenic psychopathology. Neuropsychological studies reveal that the three cardinal dimensions reflect disorder of the supervisory mental processes responsible for initiation, selection and monitoring of self-generated mental activity. Brain-imaging studies indicate that the underlying neuropathology entails disordered functional connectivity within the neural networks in multimodal association cortex that are the substrate of the supervisory mental processes, consistent with Kraepelin's own speculation about the essential nature of the condition.

### Introduction

*The complexity of the conditions which we observe in the domain of dementia praecox is very great, so that their inner connection is at first recognizable only by their occurring one after the other in the course of the same disease.* (Emil Kraepelin, 1919)

The manifestations of psychosis are strikingly diverse, yet patients whose illnesses lie far apart in this diverse spectrum of illnesses often exhibit common features. One individual experiences episodes of labile mood and disinhibited behaviour intruding dramatically, but briefly, upon a life in which personal relationships and professional achievement are enjoyed in reasonable measure; another individual exhibits incoherent speech, inappropriate affect, and suffers a sustained erosion of his aspirations and social status as his illness robs him of the ability to plan and execute a coherent pattern of activity. Yet despite

their differences, each of these individuals might experience delusions of persecution or hear hallucinatory voices talking about him; each might suffer depressed mood accompanied by hopelessness and low self-esteem.

When Kraepelin set about defining the boundaries of dementia praecox, he steered between two opposing tendencies. On the one hand, the concept of the unitary psychosis advocated by Griesinger (1867) emphasized the commonality of psychotic illnesses, and classified persistent disintegrative conditions together with transient states dominated by wild excitement or deep melancholy, within a single disease. On the other hand, Kahlbaum (1863, 1874) drew attention to the importance of taking account of the time course of illnesses as well as the presenting mental state, and identified within the persistent disorders at least three distinguishable conditions: catatonia, hebephrenia and paranoia hallucinatoria. Kraepelin followed Kahlbaum in attending to the time course of illness, and split Griesinger's unitary psychosis into two major divisions: dementia praecox, which tends to persist leading to weakening of the faculties of the mind, and manic-depressive psychosis, an episodic illness characterized by excited or melancholic passions. However, in contrast to Kahlbaum, Kraepelin emphasized the connections linking the persistent conditions and amalgamated catatonia, hebephrenia and paranoia hallucinatoria within the single entity, dementia praecox. Bleuler (1950) subsequently renamed this entity schizophrenia to denote the characteristic loss of coherence between the various aspects of mental function.

In an essay in which he sought to distil his thoughts about psychopathology, Kraepelin wrote that the essence of schizophrenia was ... *that destruction of conscious volition ... which is manifest as a loss of energy and drive, in disjointed volitional behaviour. This rudderless state leads to impulsive instinctual activity: there is no planned reflection which suppresses impulses as they arise or directs them into proper channels.* (Kraepelin 1920, trans. 1974).

Elsewhere in this issue, Jablensky et al. (1995), examine the basis for Kraepelin's decision to separate dementia praecox from manic-depressive illness. This paper ad-

Peter F. Liddle  
Department of Psychiatry, University of British Columbia,  
Vancouver, B.C., V6T 2A1, Canada

dresses the issue of the validity of his amalgamation of catatonia, hebephrenia and paranoia hallucinatoria within a single condition, and examines the extent to which his views on the psychopathological processes of schizophrenia are supported by evidence provided by the techniques of modern neuroscience.

### **Attempts to describe the heterogeneity of schizophrenia**

Kraepelin's concept of dementia praecox encompasses a bewildering variety of clinical presentations. Since the time of Kraepelin, clinicians have repeatedly sought a satisfactory way to split schizophrenia into separate sub-types, but have found it difficult to do better than Kahlbaum. The tenth edition of the International Classification of Diseases (WHO 1993) reproduces the classical sub-division into paranoid, hebephrenic, catatonic and simple sub-types. The first three of these sub-divisions are directly related to the three chronic psychosis recognized by Kahlbaum. Simple schizophrenia is a concept proposed by Diem (1903) to accommodate those patients who exhibit weakening and disjointing of volition without the relatively specific mental phenomena, such as delusions, hallucinations, formal thought disorder or catatonic motor disorder, that give each of the other three types their distinctive character. However, attempts to classify individual patients according to the classical scheme is confounded by the fact that many individuals exhibit features of several different sub-types.

