Psychosis in a Population Cohort: a four class four dimension model of schizophrenia and affective psychoses

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Abstract

Introduction

Psychosis is a low prevalence disorder with high cost to those affected, their families, and society in general. Enormous effort to determine the causes and pathophysiology of schizophrenia has been relatively unrewarded, and no robust biological markers have been identified. It is argued that reliance on the Kraepelinian dichotomy model of psychosis, as demonstrated in ICD-10 and DSM-IV, impedes research, especially in psychiatric genetics. Modelling the psychoses from first principles demands a population based atheoretical approach. By considering the whole spectrum of psychosis in a general population the natural boundaries of the underlying disorder(s) may be best understood. This thesis describes the use of both dimensional and categorical approaches in the same data, providing complementary approaches to delineating the psychosis phenotype. Classes and dimensions thus identified are validated by their pattern of associations with many variables previously known to be important in schizophrenia. The findings are anchored in the literature by making comparisons with traditional diagnostic categories and first rank symptoms in addition to comparison with other studies.

Methods

OPCRIT analysis was performed on 387 adults aged 18-65 years in an attempted ascertainment of all patients with psychosis from an area with a stable population and geographical organisation of inpatient and community mental health services with close links to local general practices. Distribution of the population on a wide range of variables was established, with comparisons made between the sexes. The data on symptoms were analysed firstly using principal components analysis with varimax rotation to identify factors, and secondly to establish latent classes. Information relating to key variables known to be of relevance in schizophrenia was coded blind to the establishment of the classes and dimensions.

Results

In a population based cohort schizophrenia and bipolar disorder accounted for only 58.4% of those affected by psychosis. One hundred and ninety-four males and 193 females were identified, ill on average for almost 15 years at time of assessment; 83% were born in Scotland. Men and women differed on almost all premorbid variables examined as well as mode of onset and course of illness, but there was no difference in deliberate self harm, receiving electroconvulsive therapy or being detained under the Mental Health Act. Men had an earlier age of onset and women showed a small second peak of incidence in mid-life. Only 29% of men were fertile, compared to 58% of women, and this difference persisted even when considering only those who were married or lived as married. For those with schizophrenia, there was a possible association between summer birth and restricted affect. Only 5% had a family history of schizophrenia, but 35% had a family history of another psychiatric disorder.

Four dimensions were identified using principal components analysis. These were named mania, reality distortion, depression and disorganisation. The disorganisation factor was significant in predicting earlier age at onset and lower fertility, with the depression factor predicting deliberate self harm. Latent class analysis revealed four classes named depression, disorganisation, bipolar and reality distortion/depression accounting for 19%, 28%, 23% and 30% of the population respectively. The four dimensions identified were the same for both sexes, although the four classes showed a skewed sex distribution, with men over-represented in the disorganisation class. The four dimensions were supported by the literature and were shown to have differential patterns of association with external validators. The latent classes were also found to have distinctive patterns of distribution on external validators and appeared to form a gradient of severity with the bipolar class occupying the least impaired pole, and with the disorganisation class at the most severe pole. The latent classes appeared to be as valid as DSM-III-R diagnoses with respect to external validators. The four latent classes were significantly different on gender ratio, age of onset, fertility, deliberate self harm, course of illness, use of electroconvulsive therapy and detention under the Mental Health Act.

Conclusion

For genetic studies, four classes which are well demarcated are a useful alternative to DSM-III-R diagnoses, comprehensively encompassing the entire range of psychosis. Likewise the four dimensions should prove useful in quantitative trait loci approaches in genetic studies, and provide a dimensional scale which could be of clinical value. While it is not suggested that the four latent classes should replace current diagnoses, their validation challenges the continued acceptance of the current plethora of diagnostic categories.

The Kraepelinian dichotomy appears to be supported by the clear distinction between the disorganisation and bipolar classes, but the other classes are less distinctively different. It is timely to consider reclassifying the psychoses from first principles, based on a series of larger population based empirical studies. The current concept of schizophrenia is probably too heterogeneous. The latent classes point to the utility of dementia praecox (disorganisation class) as being of a different substance, representing the only truly non-affective psychosis. Until the terminology is changed, the assumptions inherent in the term schizophrenia will persist and continue to restrict the recognition of the true underlying subtypes in psychosis. Factor analysis and latent class analysis are useful in attempting to reveal the latent variables in psychosis which might better represent underlying diseases compared to traditional diagnoses. While it is hoped that the four latent classes may truly be "dividing nature at its joints" this can only be proven if and when biological markers are found which are differentially distributed across these four classes.

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Murray V., McKee I., Miller P.M., Young D., Muir W.J., Pelosi A.J. and Blackwood D.H.R. (2005). Dimensions and classes of psychosis in a population cohort: a four class four dimension model of schizophrenia and affective psychoses. *Psychological Medicine,* **35,** 499-510.

Murray, V., Walker, H. W., Mitchell, C. & Pelosi, A. J. (1996) Needs for care from a demand led community psychiatric service: a study of patients with major mental illness. *British Medical Journal,* **312,** 1582-1586.

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This thesis is dedicated to all those whose lives are touched by psychosis with the hope that science will one day identify causes, find cures and ultimately prevent this puzzling and distinctively human condition.

Introduction

Psychotic illness can be defined as having the essential characteristic of abnormal experiences in which a person looses contact with reality. Changes in mood, motivation, thinking, judgement and communication are reflected in behavioural changes, with often severe functional consequences for the affected person. The National Psychiatric Morbidity Survey of Great Britain suggests a point prevalence for psychoses of 4 per 1000 adults (Jenkins *et al.* 2003). The most frequently studied psychotic illness is schizophrenia, a disorder which occurs in all populations studied to date with an incidence ranging from 0.07 – 0.14 and 0.16 0.42 per 1000 for narrow and broad definitions respectively (Jablensky *et al.* 1992). Schizophrenia is considered to be a genetically complex disorder, with polygenic transmission, locus heterogeneity and an environmental contribution (Plomin *et al.* 1994) akin to diabetes, hypertension and cancer.

Schizophrenia is a low prevalence disorder with a high cost to those affected and their families, and to society in general. Enormous effort to determine the causes, and pathophysiology of schizophrenia has been relatively unrewarded. To understand just one of the possible reasons for this it is necessary to examine the concept of schizophrenia and its relationship to the other psychotic disorders.

The psychoses: how many disorders?

Kraepelin first described the distinction between dementia praecox and manic depressive psychosis one hundred and nine years ago. This brought some order to the various presentations of insanity, providing a conceptual framework on which to build an understanding of the plethora of symptoms, presentation, course and outcomes. By meticulous clinical observation, continual sifting of symptoms and other illness characteristics, sorting and re-sorting clinical accounts he expounded these twin pillars which still underpin the main systems of psychiatric classification (World Health Organisation 1992; American Psychiatric Association 1994). Current diagnostic boundaries of schizophrenia are probably wider than those of dementia praecox, and bipolar disorder is a much narrower concept than Kraepelin's manic depressive psychosis (Jablensky 1999), but the dichotomy remains intact. It has always been recognised that many patients do not fit these prototypes. Intermediate forms are so common that separate categories are necessary, such as schizoaffective disorders, severe depressive episode with psychotic symptoms, and other non-organic psychotic disorders in ICD-10 and the concept

of cycloid psychosis in the Scandinavian countries and elsewhere. Outcomes for the intermediate forms are also intermediate between schizophrenia (relatively poor) and manic depression (relatively good). Whether or not the two disorders can be separated by a point of rarity is debatable. Psychiatry remains a discipline in search of a nosology which separates the functional psychoses along lines of natural division. By doing so it is to be hoped that the psychopathological syndromes identified are markers for underlying putative discrete disorders which will provide a sound basis for the identification of aetiologies (Kendell 1991). In no other medical discipline is this fundamental nosological problem so urgent, yet resistant to solution despite intensive research using a wide range of scientific approaches. In 1991 it was optimistically suggested that the sheer volume of new information from epidemiological, neuropathological and genetic studies may itself be delaying the integration of information to form the basis of a robust nosology (Kerr & McClelland 1991). Fifteen years later, after many robust incidence studies, structural and functional neurological studies and genome scans, the key question is as pertinent as in Kraepelin's era: are affective and non-affective psychoses distinct disorders, or at opposite ends of a continuum of psychosis, or simply expressions of varying severity of an underlying unitary psychosis?

Synopsis of early criticism of the two disorder model

From the outset, Kraepelin's categorisation was met with criticism. However, his idea of a nosological entity which consists of a close relationship between symptom profile, course, outcome and aetiology, and constituting a natural disease entity persists to this day. Lacking distinctive neuropathological findings or aetiology, the only validating criteria left to support Kraepelin's natural disease entities were the internal cohesion of the clinical picture and the course and outcome. A brief overview of the early critiques is given by Stromgren (1994) and Jablensky (1999).

Alfred Hoche held that psychiatry could distinguish between syndromes, but these syndromes of themselves could not delineate nosological entities. He argued that cerebral localisation of psychological symptoms is possible only when specific efferent pathways are interrupted by a lesion. Since many essential symptoms of the psychoses involving affect, mood, drive, will and judgement engage widely different brain areas cerebral localization is not amenable to this approach. He argued that the aim of psychopathology is to precisely describe symptom complexes which are aetiologically neutral.

Conrad in 1952 suggested that both the clinical and genetic evidence supported the two clinical forms being different expressions of a single endogenous psychosis. Other proponents of alternatives to the Kraepelinian system included Leonhard who proposed a complex classification of the psychoses. This included systematic schizophrenia, with a putative developmental or environmental aetiology and unsystematic forms which were genetic in origin, and cycloid psychoses of good outcome. He also distinguished between bipolar and unipolar affective disorders.

Kretschmer in 1927 proposed that the psychoses were not disease entities but rooted in the biological constitution of the individual with all possible transitions between subclinical manifestations and florid psychosis. Complex or mixed psychopathological pictures were due to the interaction effects of co-inherited different predispositions. In his later articles Kraepelin moved towards the notion that the manifestations of psychosis were not due to particular pathological processes but instead the reaction of pre-existing response templates of the brain to a variety of aetiological factors. The notion of different strata of responses was introduced: affective, hysterical and paranoid, the schizophrenic form and encephalopathic forms of reaction. Regarding manic depressive psychosis and dementia praecox Kraepelin stated in 1920:

> "we cannot distinguish satisfactorily between these two illnesses and this brings home the suspicion that our formulation is incorrect"

There are two major problems with the dichotomy: the existence of clinical interforms and evidence from genetic studies. If schizophrenia and bipolar disorder truly divide underlying unobserved psychopathological entities correctly, then interforms should be rare. One would expect features of both schizophrenia and bipolar disorders to co-occur at an incidence determined by the product of the incidence of each disorder. Kraepelin himself noted the existence of a large number of cases which did not fit his division. In population based surveys interforms are relatively common. For example, across the broad spectrum of psychoses, schizophrenia and bipolar disorder account for between 58% and 69% of those suffering from psychosis (Jablensky *et al.* 2000; Murray *et al.* 1996) Likewise, if these two disorders represent discrete conditions with separate genetic aetiologies then one would expect the disorders to "breed true", but instead a distinct overlap is found, as discussed below.

Modern approaches to modelling the psychoses

Summarising a debate that has been raging for 100 years is difficult, and only a very brief account is provided, concentrating on approaches of direct relevance to this thesis. Modern day proponents of the Kraepelinian dichotomy include Winokur, Kendler and Cloninger.

The Neo-Kraepelinian View

Cloninger used data from different sources to test the veracity of six different models of the relationship between schizophrenic and affective psychoses. On the basis of relationships between the observable symptom distributions he tested an admixture or bimodal model. He concluded that his discriminant analysis of lifetime symptoms in 500 patients represented an admixture of two distributions (Cloninger 1994). This was supported by a study by Brockington *et al.* (1991) confirming admixture and showing that the severity and duration of manic symptoms, and not presence or absence of these symptoms, distinguished bipolar disorder. However neither study could separate patients with psychotic depression from schizophrenia.

Likewise, a population based study of twins using narrowly defined schizophrenia found an excess of schizophrenia and other non-affective psychoses, but not bipolar disorder in monozygotic co-twins of probands. Reports of monozygotic twins where one had schizophrenia and the other bipolar disorder were refuted by Cloninger by citing Bertlesen (1992) who reported that these mixed twin pairs had schizomanic features and not narrow schizophrenia or narrow mania. Cloninger summarised the disorders displayed by affected children of parents suffering from schizophrenia or bipolar disorder as being highly homotypic, with children affected by schizophrenia always having similarly affected parents. While acknowledging that schizophrenia and schizoaffective disorder are strongly correlated in families he noted that major depression is increased in families of both bipolar disorder and schizophrenia. While there is little excess of bipolar disorder in the relatives of those with schizophrenia, complete separation is not consistently found. He deduced that these results suggested "partial homotypy" with relatives being most likely to have the same diagnoses but there being some excess of other disorders. Cloninger concluded that both the discrete dichotomy model and the continuum model could be excluded, and that the results were most consistent with a two spectra model of partially overlapping diseases. In this model the core phenotypes in the two spectra are unlikely to overlap in the same families, but individuals in the more extended part of the spectrum

have a decreasing likelihood to share the same genotype as the core phenotype in that spectrum and so more likely to overlap with the other spectrum.

Kendler's support for the Kraepelinian dichotomy is firmly supported by his landmark population based family genetic work in the affective and non-affective psychoses. The Roscommon family study (Kendler *et al.* 1993) found the risk for bipolar illness to be only 1.2% in relatives of probands with schizophrenia compared with 1.4% in general population controls. Using a latent class approach in defining empirically based psychosis phenotypes Kendler and colleagues showed increased risk for bipolar disorder only in relatives of bipolar-schizomanic probands, unipolar depression only in relatives of depressed and schizodepressed probands and schizophrenia spectrum illness predominantly in the relatives of probands with classic schizophrenia, hebephrenia, schizophreniform disorder and schizodepression (Kendler *et al.* 1998). He concluded this was inconsistent with the dichotomous model, but also inconsistent with the continuum model since his empirically defined class of major depression had a distinctive symptom pattern, family history, and outcome compared to the predominantly schizophrenic classes.

Winokur observed symptom patterns and family histories of four groups of both psychotic and non-psychotic bipolar and unipolar patients. Symptom patterns differed but across the four groups family histories were the same. He concluded that the findings did not support autonomous psychotic unipolar, psychotic bipolar or schizoaffective disorder. He held that the data also opposed the existence of a continuum of liability to affective disorder (Winokur 1984). In his view, acute schizoaffective disorder should be considered an affective disorder (Winokur 1989). This was based on noting comparisons between unipolar and bipolar patients. Since the schizoaffective patients displayed the same pattern of comparisons as both bipolar mood congruent and non-psychotic unipolar and bipolar patients he concluded that mood incongruent bipolar and unipolar patients should be considered to have affective disorders.

The Continuum View

Crow has been perhaps the most outspoken proponent of the continuum hypothesis of psychosis. This posits that rather than a binary model, or a unitary model with varying expression, there is a continuum of psychosis of varying severity, with schizophrenia at one pole and unipolar psychotic depression at the other. He challenged Cloninger's finding (Cloninger 1985) of a bimodal distribution of symptoms by suggesting that the very restrictive form of schizophrenia produced by this method excludes a large number of

people with Feighner positive schizophrenia, leaving a large proportion of schizophrenic, non-schizophrenic and non-affective psychoses unaccounted for.

Again genetic studies figure prominently in supporting Crow's theory, and he rightly emphasises the lack of family studies which included interforms of the binary model as probands. In studies where such interforms are included (Angst *et al.* 1979; Gershon *et al.* 1988) he cites the rising ratio of schizophrenic to mood disordered relatives increasing across the spectrum from unipolar illness to schizophrenia in several studies as support for a continuum of psychosis. He suggests that Kendler's data showing a genetic overlap between at least some schizoaffective disorders and schizophrenia supports the continuum hypothesis. However, Kendler, in a later debate with Crow stuck firmly to the existence classic schizophrenia as a distinct entity evidenced by differential family histories in his latent class analysis of probands with psychosis, while acknowledging such evidence did not support the binary psychosis model (Kendler & Walsh 1998).

Modelling the psychoses from first principles

Kendell asserts that the question of whether a binary system or continuum of psychosis exists is meaningless since diagnostic concepts are models which can only represent the underlying phenomena of mental illness, and should be judged on their merit of usefulness. He further states that in choosing a model it must be decided whether a typology or dimensional model is chosen. A typology could have any number of categories, which would include a unitary psychosis (einheitpsychose) or Kraepelin's dichotomy. Likewise, a dimensional model requires specification of how many dimensions are recognised and how these are related to each other. Different models may be of varying use in different situations. Kendell contends that proponents of the realist position consider schizophrenia and manic depressive psychosis as two distinct diseases, whereas nominalists would regard these as simply concepts which provide a framework to think about the phenomena of psychosis, and provide a means of communication. In his view the case for the binary model or the continuum is unproven. The former can only be shown to be correct if a point (or zone) of rarity is shown to exist between the two disorders, and in his view this has not been demonstrated. Lack of such a zone would support the continuum model, but he urged caution in prematurely dispensing with the Kraepelinian model until more comprehensive studies were undertaken.

The Kraepelinian Model: aid or hindrance?