The very limited success of attempts to divide schizophrenia into sub-types indicates that a different approach is required. One such approach is the dimensional approach advocated by Crow (1980). Crow proposed that two types of pathological process occur within schizophrenia. The type-1 process is manifest as positive symptoms, such as delusions, hallucinations and formal thought disorder, which tend to occur in transient, acute episodes. Crow suggested that these symptoms reflect biochemical imbalance such as dopaminergic hyperactivity. The type-2 process is manifest as negative symptoms, such as poverty of speech and flat affect, and tends to be chronic. Crow proposed that this process entails structural abnormality of the brain, such as enlargement of the cerebral ventricles. It is important to emphasize that Crow did not consider that these two types of pathological process were separate illnesses. He regarded them as two manifestations of a single illness, and hence, likely to co-exist in many individual cases.

While Crow's formulation has been very successful in stimulating research into the nature of the heterogeneity of schizophrenia, empirical evidence has provided only partial support. For example, in a review of X-ray computed tomographic studies, Lewis (1990) found that only 5 of 18 studies that had addressed the issue had found an association between enlargement of cerebral ventricles and negative symptoms of schizophrenia. On the other hand, the limited, but definite, efficacy of clozapine in al-

leviating negative symptoms implies that biochemical imbalance is implicated in the production of negative symptoms. Furthermore, in view of the fact that positive symptoms can be persistent, whereas negative symptoms are sometimes transient, Crow's formulation also raises the question of whether it is symptom type or degree of symptom persistence that is intrinsically linked to each of the two proposed pathological processes.

### **Factor analysis of schizophrenic symptoms**

If the heterogeneity of schizophrenia reflects the occurrence of several distinguishable, but related, pathological processes, such heterogeneity is best described in terms of multiple dimensions of a single illness. An appropriate technique for delineating the pattern of relationships between the symptoms of a multi-dimensional illness is factor analysis. Factor analysis identifies groups of related symptoms that tend to co-exist in an individual. Closely related symptoms load onto a single factor. If several different pathological processes lead to clustering of symptoms into several discrete groups (or syndromes), factor analysis should demonstrate that several factors are required to account for the pattern of correlations between symptoms. Factor analysis does not identify discrete clusters of patients. An individual patient generally might exhibit substantial scores for several factors, or in other words, exhibit the features of several of the syndromes.

If we wish to determine the links between symptoms based on symptom type alone, without the potentially confounding influence of factors related to degree of chronicity, it is preferable to study patients who are relatively homogeneous with regard to chronicity. In a cohort of chronic schizophrenic patients who had stable symptoms persisting over a period of 6 months or more, a factor analysis revealed that 74% of the shared variance could be accounted for by three factors, indicating three major groups of persistent symptoms: psychomotor poverty (poverty of speech, flat affect, decreased spontaneous movement), disorganization (disorders of the form of thought, poverty of content of speech, inappropriate affect); and reality distortion (delusions and hallucinations) (Liddle 1987). A similar factor structure has been reported in many other studies of chronic schizophrenic patients (Bilder et al. 1985; Kulhara et al. 1986; Mortimer et al. 1990; Liddle and Barnes 1990; Pantelis et al. 1991; Schroder et al. 1992; Brown and White 1992). A similar factor structure has also been reported in many studies that have included non-chronic patients (Arndt et al. 1991; Peralta et al. 1992; Frith 1992; Malla et al. 1993; Thompson and Meltzer 1993). Thus, there is a large body of evidence suggesting that the characteristic symptoms of schizophrenia segregate into three major syndromes.

The range of symptoms covered in these studies, however, did not embrace the full range of schizophrenic symptoms. If transient symptoms are taken into account, a more complex picture emerges. Firstly, schizophrenic patients are prone to suffer from depressive episodes charac-

terized by depressed mood, a sense of hopelessness and low self-esteem (Kibel et al. 1993). These depressive episodes can occur in association with acute psychotic episodes (Knights and Hirsch 1981) or a transient interlude superimposed upon the chronic, relatively stable phase of the schizophrenic illness (Barnes et al. 1989). Provided the range of symptoms entered into a factor analysis includes a sufficiently comprehensive range of affective items, factor analysis yields a depression factor in addition to the other three more characteristic schizophrenic factors (Liddle et al. in preparation).