The Kraepelinian model has served a valuable purpose in providing a framework upon which modern operationalised criteria of the psychoses have grown. Such criteria have enabled the identification of reliably diagnosed categories of disorder, facilitating communication both within psychiatry and between disciplines. However the validity of the disorders so described is not yet proven. There is a danger that these diagnoses take on a life of their own, implicitly accepted as having a basis in truth. This is argued eloquently by Kendell:

> "For the last 20 years I have been dismayed by the widespread assumption that schizophrenia and manic-depressive illness are distinct diseases simply because we have given them different names, because the distinction between them is regarded as an important matter in everyday clinical practice, and because they are usually treated differently. I have therefore tried again and again to convince my students and colleagues that these assumptions are unjustified and that we must be prepared to consider other possibilities and to think in dimensional terms." (Kendell 1991)

That the current operationalised diagnostic criteria for psychoses are an improvement on previous attempts is generally accepted but the use of these instruments in communicating the nature of a person's illness is limited. Sometimes the diagnostic criteria are so inclusive that two people may meet these criteria without sharing a single cardinal feature. Despite this, there are many people whose illness characteristics place them in the realm of "not otherwise specified". This puzzles the person, their families and agencies providing care. Likewise, a high incidence of comorbid disorders can make conceptualisation of a person's problems more complex than is necessary. In recent years the early intervention movement has sidestepped the dogma of Kraepelinian division to recognise the need for timely and efficient intervention no matter what particular shade of psychosis is experienced. This has allowed a better appreciation of the continuities within psychoses, previously unappreciated because they were relatively unexamined.

Kraepelinian dichotomy as a hindrance

The question of the validity of the Kraepelinian dichotomy is relevant for these practical problems encountered in everyday practice, but is of fundamental importance for a different reason. It is probable that the current nosological status of the functional

psychoses is stifling research in the field (Jablensky 1999; Parnas 2000). The problem is difficult to unravel. Without a classification system that correctly identifies underlying disorders representing different disease entities (with different course, outcomes and treatment responses) the identification of the psychoneuropathological substrate of these "diseases" will remain elusive. Without identification of such substrates the different aetiological factors responsible and how their effect is exerted will remain obscure. This co-dependency is brought sharply into focus in the field of psychiatric genetics: without correct identification of the psychosis phenotypes susceptibility genes are unlikely to be identified.

Genes, epidemiology and an empirical approach

Genetic susceptibility to psychosis is probably the most robust aetiological factor yet identified (Gottesman & Shields 1982). In both bipolar disorder and schizophrenia the risk of illness in siblings is about tenfold greater than the population risk. But psychotic disorders do not "breed true". Relatives of probands with schizophrenia have increased genetic liability not only for schizophrenia but for a range of psychotic disorders including psychotic depression (Kendler *et al.* 1998; Erlenmeyer-Kimling *et al* 1997). This is supported by a twin study showing an overlap in the genetic risk contributing to syndromes defined as schizophrenia, schizoaffective disorder and bipolar disorder (Cardno *et al.* 2001). However one criticism of the methodology of diagnosis in the latter study was the categorisation as manic for any proband who had ever had an episode of mania (Kendler 2002). This illustrates the interdependent problems of diagnosis and identifying genetic factors in psychosis. It also raises the issue of how one conceptualises the relationship between mania and schizophrenia. There appears to be a longstanding assumption that schizophrenia is at the apex of a hierarchy, so that once an episode of schizophrenia is experienced a person's illness will always be interpreted in these terms.

The current consensus model for psychosis susceptibility genes is the multifactorial threshold model (Gottesman & Shields 1967). This posits that there is a range of susceptibility to psychosis within the population, and that many more people carry susceptibility genes than ever express them as psychosis. A crucial component of this model is an environmental factor that interacts to tip those carrying the requisite loading of genetic susceptibility into manifest disorder.

While family and twin studies support the genetic basis of psychosis, it is the adoption studies which offer unequivocal evidence for the genetic effects distinct from the combined effects of genes and shared *ex utero* environment influence. The Finnish Adoptive Family Study of Schizophrenia (Tienari *et al.* 2000) reported a lifetime prevalence of schizophrenia of 6.7% in the adopted-away offspring of mothers with schizophrenia compared to 2% in controls, but more strikingly 17% of adoptees whose biological mother had schizophrenia and 4% of control adoptees were diagnosed with either schizophrenia or a broadly-defined schizophrenia spectrum disorder. Spectrum disorders included schizoaffective disorder, delusional disorder, bipolar disorder, psychotic depression and the schizotypal and paranoid personality disorders. These findings support a shared genetic liability for both narrowly defined schizophrenia and broadly defined spectrum disorders including affective psychoses.

This shared genetic liability is reflected in linkage and association findings at several chromosomal locations where there is evidence that identical loci contribute to the risk for both schizophrenia and bipolar disorders (Wildenauer *et al.* 1999; Berrettini 2000; Blackwood *et al.* 2001; de Lisi 1999). In considering all those affected by psychosis in a population, the Kraepelinian dichotomy presents a substantial difficulty. Linkage and association studies that include everyone with psychosis must involve arbitrary judgements e.g. deciding whether schizoaffective disorder should be included with schizophrenia, or with bipolar disorder. In the past many studies circumvented this by using very pure samples of either narrowly defined schizophrenia or manic depression, but the results described above suggest that this is no longer tenable. However, deciding how to best sort the psychoses for genetic studies inevitably makes assumptions about the "true" underlying diseases which may be erroneous and cause false negative results. Therefore it is important to determine, at a population level, how symptoms of bipolar disorder and schizophrenia overlap.

Thus there is an argument for reconsidering the boundaries of the functional psychoses to facilitate psychiatric genetic research. This aside, personal experience would suggest other reasons for such an undertaking. For example, as an adolescent psychiatrist responsible for a patient with a particularly malignant psychosis I sought help from an eminent psychiatrist. No advice was forthcoming until I decided if the patient had schizophrenia or manic depression, notwithstanding evidence that medication has effects at the level of symptoms of psychosis and is not diagnosis specific (Johnstone *et al.* 1988). Perhaps after a year or two such a distinction would be obvious, but at the point of consultation the symptom profile was emphatically schizoaffective, placing the patient in the no-man's land

of failing to be a prototype in a binary catergorisation of psychosis. But this was not the first suspicion that the dichotomous viewpoint was unhelpful.

In 1993-4 a needs assessment of all adults suffering from functional psychosis in a treated prevalence study was attempted. This involved careful examination of symptoms and illness course in addition to measurement of patient morbidity and carer stress (Murray *et al.* 1996). Familiarisation with those affected, and their carers strengthened impressions from clinical practice that the disability suffered in psychosis was not diagnosis dependent; that across the psychoses there were more similarities between diagnostic groups than dissimilarities; and that very few had a less than severe outcome, with profound effects on all aspects of the lives of the affected person and their families. The limited effectiveness of treatments combined with the inability to discover why this had happened to this particular person fired enthusiasm for psychiatric genetics. Surely if a breakthrough was imminent it would be in genetics, which was successfully constructing new aetiologically based nosologies in other areas of medicine, notably neurology.

The Hamilton Psychosis Study

Thus from 1996-2000 the previously established treated prevalence population was expanded and those identified were asked to participate in an ongoing programme of psychiatric genetics research led by Professor Douglas Blackwood and Dr Walter Muir in the University of Edinburgh. By participating, those involved and their families contributed to multinational association studies of the psychoses in addition to the body of large multiply affected pedigrees for linkage studies (Boorglum *et al.* 2003; Souery *et al.* 1998). Searching for susceptibility genes continues apace, but the central question remains: could psychoses be categorised differently to better identify true psychopathological substrates? Could a population based approach provide new insight into the characterisation of the functional psychoses?

A comment by Kendler and Walsh (1998) is apt:

> "Psychiatric nosology has been too long the province of speculation and pronouncement, particularly in the area of psychotic disorders where powerful empirical studies are rare."

This supports an approach to defining psychosis which makes no prior assumptions about the nature of the relationships between the various forms of functional psychosis but

instead approaches the problem empirically. The population setting for such a study should be characterised by a stable and ethnically uniform population which can offer the possibility of complete ascertainment. The study was based in the district of Hamilton, in central Scotland. This setting offered many advantages. There was very good communication between primary and secondary care services with a unified Community Mental Health Team. One local hospital served the district, with little non-NHS service uptake. In addition there was a very stable and ethnically homogenous population hitherto unexamined by any prior psychiatric research.

The work described in this thesis (hereafter called the Hamilton Psychosis Study) which sought to provide an empirical solution to categorising the functional psychoses was predicated on the following suppositions:

- That the natural boundaries of psychosis could be best understood by considering the whole spectrum of psychotic disorder in a general population.

- That taking such an empirical approach sidestepped the Kraepelinian riddle and instead sought to identify psychoses from first principles.

- That using both dimensional and categorical approaches in the same data set could potentially provide different yet complementary approaches to delineating the psychosis phenotype(s).

- That symptom complexes should be the basic unit of measurement with all other variables (including putative actiological and prognostic indicators as well as course of illness and associated illness characteristics) studied separately.

The latter two suppositions underlying the study require some further explanation. Utilising symptom complexes uncontaminated by other variables makes no assumptions regarding their relationship with such variables and permits examination of relationship with other variables *de novo*. Given the relative lack of success of the categorical approach in aetiological studies, a dimensional approach to psychosis could offer certain advantages. Firstly, dimensions are useful for quantitative trait loci approaches which have been highly successful in delineating complex traits in animal models and have been applied in psychiatric disorder (Flint 2003). Secondly, dimensional approaches present a more complete synthesis of all available data about a patient. By fitting people into a limited number of classes categorical approaches must inevitably lose information and introduce

error. Thirdly, dimensional approaches offer an opportunity to quantify longitudinal variation in symptom evolution. Fourthly, it has been shown that dimensional approaches can be more effective in predicting certain clinical variables compared with traditional categorical diagnoses (Rosenman *et al.*2003; Van Os *et al.* 1999).

However the categorical approach has nurtured medical progress, with delineation of disease, identification of pathology and hence identification of aetiologies the usual order of events. In the absence of diseases in the functional psychoses, categories of disorders, or more correctly syndromes, are influential and provide a framework for the nature of psychiatric morbidity. The dangers of treating such syndromes as real has been discussed previously. However the question remains: how would psychosis appear when derived empirically, without any *a priori* theories as to the veracity or otherwise of the Kraepelinian model?

Overview of previous models of psychosis

Prior to outlining how this question could be addressed it is useful to place the current study in the context of past findings in this field. From the viewpoint that schizophrenia is a subtype of psychosis which is yet to be validated, studies subtyping schizophrenia are inherently flawed (McGorry *et al.* 1998; Stuart *et al.* 1999). Others have argued that schizophrenia is not heterogeneous, but has variability in severity expression (Goldberg & Weinberger 1995). Nevertheless there has been considerable effort in trying to find latent structures underlying schizophrenia, producing a variety of models. For example the one factor model produces one factor with positive and negative symptoms at the extremes (Andreasen & Olsen 1982). Crow's type I and type II schizophrenia consisting broadly of positive and negative symptoms respectively (Crow 1985) was supported by confirmatory factor analyses (Lenzenweger & Dworkin 1996). A three factor model with negative, positive and disorganised factors (the latter consisting of thought disorders, inappropriate affect and bizarre behaviours) was developed and appeared supported by several studies (Andreasen *et al.* 1995; Lenzenweger *et al.* 1989; Liddle 1987; Peralta *et al.* 1992; Toomey *et al.* 1997) and appeared to be of functional relevance. The same three factors have been found in subjects with a broader range of psychoses (Klimidis *et al.* 1993; Toomey *et al.* 1997). However a five factor model was found by Salokangas and colleagues (1997).

Considering mood disorders, Maziade *et al.* (1995) found that the three dimensions model of schizophrenia was also found in bipolar subjects, and a four factor solution was found in a sample of people with schizophrenia, schizoaffective and bipolar patients, the

additional factor being mania (Ventura *et al.* 2000). In contrast, a study exclusively on patients with mania found seven factors (Sato *et al.* 2002).

Classes, dimensions and validity

When considering what constitutes the essential measurable unit of psychosis, it is important to avoid conflating symptoms with other illness characteristics such as age of onset, or illness course and outcome. This ensures that the character of psychosis is constructed of elements which are as discrete as possible.

Latent class analysis

Latent Class Analysis (LCA) is a statistical technique which is capable of determining the number and composition of unobserved latent classes that produce observed data. In effect LCA examines a set of categorical observable variables and investigates an association between these. Latent classes are defined by the criterion of "conditional independence", which means that within each class, each variable is statistically independent of every other variable. Thus within the latent classes constructed in this study the presence or absence of one symptom is viewed as unrelated to the presence or absence of all other symptoms comprising the latent class. In other words, if one removes the effect of latent class membership on the data, all that remains is randomness (i.e. as complete independence among measures). Thus within the latent classes the conditional independence assumption implies that the probability of an individual's response to any item is dependent only on LCA membership (McCutcheon 1987).

LCA has at least two uses relevant to the question of psychiatric classification. Firstly, the latent classes identified can represent diagnostic subtypes, and this will be the way the method is utilised in this thesis (Young 1983). Secondly, LCA can be used to provide estimates of diagnostic accuracy by enabling comparison between sensitivity, specificity and positive predictive power for different measures of diagnosis and so provide some evidence of validity in the absence of a gold standard (Faraone & Tsuang 1994).

The latent class approach has lacked the popularity of the second data reduction analysis, namely factor analysis. This has no doubt been due to the computational power and command language programmes required for LCA. This is likely to change with the

availability of programmes like LATENT GOLD allowing a graphical interface and hence access for the less skilled.

Principal components analysis

The dimensions in the Hamilton study were constructed using principal components analysis, a form of factor analysis. In delineating dimensions of psychosis factor analysis has been popular. However, much of the work in this field has been open to criticism. The general technique has been criticised (Streiner 1994) and in particular its application in psychosis (McGorry *et al.* 1998). The pitfalls and limitations of factor analysis and LCA are discussed in the methods chapter. However, some general observations are noteworthy. The results of factor analysis are exquisitely sensitive to the nature of the data. In particular, data produced by instruments with an underlying factorial structure such as SANS and SAPS inevitably produce factors reflecting this structure (Stuart *et al.* 1999). Thus data must be gathered using instruments free of such underlying structure. Also, the factors produced are necessarily constrained by the variety of the items of information used in their construction. These must be as comprehensive and wide-ranging as possible. Over-representation of certain items may produce a series of factors related to these items, at the expense of other factors whose loading items were less numerous. The means of addressing these issues are discussed in the methods chapter.

Validity

Dimensions and classes of psychosis identified may be aesthetically pleasing, but demonstrating their validity is difficult. Given the lack of biological markers many authors suggest establishing association with clinically relevant or aetiological information as a means of demonstrating that classes or dimensions have clinical validity. Thus classes and dimensions which differ on several aspects such as illness course and outcome, aetiology or treatment response may be held to have some degree of validity. The term "external validators" will be used to describe these items of clinical relevance, but it must be acknowledged that it is debatable if these can truly validate the classes and dimensions. Robins and Guze (1970) in a frequently quoted paper listed five criteria for establishing the validity of psychiatric diagnosis: clinical description; laboratory studies including psychological tests; delineation from other disorders; follow-up studies (including evidence of diagnostic stability) and family studies. Kendler refined this by distinguishing between antecedent validators (family history, premorbid personality and precipitating factors), concurrent validators (including psychological tests) and predictive validators

(treatment response, relapse rates and diagnostic consistency). Application of advances in the fields of neuroscience and genetics were advocated by Andreasen (1995) as validators, i.e. molecular genetics, cognitive neuroscience, neurochemistry neurophysiology and neuroanatomy. However Kendell and Jablensky (2003) clarify the difference between the utility of the diagnosis, and the validity which can only be proven by demonstration of a "point of rarity" between the diagnostic boundaries and those of other disorders. They suggest that diagnostic syndromes are useful whether they are valid or not, since clinicians think in terms of these, and they are valuable for epidemiological, outcome studies and clinical trials

Despite the attractiveness of Kendell and Jablensky's argument, the concept of external validators, as described by Young (Young 1983) is used in this study. He distinguishes between two types of external validity: criterion validity and construct validity. One example of criterion validity would be predictive validity. It is assumed that the criterion is fully valid, i.e. perfectly associated with the presence or absence of the disorder. However there are no absolute validating criteria in psychiatry. He therefore suggests utilising construct validity, whereby a set of diagnostic criteria is validated by correlating the diagnoses it produces with multiple empirical variables. In doing so the study can be compared with others in the literature. Choosing which aspects of the disorder to use as these "external validators" in the Hamilton Psychosis study were driven by two main considerations: given that the functional psychoses as a group were relatively unexamined what did the literature suggest was important in schizophrenia, and what were the pragmatic constraints of the methodology?

Since case notes provided most of the data for the study, the external variables were limited to that which is recorded in a clinical account of illness. Given this restriction the literature suggested that the following were of interest.

Age at onset and gender ratio

Age at onset and gender ratio are epidemiological features of great value when considering diagnostic classification. Kraepelin recorded the earlier age at onset in men in dementia praecox and since then this finding has been replicated (reviewed by Lewine 1988), with many studies finding a five year difference. This age difference has been found in a variety of cultural settings as shown by the WHO determinants of outcome study and others (Hambrecht *et al.* 1992). In the latter study there was a 3.4 years mean increase in age at onset for women. This was confirmed by Hafner and collegues (2003) using

multiple parameters to estimate age at onset (emergence of first sign, first negative and first positive symptom) in a first episode sample with a broad definition of schizophrenia. The mean age of onset was 25.5 years for men vs 30.6 years for women, close to that of the WHO study (26.7 years and 30.1 years respectively).