Secondly, when transient symptoms are taken into account, it becomes clear that the psychomotor poverty syndrome lies at one pole of a bipolar syndrome. The other pole is psychomotor excitation characterized by increased spontaneous movement, pressure of speech and emotional lability. In patients who exhibit prolonged periods of profound psychomotor poverty, a sudden psychological or physiological stimulus can precipitate a transient episode of marked psychomotor excitation. (An illustrative case is presented in Liddle 1994.) This phenomenon is consistent with the observation by Venables and Wing (1962) that socially withdrawn schizophrenic patients are prone to exhibit abnormally high levels of physiological arousal.

In summary, there are four major syndromes of schizophrenic psychopathology, one of which is bipolar. The four syndromes are psychomotor poverty/excitation, disorganization, reality distortion and depression (Table 1). These syndromes differ in their tendency to be persistent. Depression and the excited phase of the psychomotor poverty/excitation syndrome are usually very transient. Reality distortion is often transient, but tends to endure longer than excitation, and in a substantial minority of cases, persists into the chronic phase of illness. Disorgani-

zation, like reality distortion, is most marked during acute episodes, but has an even greater tendency to persist (Pogue-Geile and Harrow 1984). Most persistent of all are the core negative symptoms, poverty of speech and flat affect, which characterize the psychomotor poverty syndrome (Pfohl and Winokur 1982). It is important to emphasize that the various syndromes reflect distinguishable dimensions within a single illness, and an individual patient might exhibit evidence of more than one syndrome. Of the four syndromes, psychomotor poverty/excitation, disorganization and reality distortion might be regarded as characteristic of schizophrenia, whereas depression is observed commonly in other psychiatric conditions.

The three characteristic syndromes embrace the phenomena to which Kraepelin attributed special importance in his description of schizophrenia. In particular, the weakening and disjointing of volition, which he regarded as the most characteristic features of the condition, lie at the heart of the psychomotor poverty and disorganization syndromes. While Kraepelin also attributed importance to delusions and hallucinations (features of the reality distortion syndrome) he was disinclined to include illnesses dominated by delusions, but lacking volitional or emotional disturbance, within dementia praecox. In the introduction to *Dementia Praecox and Paraphrenia* (Kraepelin 1919), he acknowledged the debate on this issue and decided in favour of separating those illnesses that ... *are distinguished in their whole course by very definite manifestations of peculiar disturbances of intellect while lacking enfeeblement of volition and especially of feeling* (p. 4) from the compass of dementia praecox, and instead classified them under the heading of paraphrenia. On the other hand, in the chapter from the same book devoted to psychic symptoms, Kraepelin makes clear that he considered both auditory hallucinations and the delusional experiences of alien influence as characteristic of schizophrenia.

To what extent does the multi-dimensional picture of schizophrenia generated by factor analysis provide a basis for establishing the nature of the underlying pathophysiological processes and for identifying the inner connections that Kraepelin assumed must link the various clinical conditions that are observed in the domain of dementia praecox?

**Table 1** Syndromes of schizophrenia

---

*Reality distortion*

Delusions

Hallucinations

*Disorganization*

Formal thought disorder

Distractibility

Inappropriate affect

*Psychomotor poverty*

Poverty of speech

Flat affect

Motor underactivity

*Psychomotor excitation*

Pressure of speech

Irritability/lability

Motor overactivity

*Depression*

Depressed mood

Pessimism/hopelessness

Low self-esteem/guilt

Anhedonia

---



---

## Neuropsychological impairments

Each of the three characteristic syndromes is associated with a specific pattern of neuropsychological impairment. The psychomotor poverty syndrome is associated with slowed performance in tasks that demand the generation of a plan to act. For example, severity of psychomotor poverty is associated with reduced output in word generation tasks in which the subject is required to produce as many words as possible within a given category within a limited time (Liddle and Morris 1991; Frith et al. 1991 a; McGrath 1992; Allen et al. 1993). When patients are asked to repeat the task on multiple different occasions,

the total number of different words produced is within the normal range, indicating that the deficit is not a reduction in number of words stored in the patient's internal lexicon, but rather a difficulty in generating a plan to retrieve the stored words (Allen et al. 1993). It is reasonable to speculate that psychomotor excitation might represent a pathologically excessive generation of mental activity, although this hypothesis has not been tested by formal neuropsychological investigation.