Marital status has been identified as a potential confounder by Jablensky and Cole (1997), again using data from the WHO determinants of outcome study. The sample was large and diverse, with 778 men and 653 women from 13 countries. They estimated unconfounded contributions of gender, family history, premorbid personality and marital status, finding strong effects for marital status and premorbid personality and a weak effect for family history, with no effect for gender. Hafner *et al* (1989) concluded that if only single men and women with schizophrenia were compared, the differing age of onset disappeared.

The variability of the gender ratio in psychosis both with respect to affective and non-affective psychoses and how the ratio varies across the life cycle is important. These observations have underpinned aetiological theories such as the neurodevelopmental theory and the oestrogen theory. The sex differences in schizophrenia have been reviewed in detail (Hafner 2003).

Fertility

Reduced fertility in schizophrenia compared to the general population is a persistent finding although there has been some contradictory evidence (Nimgaonkar 1998). A national cohort study from Finland confirmed the lower than average fertility in men and women with schizophrenia, which is not counterbalanced by an increase in fertility of siblings (Haukka *et al.* 2003).

Onset, course and outcome

In the absence of biological validators, Kraepelin justified his binary model by the cohesive nature of the clinical picture, and by the strong association with course and outcome. This has continued to the present, with the better course for bipolar disorder compared to schizophrenia being generally upheld (Johnstone *et al.* 1992) although the picture is not quite so sharply defined as once thought (MacQueen *et al.* 2001). Thus the chronicity of some bipolar disorders and associated deficit states have been noted, and when the diagnostic boundaries of schizophrenia are relaxed to include those illnesses of a shorter duration the apparent outcome of schizophrenia is improved. The nature of the

onset of illness is relevant, with insidious onset characteristic of poor outcome schizophrenia, with a chronic or deteriorating course.

Premorbid characteristics

Those who go on to develop schizophrenia in later life as a group display subtle neurodevelopmental variations (Jones *et al.* 1994). A few premorbid characteristics, which together provide an impression of premorbid functioning, are investigated in this thesis.

Deliberate self harm

Deliberate self harm is a feature of both affective and non-affective psychoses, but studies in population based samples across diagnostic boundaries are rare.

Season of birth

There would appear to be a small excess of people with schizophrenia having a birthday in the winter months, and the aetiological significance of this has been debated. More recently there have been several reports of a relationship between the deficit syndrome in schizophrenia and summer birth.

Family History

The case for family history as an important aetiological factor has been already discussed. As much information as possible was collected in this study (see Methods).

Other variables used as "external validators"

ECT is often used in psychotic illness, usually when affective symptoms are prominent but occasionally when this is not the case, and so this treatment was included. Detention under the Mental Health Act involves many different aspects but may be considered to be an approximate indicator of severity, lack of insight and/or dangerousness. Forensic history is included as a proxy measure for degree of social adaptation or illness severity. It is a crude measure of the extent to which the person's behaviour strays beyond that which the law allows.

Conclusion

All of the above "external validators" are examined to see if a data-driven, atheoretical approach can identify meaningful categories and dimensions in psychosis. However it is also useful to anchor the findings in the literature by making comparisons between the "external validators" and other aspects of the population such as traditional diagnostic categories and first rank syndromes. Otherwise the main purpose of the study remains the identification and validation of empirically defined dimensions and classes of psychosis in a treated prevalence population.

Method

Overview

This chapter starts with a description of ascertainment of the study population. An account of case definition leads on to a short critique of the research instrument used for diagnosis. This instrument forms the basis for the structure of much of the data used in the study. Then coding of other items of information is described, followed by an account of the main analytical tools used to identify dimensions and classes and how these are validated.

Sample ascertainment

The Hamilton District of central Scotland consists of the towns of Hamilton, Bothwell, Blantyre and a small part of southern Uddingston, and may be considered typical of small town urban life in Scotland. The total population in 1991 was 80,380 with approximately 45,396 aged between 18 and 65 years of age. The old Hamilton local government district was rated as the eighth most deprived district in Scotland (out of 56) based on the analysis of 1991 census data (McLoone 2000) using deprivation indices by Carstairs and Morris (1991), although affluent areas exist within the district. For example, although the overall Carstairs deprivation score was 0.61, this included scores ranging from the highest level of deprivation in Lanarkshire (3.7 in Blantyre) to -2.3 for Uddingston and Bothwell. In 1993 an epidemiologically based sample of people with psychosis was ascertained for the purposes of a needs assessment in the Hamilton District. The clinicians involved continued to add to this sample as new cases were identified. From 1996 to 1999 these cases were assessed along with all subsequent new cases. Case ascertainment was facilitated by the geographical organisation of in-patient and Community Mental Health services and close links with local General Practices. Methodology differed slightly for the two time periods.

Sample ascertainment (1993 – 1994)

Inclusion Criteria

Patients were included for investigation if aged 18-65 years, if they had a permanent address in the Hamilton District for at least one month between 1st June 1993 and 31st May 1994, and if they had a psychotic illness (as defined below) at any time in the previous five years. We did not include people meeting our diagnostic criteria currently living in the local learning disability hospital or in long stay psychiatric wards. Ethical approval was obtained from the local ethics committee and Information Services Division of the Scottish Office.

Identifying study subjects

Hospital and outpatient records

1. Hospital records for the previous five years were examined. We were deliberately over inclusive at this stage and any ICD-9 diagnosis which could indicate a psychotic illness led to full examination of all casenotes (Table 1).

2. Consultants were asked to identify potentially suitable outpatient attenders; this was facilitated by the use of appointment diaries and a computerised database of recent attenders at clinics.

3. Community Psychiatric Nurse (CPN) records over the previous five years were examined.

4. Day Hospital records were examined.

5. Daily nursing report returns were obtained. These indicate which inpatients require special observations, many of whom suffered from psychotic disorders.

Scottish Morbidity Record Returns (SMR04)

These are centrally held data on all in-patient and day patient episodes in Scotland. Admissions and discharge records for 1988-93 for patients from the Hamilton area with the relevant diagnoses were supplied by the Information Services Division of the Scottish Office.

General Practice cases

An attempt was made to identify cases known only to General Practitioners (GPs). Agreement was sought from the local medical committee prior to contacting local GPs by letter. We explained the nature and purpose of the study and provided each doctor with a list of people already included who were registered with them. The doctors were asked to identify any additional cases matching our inclusion criteria. GPs who did not respond were followed up by further letters or phone calls.

Sample ascertainment (1996 – 2000)

This was identical to above except in the following respects

1. ICD10 categories were used instead of ICD 9 categories (as shown in Table M1).

2. SMR04 returns and GP cases were not pursued since, from experience, these sources were unlikely to identify new cases. SMR04 returns did not identify any additional cases in the first survey, and a substantial proportion of cases identified elsewhere were not included in SMR04 returns. GPs were reluctant to identify people not known to psychiatric services; they indicated that 20 people with psychosis were known only to their GP and withheld their name.

Some cases were likely to be suitable for case inclusion, but were excluded. Thus three people were known only to CPNs. In each case the CPN was attempting to establish a relationship with a reclusive person, possibly psychotic, but not enough was known to establish whether or not the individual would fulfil inclusion criteria.

Table M1 Diagnoses in medical records which led to *full* evaluation with OPCRIT

1993 ICD 9 categories	
295 schizophrenia	292.1 paranoid and hallucinatory states induced by drugs
291.9 unspecified psychoses	297 paranoid states
296 affective psychoses	294.8 other non organic psychoses
298 other non organic psychoses	301.0 paranoid personality disorder
291.3 other alcoholic hallucinosis	301.2 schizoid personality disorder
291.5 morbid jealousy	

1996 ICD 10 categories	
F1x.5 psychotic disorder due to psychoactive substance use	F1x.7 residual and late onset psychotic disorder due to psychoactive substance misuse
F60.0 paranoid personality disorder	F60.1 schizoid personality disorder
F20.x schizophrenia	F21 schizotypal disorder
F22.x and F24delusional disorders	F23.x acute polymorphic psychotic disorder
F25.x schizoaffective disorders	F28 other non-organic psychotic disorders
F29 unspecified nonorganic disorders	F30.x manic episode
F31.x bipolar affective disorder	F32.3 severe depressive episode with psychotic symptoms
F33.3 recurrent depressive disorder with psychotic symptoms	F34 cyclothymia

Case Definition

To ensure standardised definition of a case we used the OPCRIT system (McGuffin *et al.* 1991a), which generates diagnoses according to several different classification systems from 90 pieces of information obtained from patients' medical records or interview. DSM-III-R criteria were used in this study (American Psychiatric Association 1987). OPCRIT has proven reliability (Williams *et al.* 1996) and performance compared to lifetime ever best estimate diagnosis (Craddock *et al.* 1996). All casenotes were examined and coded by the author after training in the use of OPCRIT with a series of 30 abstracts provided by Professor McGuffin's group in Cardiff plus 20 records of Lanarkshire patients.

Any mention in the case records of psychotic symptoms or signs necessitated full evaluation with OPCRIT. Where current clinical opinion disagreed with OPCRIT, clinical consensus was final. This is in keeping with the philosophy on which OPCRIT is based (McGuffin *et al.* 1991). This occurred in six cases: one case scored zero on OPCRIT (ie no diagnosis) but the clinicians adjudged there to be bipolar disorder; the other five cases scored major depression on OPCRIT and were judged to be depression with psychosis (four) or bipolar disorder (one). One case, which scored positively on OPCRIT, was excluded on clinical grounds. We chose to include people with co-morbid diagnosis of substance misuse since this is common in people suffering from a psychotic disorder. However we were careful to exclude those whose psychotic symptoms were thought to be due primarily to intoxication or delirium due to substance misuse. This was discussed in detail with the relevant clinician and a consensus agreed. Data for associated items of information were collected prior to the data reduction analyses.

An attempt was made to obtain all information from every case note for each individual and the "lifetime ever" criterion was employed, as recommended for genetic studies (Farmer *et al.* 1992). Where the medical account was very detailed and comprehensive this was straightforward, but in a few cases the notes were less rich. In such circumstances nursing and paramedical records were examined in detail to obtain as robust an account of symptomatology as possible. Notes were coded exclusively by the author. Intra-rater reliability was not formally tested. Occasionally a "natural experiment" occurred with the same patient being assessed repeatedly via different sets of case notes. This did not compare like with like since the case notes described different illness episodes. Prior to the analyses such duplicate cases were combined and recoded.

Note on the use of OPCRIT

Since OPCRIT provides the structure for most of the data in this study, it is necessary to describe this instrument, outlining its strengths and limitations. In essence, the impetus for development of the instrument was the emergence of various systems to define schizophrenia which were reliable, but of uncertain validity. Faced with a lack of a gold standard diagnostic measurement, the OPCRIT group aimed to devise an instrument which would produce diagnoses from all the major classification systems from a single dataset (Farmer *et al.* 1993; McGuffin *et al.* 1991), allowing a polydiagnostic approach for biological studies as suggested by Kendell (Kendell *et al.* 1975).

The OPCRIT diagnostic system consists of a 90 item checklist constructed from operationalised criteria for several major psychiatric classification systems, and software which generates diagnoses according to each of the different classification systems. OPCRIT thus allows a polydiagnostic approach in psychosis and was used in several studies of the genetics of psychosis (Cardno *et al.* 2001), as well as in health services (Rosenman *et al* 2003; Van Os *et al.* 1999) and epidemiological studies (Allardyce *et al.* 2001). Version 3.31 was used in this study, which included diagnostic output for DSM-III-R as well as ICD 10. An updated version which produced DSM-IV diagnoses was unavailable at the start of the study. The OPCRIT software also provides OPCOM, a means of displaying comorbid diagnoses which ignores the hierarchical nature of classification (e.g. a person could meet the criteria for both schizophrenia and depression).

A glossary provides precise definitions for each of the 90 items in the checklist. Information sources used can be multiple, including interviews and case records or detailed abstracts. OPCRIT can be rated on individual episodes, or a life-time ever basis. Within the checklist are items relating to premorbid characteristics, demographics, symptoms and course of illness, in addition to items relating to substance misuse. The checklist is reproduced in its entirety in Appendix 1.

Within OPCRIT, some items of psychopathology are scored in terms of increasing severity or duration, but most are dichotomous (present/absent). OPCRIT also allows for recording missing items, which are then treated as absent by the diagnostic algorithms.

OPCRIT is of proven reliability (Williams *et al.* 1996) and compares well with a consensus best estimate lifetime diagnosis (Azevedo *et al.* 1999; Craddock *et al.* 1996). However, at least one study contradicts the validity of the instrument. Mihalopoulos and colleaugues found that OPCRIT was of poor validity (2000), although it is unclear from the methodology if the raters received adequate training in the use of the instrument. For example, only four case notes were coded by all four raters simultaneously, prior to coding notes for the study. Personal experience suggests that to train people in the use of the instrument simultaneous coding and detailed discussion of discrepancies between the raters, on at least 10 case notes is required. For example if the raters had coded four notes for prototypical bipolar disorder acceptable inter-rater reliability could have been achieved, but whether the coding would be valid or reliable for the highly variable symptom presentations across the wide range of psychoses is open to debate.

Strengths of OPCRIT

1. The polydiagnostic nature of OPCRIT makes maximum use of available diagnostic systems, allowing flexibility in case definition. This allows comparison with other studies and provides a means for testing out which diagnostic system is the most valid in a particular situation, which is a vital process in establishing validity in the absence of biological markers. For example, applying different diagnostic systems to the Maudsley twin dataset demonstrated better MZ/DZ concordance rates for a broader definition of schizophrenia which included affective disorder with mood incongruent delusion, schizotypal disorder and atypical psychosis (Farmer *et al.* 1987).

2. OPCRIT provides a standardised method of recording case note data.

3. A detailed glossary for deciding if item is present or not is provided, often with advice on how to rate if uncertain eg "rate up if in doubt". This allows good item by item reliability, although this is less reliable than the diagnostic categories.

4. Diagnoses produced accord well with clinical impression, as would be expected from the proven consensus with best estimate lifetime diagnosis.

5. This instrument is widely used thereby allowing comparison across study populations. The inclusion of older diagnostic systems (such as DSM-III) allows direct comparison with previous studies.

Weaknesses of OPCRIT

1. OPCRIT omits many items of relevance to genetic studies (e.g. anxiety, obsessions and compulsions, phobias, neurodevelopmental indices). Inclusion of such items may have enhanced phenotypic definition in this study. However, the case notes often lacked robust account of neurodevelopment.

2. Many of the items in the checklist are very similar (since they are derived from different classification systems whose criteria vary only slightly) and an effort has to be made to distinguish each item from similar items. Sometimes a symptom would meet a criterion from one system, but slightly different definition would exclude this from another. This is not a weakness on the part of OPCRIT, which is being faithful to the original operationalised criteria for diagnosis, but makes completion of the form tedious. It would be advantageous to have a selection of different versions which produce diagnoses only under DSM and ICD classifications, for example. However, it is recognised that this is antithetical to the philosophy and purpose of OPCRIT.

3. Regarding the generation of diagnostic categories, OPCRIT stipulates that symptoms coded must occur during an episode of illness. However, using the "lifetime ever" stipulation must run the risk of spurious diagnoses occurring. For example, in theory a person could have a mixture of symptoms in each episode which would not meet a particular diagnostic threshold, yet combined together in the lifetime ever perspective a diagnosis would be reached. This is not dissimilar to a three dimensional sculpture whose individual components are not recognisable, but when seen from a particular angle appear to form a recognisable solid shape. The solid recognisable shape is illusionary, as revealed when considered from every other viewpoint. However, given that the purpose of the study is to examine *a priori* symptom groupings in a lifetime perspective this presents no difficulty. In any case the OPCRIT diagnoses were revised in the light of clinical judgement and

in the vast majority of cases the OPCRIT diagnosis was congruent with the clinical diagnosis, with six exceptions previously mentioned. Thus this theoretical problem is probably of little practical importance.

4. The diagnostic algorithms are not explicit, and so not open to evaluation or criticism.

5. Question number 52 is especially problematic in that diagnosis is critically dependent on this question (Farmer *et al.* 1992; Farmer *et al.* 1993): This asks about the relationship between psychotic and affective symptoms and forces a choice between the following options: "No co-occurrence"; "Psychotic symptoms dominate the clinical picture although occasional affective disturbance may also occur"; "Psychotic and affective symptoms are balanced, with neither group of symptoms dominating the overall course of the illness"; "Affective symptoms predominate although psychotic symptoms may also occur" or "As in rating '2' (see above) plus delusions or hallucinations for at least 2 weeks but no prominent mood symptoms". OPCRIT cannot compensate for deficiencies in operationalised criteria, but deciding on the balance of affective and psychotic symptoms can be difficult. In practice, concerted effort was employed to resist the temptation to answer this question by substituting another i.e. "do I think this person has schizophrenia or schizoaffective disorder?" which negates the purpose of using OPCRIT in systematically producing diagnoses based solely on the data, and not on prior assumptions about the nature of the diagnosis. In this study question 52 is of little relevance because the novel symptom groups derived are based upon 62 items which are of equal importance, thus reducing the impact of any error in question 52 and removing its pivotal role.

6. The meaning of "missing" when coding can vary, but this cannot be reflected in OPCRIT. For example, it is impossible to record that no effort was made to elicit this item, or that this was attempted but the information was unavailable, or the interviewer could not reach a decision on how to code the item, given the information available.