The disorganization syndrome is associated with impairment in tasks that demand the suppression of inappropriate responses. For example, severity of disorganization is correlated with impaired performance in the Stroop test (Liddle and Morris 1991; McGrath 1992). In this test the subject is presented with colour names printed in ink of a colour that is not congruent with the colour name, and asked to state the colour of the ink. To perform efficiently, the subject must ignore the tendency to respond to the colour name. Disorganization is also correlated with the production of unusual words in word generation tasks (Allen et al. 1993) and with impaired ability to suppress inappropriate responses during the Continuous Performance Test (Frith et al. 1991a).

In contrast to psychomotor poverty and disorganization, reality distortion is not associated with readily discernible neuropsychological impairment (Liddle and Morris 1991; Frith et al. 1991a). The essence of reality distortion is a defect in evaluating the origin or validity of one's own mental activity. Consistent with this, Frith and Done (1989) demonstrated that delusions of control were associated with impaired ability to correct errors under circumstances where error correction relied upon internal monitoring of self-generated action.

Overall, the evidence from neuropsychological studies indicates that each of the three characteristic schizophrenic syndromes is associated with impairment of an aspect of the supervisory mental processes responsible for the initiation, selection and monitoring of self-generated mental activity. In contrast to the routine mental functions required to produce responses that are largely dictated by circumstances, the supervisory mental processes are called into play whenever there is ambiguity in what action, if any, is required.

This evidence for the cardinal role of impaired supervisory mental functions is consistent with Kraepelin's clinical observation (Kraepelin 1919):

They often move with tolerable certainty in accustomed paths, but in the psychic elaboration of new experiences, in the judgement of circumstances not hitherto experienced...they not infrequently commit the grossest blunders (p. 25). It is true that they are often able to carry out quickly and correctly tasks depending solely on memory or practice, but fail completely as soon as it is a question of independent mental activity and the overcoming of difficulties (p. 23).

On the basis of these observations, Kraepelin concluded that there were two major deficits: *A weakening of the mainspring of volition*, and *a loss of inner unity of mental activities* (p 74, 75). These two proposed deficits are consistent with the evidence from neuropsychological studies that two of the principal deficits in schizophrenia are im-

paired ability to initiate a plan to act and impaired ability to suppress inappropriate mental activity.

---

### Patterns of cerebral malfunction associated with schizophrenic syndromes

Regional cerebral blood flow (rCBF), which can be mapped using functional brain-imaging techniques, such as positron emission tomography (PET) or single photon emission tomography (SPET), provides a sensitive index of regional neuronal activity. In a PET study of medicated patients with persistent, stable symptoms, Liddle et al. (1992a) demonstrated that each of the three cardinal syndromes is associated with a specific pattern of rCBF. In particular, psychomotor poverty is associated with decreased rCBF in prefrontal cortex bilaterally and in left parietal cortex, and with increased rCBF in the caudate nuclei. Disorganization syndrome is associated with increased rCBF in right medial prefrontal cortex, anterior cingulate cortex and thalamus, and with decreased rCBF in right ventral prefrontal cortex and contiguous insula. Reality distortion syndrome is associated with increased rCBF in left medial temporal lobe and ventral striatum, and with decreased rCBF in the posterior cingulate cortex and in the left lateral temporal lobe. Each of these three rCBF patterns includes areas of underactivity and areas of overactivity, suggesting dynamic imbalance between brain regions, rather than irreversible neuronal loss.

The main features of these patterns of rCBF have been confirmed in other studies. For example, in a SPET study of unmedicated patients, Ebmeier et al. (1993) found that psychomotor poverty is associated with underactivity of prefrontal cortex, disorganization is associated with overactivity of the right medial prefrontal cortex and reality distortion is associated with underactivity of the left temporal lobe. Although their finding of an association between reality distortion and underactivity in the left temporal lobe is consistent with the finding by Liddle et al. (1992a) of an association with underactivity in the left lateral temporal lobe, they did not observe the association with left medial temporal overactivity found by Liddle et al. (1992a). However, other evidence does support the proposal that reality distortion can be associated with both underactivity and overactivity in parts of the left temporal lobe. In particular, Kurachi et al. (1985), Musalek et al. (1989), Matsuda et al. (1989) and Suzuki et al. (1993) all reported an association between left temporal overactivity and hallucinations.