One practical criticism of the OPCRIT software is the fussy nature of the editing options and the ease with which files are corrupted, making input errors difficult to rectify.

The authors of OPCRIT out lined some "pit-falls for the unwary" which included the massive shifts in diagnosis which occur following small or subtle changes in rating, and the impact this could have on identification of cases and non-cases in biological research. They caution against reliance on single accounts of cross-sectional psychopathology, or using information from lay interviewers. Their view is that consensus diagnostic assessments are more robust, and that major and more severe psychiatric syndromes are likely to be diagnosed more accurately than less severe or clearly defined conditions (Farmer *et al.* 1992).

OPCRIT aside, the retrospective case note approach in general is flawed. Data which is not gathered prospectively using strict and explicit criteria for coding will always be prone to errors of interpretation. Also, only prospectively gathered data is reliable in untangling the relationship between findings and putative aetiological factors. In this current study the bias of any one particular clinician towards a particular diagnosis would presumably been diluted by the input of other clinicians within a single case. Since the average time from illness onset was 14 years, most case notes were substantial, in some cases running to five volumes. Thus one would hope that although one particular clinician might fail, for example, to record affective symptoms, this would be balanced by the input of other clinicians.

Family history data collection

Family history information was obtained from the case notes for all subjects and from affected individuals and key informants in some cases. This variability occurred when the study population was approached to participate in a genetic study of psychosis. Those who agreed to participate provided an account of the health of relatives insofar as they knew. This approximates to the family history method of information gathering, but no research instrument was used (Faraone & Tsuang 1995). Instead the proband or key informant was interviewed using standard clinical genetic methods. However, the interview for gathering family information was often unsatisfactory. There were a variety of reasons for this, from practical reasons such as lack of time in a busy clinic to less tangible such as reluctance to disclose information about third parties. Often the proband, while agreeing to discuss family history, gave the impression of being intruded upon, or at least reluctant, and it felt unethical in such circumstances to proceed with detailed questioning. Such interviews were therefore cursory. Overall people appeared more at ease with providing a blood

sample than details of their family history. Others were happy to discuss these details but even so information was of variable reliability. Occasionally, people were identified within the study group as being related who were unknown to each other as affected relatives, highlighting the inherent weakness in the family history approach.

Family history information was coded in two ways. Firstly, OPCRIT items 13 and 14 were coded on all available information ("family history of schizophrenia" and "family history of any other psychiatric disorder severe enough to warrant psychiatric referral"). These items include both first and second degree relatives. Secondly, a more detailed coding was undertaken as described in table M2 below.

Table M2: Family history data coding

Family History Variable	Definition	Degree of relatedness to proband
Psychosis	Any affective or non-affective psychosis (but including bipolar disorder without psychosis)	1st, 2nd, 3rd or 4th degree (recorded separately)
Neurosis	Anxiety, depression, panic disorder severe enough to warrant treatment	1st, 2nd, 3rd or 4th degree (recorded separately)
Other psychiatric disorder	OCD, developmental disorders (autism spectrum disorders, ADHD, dyslexia, dyscalculia, developmental co-ordination disorder)	1st, 2nd, 3rd or 4th degree (recorded separately)
Substance misuse	Substance misuse severe enough to warrant treatment or causing major functional consequences	1st, 2nd, 3rd or 4th degree (recorded separately)
Learning Disability	Mild, moderate or severe	1st, 2nd, 3rd or 4th degree (recorded separately)
***Number of affected relatives**	Sum of all known relatives affected with psychiatric disorder	1st, 2nd, 3rd or 4th degree

* This crude measure does not take into account the size of the pedigree, or what proportion of those in the pedigree passed though the period of greatest risk of psychotic disorders.

Within the study population there were inevitably groups of individuals with psychosis who were related. Also, some further information was recorded about the DSM-III-R diagnosis of affected relatives who were outwith the epidemiological sample, but who had agreed to participate in the genetics study and underwent diagnosis by OPCRIT.

Other variables (non-OPCRIT)

Other items of information were coded from information in the case notes. Definitions of these items and coding details are described in table M3.

Table M3: definitions of non-OPCRIT variables (excluding Family History)

Variable	Definition
Deliberate self-harm	Scored positive if there had been an episode of self harming behaviour at any time. Included self-harm with apparent suicidal intent as well as non-lethal activities such as repeated superficial wrist cutting.
Detained	Ever detained under the provisions of the Mental Health (Scotland) Act 1984, or equivalent
ECT ever received	ECT ever administered whether or not course was completed
Fecundity	Number of live births
Fertility	For women, ever had a live birth; for men, ever fathered a child
Forensic	Ever charged with an offence, or had police involvement
Learning disability	Evidence of known or strongly suspected global learning disability
Organic confounder	Evidence of neurological disorder or insult which may account for some of the symptoms, but could not be considered to be wholly responsible
Substance misuse	Use of alcohol, drugs or volatile substances to the detriment of mental and/or physical health

Analysis

Data were held on an Access database with statistical analysis using SPSS version 11.5 except where otherwise specified (www.SPSS.com). Details of between-groups analyses are provided in the relevant results section.

Data reduction analyses

Two data reduction analyses were carried out: a factor analysis and a latent class analysis. In both cases 62 OPCRIT items representing psychiatric symptoms were included and items measuring substance use were excluded. Of the 62 items included 35 are dichotomous and 27 are interval. The latter are a mixture of items which could be considered to be scaled, but not ratio.

Principal Components Analysis: selection of variables

The structure of the OCRIT items presents two problems for factor analysis. Firstly, principal components analysis assumes normal distribution of the variables under test, and all interval variables are treated as ratio. Secondly, because of the normal distribution assumption, dichotomous variables should not be used, although there are specific software packages designed for this contingency eg LISCOMP. However, factor analysis appears robust to violation of this assumption (Hair *et al.* 1998; Tabachnick & Fidell 1996). In this study there was the opportunity to make a direct comparison with a latent class analysis of the same data to test this assertion. Regarding the interval items, the principal components analysis was run under two conditions. Firstly, the interval items were entered unaltered and secondly these items were dichotomised, to ascertain the effect of dichotomisation upon the result. This introduces a possible error since judgement must be made regarding where to delineate the dichotomy. Clinical judgement was employed. Thus the variable dysphoria, which scores 1 for one week, 2 for two weeks and 3 for a month was scored positively if scoring 2 or above. In contrast, elevated mood was scored positive if present for one week, since hypomania of one week duration is more likely to be of clinical significance than dysphoria for the same time period. The analysis was run using this "conservative" dichotomisation, and also dichotomising without introducing judgement ie scoring positively if a symptom was present at all. A list of the conservative and non-conservative dichotomisation is provided in Table M4. It has been suggested that ordinal scales with at least three points can be safely included in a principal components analysis since the correlations between the variables can tolerate deviations from normality (Streiner 1994).

Table M4 Scoring of interval OPCRIT items under conservative and non- conservative restraints.

OPCRIT Item	OPCRIT score	Dichotomised score (conservative)	Dichotomised score (non-conservative)
Dysphoria	0-3	2-3 score positive	1-3 score positive
Loss of pleasure	0-3	2-3 score positive	1-3 score positive
Poor concentration	0-3	2-3 score positive	1-3 score positive
Early morning wakening	0-3	2-3 score positive	1-3 score positive
Excessive sleep	0-3	2-3 score positive	1-3 score positive
Increased appetite	0-3	2-3 score positive	1-3 score positive
Elevated mood	0-2	1-2 score positive	1-2 score positive
Thoughts racing	0-2	1-2 score positive	1-2 score positive
Irritable mood	1-2	1-2 score positive	1-2 score positive
Pressured speech	0-2	1-2 score positive	1-2 score positive
Excessive self reproach	0-3	1-3 score positive	1-3 score positive
Suicidal ideation	0-3	1-3 score positive	1-3 score positive
Initial insomnia	0-3	1-3 score positive	1-3 score positive
Early morning wakening	0-3	1-3 score positive	1-3 score positive
Poor appetite	0-3	1-3 score positive	1-3 score positive
Weight loss	0-3	1-3 score positive	1-3 score positive
Weight gain	0-3	1-3 score positive	1-3 score positive
Increased sociability	0-2	1-2 score positive	1-2 score positive
Increased self esteem	0-2	1-2 score positive	1-2 score positive
Grandiose delusions	0-2	1-2 score positive	1-2 score positive
Excessive activity	0-2	1-2 score positive	1-2 score positive
Reckless activity	0-2	1-2 score positive	1-2 score positive
Distractibility	0-2	1-2 score positive	1-2 score positive
Reduced need for sleep	0-2	1-2 score positive	1-2 score positive
Agitated activity	0-3	1-3 score positive	1-3 score positive
Slowed activity	0-3	1-3 score positive	1-3 score positive
Loss of energy	0-3	1-2 score positive	1-2 score positive

(One interval item "relationship psychotic/affective" was not dichotomised for the factor analysis)

OPCRIT permits the coding of missing information. For the purposes of the LCA and principal components analysis the missing variables were recoded as absent. Thus the input dataset can be regarded overall as being coded conservatively, with a symptom definitely present before scoring positively, but lack of a symptom does not mean it was definitely not present.