For each of the three syndromes, the cerebral regions involved in the pattern of altered rCBF include the sites maximally activated in normal individuals when performing the type of supervisory mental process implicated in that syndrome (Liddle et al. 1992b). For example, the area of left prefrontal cortex in which there is a negative correlation between rCBF and psychomotor poverty coincides with the area maximally activated in normal individuals during a word-generation task (Frith et al. 1991b), consistent with the finding that psychomotor poverty is

associated with impaired ability in such tasks. The right anterior cingulate region in which there is a correlation between rCBF and severity of disorganization includes the site maximally activated in normal individuals during the Stroop task (Pardo et al. 1990). The area of left medial temporal lobe in which there is a correlation between rCBF and reality distortion includes the left para-hippocampal site activated in normal individuals during the learning of an eye-movement task that makes heavy demands on the internal monitoring of self-generated action (Frith et al. 1992).

When rCBF is measured in schizophrenic patients during the performance of tasks such as word generation, the findings depend on whether the task is paced. When it is unpaced, patients tend to produce a lesser degree of frontal activation than normal individuals. However, when the task is paced so that patients are required to perform at the same rate as normal controls, they produce the same magnitude of activation in the prefrontal cortex as normal individuals, indicating that the frontal hypofunction is a dynamic imbalance, rather than an irreversible deficit (Liddle et al. 1994). However, in normal individuals prefrontal activation is accompanied by suppression of activity in the lateral aspect of the left temporal lobe, whereas in schizophrenic patients, the prefrontal activation is accompanied by increased rCBF in the left lateral temporal lobe, implying an abnormal pattern of functional connectivity between frontal and temporal lobes. Furthermore, under paced conditions, those patients with poverty of speech produce a far more extensive cerebral activation than patients without poverty of speech, perhaps indicating a tendency to greater degree of cerebral arousal when stressed, consistent with the proposal that psychomotor poverty and psychomotor excitation are opposite poles of a single dimension.

In view of the evidence from clinical observation that the various syndromes of schizophrenia should be regarded as dimensions of a single illness, it is of importance to establish whether there are features of the rCBF patterns that are common to all three syndromes. To address this question, Friston et al. (1992) performed a canonical correlation analysis designed to determine the areas of overlap between the rCBF patterns. This analysis identified two sites, one in the left para-hippocampal gyrus and the other in the left globus pallidus, as sites involved in all three syndromes. Although this result must be interpreted with some caution until replicated, it provides support for the proposal that the three characteristic syndromes of schizophrenia reflect three distinguishable pathological processes that are nonetheless linked by a shared fundamental deficit.

## Conclusions

Analysis of the relationship between the diverse symptoms of schizophrenia produces a multi-dimensional picture. Each of the four dimensions is based on cardinal features of the various chronic psychotic illnesses described

by Kahlbaum. The symptoms of reality distortion are similar to those of paranoia hallucinatoria. The features of the disorganization syndrome resemble those of hebephrenia. Both the bipolar psychomotor poverty/excitation dimension and the depression dimension comprise cardinal features of catatonia. It should be noted that Kahlbaum's (1874) description of catatonia included depressed, stuporose and excited phases. (Although we have contrasted Kraepelin's decision to amalgamate various chronic psychoses within a single condition, with Kahlbaum's approach, which treated these illnesses as separate conditions, Kahlbaum had been one of the earliest proponents of the concept of distinguishable symptom complexes within a disorder. The multi-dimensional picture of schizophrenia that we have presented is as much a tribute to Kahlbaum as to Kraepelin.)

Neuropsychological evidence indicates that the three relatively persistent characteristic syndromes, psychomotor poverty, disorganization and reality distortion, reflect disorders of the supervisory mental processes responsible for the initiation, selection and monitoring of self-generated mental activity, respectively. The patterns of rCBF associated with each of the three characteristic syndromes involve the areas of multi-modal association cortex engaged in the relevant supervisory mental functions. The rCBF patterns indicate dynamic imbalance between activity in the variously associated cortical areas and related subcortical nuclei, suggesting that the fundamental abnormality in schizophrenia is disorder of the connections within the neuronal networks that serve the supervisory mental functions. Furthermore, preliminary evidence demonstrates anatomical overlap between the cerebral sites implicated in the various syndromes.

The evidence we have reviewed yields a picture of schizophrenia as an illness in which the disparate features of catatonia, hebephrenia and paranoia hallucinatoria can arise from an underlying disturbance of connections within the neural networks serving the supervisory mental functions. The symptom profile exhibited by a particular individual at a specific point in time would be expected to reflect both constitutional factors and situational factors unique to that individual. This picture of schizophrenia supports Kraepelin's amalgamation of catatonia, hebephrenia and paranoia hallucinatoria within a single condition, and, furthermore, reinforces his views concerning the nature of psychopathological processes. In particular, it is consistent with his conclusion that the basic deficits of schizophrenia are a weakening of the main-spring of volition and a loss of the inner unity of mental activity.

## References

- Allen HA, Frith CD, Liddle PF (1993) Negative features, retrieval processes and verbal fluency in schizophrenia. *Br J Psychiatry* 163:769-776
- Arndt S, Alliger RA, Andreasen NC (1991) The distinction of positive and negative symptoms: the failure of a two-dimensional model. *Br J Psychiatry* 158:317-322

- Barnes TRE, Curson D, Liddle PF, Patel M (1989) The nature and prevalence of depression in chronic schizophrenic in-patients. *Br J Psychiatry* 154:486-491
- Bilder RM, Mukherjee S, Rieder RO, Pandurangi AK (1985) Symptomatic and neuropsychological components of defect states. *Schizophr Bull* 11:409-419
- Brown KW, White T (1992) Syndromes of chronic schizophrenia and some clinical correlates. *Br J Psychiatry* 161:317-322
- Crow TJ (1980) The molecular pathology of schizophrenia: More than one disease process. *Br Med J* 280:66-68
- Ebmeier KP, Blackwood DHR, Murray C, Souza V, Walker M, Dougall N, Moffoot APR, O'Carroll RE, Goodwin GM (1993) Single photon emission tomography with 99mTc-exametazime in unmedicated schizophrenic patients. *Biol Psychiatry* 33:487-495
- Frith CD, Done DJ (1989) Experiences of alien control in schizophrenia reflect a disorder in the central monitoring of action. *Psychol Med* 19:359-363
- Frith CD, Leary J, Cahill C, Johnstone EC (1991 a) Disabilities and circumstances of schizophrenic patients - a follow-up study. IV. Performance on psychological tests. *Br J Psychiatry* 159 (Suppl 13):26-29
- Frith CD, Friston KJ, Liddle PF, Frackowiak RSJ (1991 b) Willed action and the prefrontal cortex in man: a study with PET. *Proc R Soc Lond [Biol]* 244:241-246
- Frith CD, Friston KJ, Liddle PF, Frackowiak RSJ (1992) PET imaging and cognition in schizophrenia. *J Roy Soc Med* 85:222-224
- Friston KJ, Liddle PF, Frith CD, Hirsch SR, Frackowiak RSJ (1992) The left medial temporal region and schizophrenia; a PET study. *Brain* 115:367-382
- Kahlbaum K (1863) *Die Gruppierung der psychischen Krankheiten*, Kafemann, Danzig
- Kahlbaum KL (1874) *Die Katatonie oder das Spannungsirrescien*. Hirschwald, Berlin
- Kibel DA, Laffont I, Liddle PF (1993) The composition of the negative syndrome of chronic schizophrenia. *Br J Psychiatry* 162:744-750
- Knights A, Hirsch SR (1981) Revealed depression and drug treatment for schizophrenia. *Arch Gen Psychiatry* 38:806-811
- Kraepelin E (1919) *Dementia praecox and paraphrenia* (trans. Barclay RM; Robertson GM, ed). Livingstone, Edinburgh
- Kraepelin E (1920) *Die Erscheinungsformen des Irresciens*. (trans. Marshall H, 1974, as *Patterns of mental disorder*. In: Hirsch SR, Shepherd M (eds) *Themes and variations in European psychiatry*. Wright, Bristol
- Kulhara P, Kota SK, Joseph S (1986) Positive and negative subtypes of schizophrenia: a study from India. *Acta Psychiatr Scand* 74:353-379
- Kurachi M, Kobayashi K, Matsubara R, Hiramatsu H, Yamaguchi N, Matsuda H, Maeda T, Hisada K (1985) Regional cerebral blood flow in schizophrenic disorders. *Eur Neurol* 24:176-181
- Lewis SW (1990) Computerised tomography in schizophrenia 15 years on. *Br J Psychiatry* 157 (Suppl 9):16-24
- Liddle PF (1987) The symptoms of chronic schizophrenia: a re-examination of the positive-negative dichotomy. *Br J Psychiatry* 151:145-151
- Liddle PF (1994) Schizophrenia: the clinical picture. In: Stein G, Wilkinson G (eds) *Seminars in adult psychiatry*. Gaskell, London
- Liddle PF, Barnes TRE (1990) Syndromes of chronic schizophrenia. *Br J Psychiatry* 157:558-561
- Liddle PF, Morris D (1991) Schizophrenic syndromes and frontal lobe performance. *Br J Psychiatry* 158:340-345
- Liddle PF, Friston KJ, Frith CD, Jones T, Hirsch SR, Frackowiak RSJ (1992 a) Patterns of cerebral blood flow in schizophrenia. *Br J Psychiatry* 160:179-186
- Liddle PF, Friston KJ, Frith CD, Frackowiak RSJ (1992 b) Cerebral blood flow and mental processes in schizophrenia. *J Roy Soc Med* 85:224-227
- Liddle PF, Herold S, Fletcher P, Friston KJ, Silbersweig D, Frith CD (1994) A PET study of word generation in schizophrenia. *Schizophr Res* 11:168
- Malla AK, Norman RMG, Williamson P, Cortese L, Diaz F (1993) Three syndrome concept of schizophrenia, a factor analytic study. *Schizophr Res* 10:143-150
- Matsuda H, Gyobu T, Hisada K, Ii M (1989) SPECT imaging of auditory hallucination using 123I-IMP. *Adv Funct Neuroimaging* 2:9-16
- McGrath JJ (1992) The neuropsychology of thought disorder. *Schizophr Res* 6:157
- Mortimer AM, Lund CE, McKenna PJ (1990) The positive-negative dichotomy in schizophrenia. *Br J Psychiatry* 157:41-49
- Musalek M, Podreka I, Walter H, Suess E, Passweg V, Nutzinger D, Strobl R, Lesch OM (1989) Regional brain function in hallucinations: a study of regional cerebral blood flow with 99mTc-HMPAO-SPECT in patients with auditory hallucinations, tactile hallucinations and normal controls. *Compr Psychiatry* 30:99-108
- Pardo JV, Pardo PJ, Janer KW, Raichle ME (1990) The anterior cingulate mediates processing selection in the Stroop attentional conflict paradigm. *Proc Natl Acad Sci USA* 87:256-259
- Pantelis C, Harvey C, Taylor J, Campbell PG (1991) The Camden schizophrenia surveys: symptoms and syndromes in schizophrenia. *Biol Psychiatry* 29 (Suppl):646S
- Peralta V, de Leon J, Cuesta MJ (1992) Are there more than two syndromes in schizophrenia? A critique of the positive-negative dichotomy. *Br J Psychiatry* 161:335-343
- Pfohl B, Winokur G (1982) The evolution of symptoms in institutionalized hebephrenic/catatonic schizophrenics. *Br J Psychiatry* 141:567-572
- Pogue-Geile MF, Harrow M (1984) Negative and positive symptoms in schizophrenia: a follow-up. *Schizophr Bull* 10:331-337
- Schroder J, Geider FJ, Binkert M, Reitz C, Jauss M, Sauer H (1992) Subsyndromes in chronic schizophrenia: do their psychopathological characteristics correspond to cerebral alterations? *Psychiatry Res* 42:209-220
- Suzuki M, Yuasa S, Minabi Y, Murata M, Kurachi M (1993) Left superior temporal blood flow increases in schizophrenic and schizophreniform patients with auditory hallucinations: a longitudinal case study using 131-IMP SPECT. *Eur Arch Psychiatry Clin Neurosci* 242:257-261
- Thompson PA, Meltzer HY (1993) Positive, negative and disorganisation factors from the Schedule for Affective Disorders and Schizophrenia and the Present State Examination. *Br J Psychiatry* 163:344-351
- Venables PH, Wing JK (1962) Level of arousal and subclassification of schizophrenia. *Arch Gen Psychiatry* 7:114-119
- World Health Organization (1993) *The international classification of diseases* (10th edn). WHO, Geneva