Principal Components Analysis: retention of items and factors

The 62 items relating to symptoms were subjected to principal components analysis. The correlation matrix was inspected to ensure that no variables were nearly perfectly correlated. Some items in OPCRIT may be considered to be paraphrases of each other – some redundancy might be expected in a system which produces diagnoses under many different classifications. In practice this did not appear to be the case, but it was necessary to confirm this since items which are essentially the same will load a factor ("bloated specifics"). It was seen that subtle differences in definition of similar items were enough to preclude near-perfect correlation. The frequencies of the items included in the analysis are shown in appendix 2. (The correlation matrix is not shown, being a 62 by 62 table). Inspection revealed no problems amongst items which were closely related, therefore all 62 items were included. Correlation between similar items was not perfect because the instructions for each item in the glossary were followed pedantically thus even very similar items had different responses. Unlike other authors (Cardno *et al.* 1996) symptoms which scored positive less than 10% of the time have been retained. Also, reduction of the items to groups of similar symptoms has not been followed. Since the purpose of the factor analysis is to identify items that tend to occur together such grouping prejudges the outcome, and excluding rare items risks losing valuable information.

In deciding how many factors to retain, the scree test was used. This indicates where the smooth decrease of the eigenvalues appears to level off, demarcating factors which account for little of the variance. This was selected instead of the Kaiser criterion (eigenvalues >1) which is likely to produce too many factors. The axes for rotation were orthogonal because this exploratory analysis makes no assumptions about the underlying structure, in keeping with an empirical, atheoretical approach and varimax rotation was employed.

Latent Class Analysis

Since LCA is being used here to construct a new diagnostic system, it will be described in these terms, as expounded by Young (1983). Latent class analysis differs from factor analysis in that it identifies groups of people, in contrast to groups of symptoms. In LCA, variables are nominal. Essentially, relationships amongst observed variables are explained by unobserved (latent) variables. Patients are classified on several observable variables, such as the presence or absence of symptoms. A cross classification table is produced,

representing all possible combinations of categories. Then, in each cell the number of patients with that joint classification is entered. Thus if there is only chance association among the symptoms the cell entries can be predicted, from the model of independence. If the model of independence does not agree with the data, then the clinical features are related to each other, presumably because they are all related to the same latent diagnostic features. The model assumes that the categories are mutually exclusive and exhaustive (Young 1983).

As used in this study, the latent class analysis represents the most likely syndrome classification based on the symptoms with no *a priori* decision rules. Symptom selection is important since the classification is based exclusively on this. Including a symptom makes a hypothesis that it and the other features selected are jointly indicative of a diagnostic category. The adequacy of the single model can be compared by stepwise addition of latent variables to see how many latent categories are needed to describe a dataset. Further studies are then required to validate the latent classes based on based on external criteria.

In the Hamilton study the LCA was performed using the LEM programme (Vermunt 1997), a command language programme. The dataset used was the same as that for the principal components analysis. Model selection was determined by minimising the BIC statistic. This analysis was undertaken by Dr Patrick Miller of Edinburgh University.

Comparison between Latent Class analysis and Principal Components Analysis

Two methods were used. Firstly, correlations were run between the component loadings and the conditional probabilities (which are analogous to component loadings). Secondly, the mean values of the principal component scores for the latent classes were compared using one way analyses of variance followed by the Scheffé test.

Association of latent classes with relevant clinical data

The latent classes may have internal construct validity, which demonstrates that a set of diagnostic criteria identifies a valid syndrome. However this alone does not indicate that the latent classes are clinically meaningful. To show this it is necessary to examine the correlations between the latent classes and external variables which could be considered to validate the classes. Young (1983) describes two types of criterion validity. In the first, "concurrent validity", the criterion is obtained at the same time as the classes being validated. In contrast, in "predictive validity" criteria are identified after the classes are established. Criterion validity assumes that the criterion indicates perfectly the presence or absence of the disorder. In psychiatry there is no perfect relationship between any criterion and the latent classes, and any external variables will be related to particular latent classes to a limited extent. Therefore the validity of the criterion may be as uncertain as the validity of the latent class.

In this situation Young proposes construct validity where a set of diagnostic criteria (latent classes) is validated by correlating the diagnoses it produces with multiple empirical variables. No single variable is an absolute indicator, but each, according to theory is related to the disorder. As Young describes it:

> The disorder itself is not actually observed but is a *construct* defined by the network of interrelated variables related to it. Validity is established by demonstrating that the diagnostic variable correlates as expected with *multiple* validating variables, thus taking its proper place in the network which defines the construct....

In general, for the latent classes identified, the symptoms which comprised the dataset are jointly indicative of the unobserved (latent) disorder. However, if external construct validity is also demonstrated, both the latent classes and the external validators are jointly indicative of the unobserved disorder. Thus the argument for the validity of unobserved (latent) disorder is strengthened.

In the Hamilton study the latent classes identified were validated using several measures known to be of relevance in schizophrenia. This consisted of ten items from OPCRIT for illness characteristics and outcome (Appendix 1), and additional items detailed in table M3 above.

Key outcome measures were compared between latent classes using χ^2 tests for categorical variables (with Fisher's Exact Test where necessary) and Kruskal-Wallis tests for continuous data. Multivariate analysis was performed with the assistance of Dr David Young of Yorkhill Hospital using MINITAB Version 13 (www.minitab.com). A significance level of 5% used throughout except where otherwise specified.

Aims

The overarching aim is to identify, from first principles, the characteristics of psychosis in a population based sample, using psychopathological signs and symptoms to identify underlying classes and dimensions which are then validated by association with demographic and clinical variables known to be of relevance in schizophrenia.

A subsidiary aim is to describe the features of the identified population with regard to demographic and diagnostic variables in addition to features indicative of social functioning.

These aims will be met by the following means.

1. Identify all people who had suffered a psychotic disorder which resulted in contact with secondary health care services within the Hamilton District from 1988 - 1999.

2. Describe the demographic characteristics and psychosocial morbidity in this identified population of people with psychosis.

3. Describe the distribution of the population with respect to ICD-10 and DSM-III-R diagnoses.

4. Describe the distribution of the population with respect to the following variables previously identified as being relevant in schizophrenia: gender; age of onset; fertility; family history; season of birth; premorbid characteristics such as social isolation and premorbid personality disorder; illness course and treatment; first rank symptoms.

5. Describe the distribution of the treated prevalence sample on other variables of interest: forensic history, detention under the Mental Health Act and use of Electro Convulsive Therapy (ECT).

6. Identify symptom patterns within this population by two different data reduction methods namely principal components analysis and latent class analysis.

7. Compare and contrast the results of these two methods.

8. "Validate" the dimensions and classes identified using the previously described variables of relevance.

9. Compare the dimensions and classes with DSM-III-R diagnoses.

Results

Overview of results

The results are arranged following a natural sequence of information evolution. Firstly the basic data describing the study subjects, co-morbidities and diagnoses are reported. Then the distribution of various characteristics of interest are listed, often comparing men with women. These characteristics are: age of onset; winter birth; fertility; premorbid characteristics, forensic history and employment; illness course and treatment. Further small tables display finer details of some of these variables. For some analyses results for the latent classes are shown, which means these are presented before the latent classes are derived and described. Although slightly out of sequence, this facilitates comparison with other variables.

This is followed by a descriptive section on family history of psychosis. The family history data is aggregated and described in three different ways. Thereafter data reduction methods are presented. A principal components analysis is followed by a latent class analysis, and the two outcomes are compared. The dimensions and classes thereby identified are explored with respect to variables of interest, to determine to what extent the dimensions and classes can be "validated".

Demographics

In total, 387 people met inclusion criteria, 194 males and 193 females. Due to the prolonged period of assessment a virtual age was calculated, i.e. age at OPCRIT assessment. The mean age was 42.8 (SD 12.6, range 17 - 69) of whom 50.1% were male. Of these, 258 were identified in the 1993 sample (mean age 43.3, SD 12.5, range 18 – 69, 46.5% male) and 129 identified in the 1996 sample (mean age 41.8, SD 12.7, range 17 – 66, 57.4% male). The mean age at assessment was 41.1 years (SD 12.7) and 44.6 years (SD 12.2) for men and women respectively, a significant difference ($t= -2.73$, $p=0.007$). The estimated length of illness as calculated by the difference between age at assessment and age at onset was 14.8 years for males and 14.9 years for females.

The stability of the population is illustrated by place of birth. Information was not available for 52 cases but of the remainder 266 (69%) were born in Lanarkshire, 54 (14%)

elsewhere in Scotland, 14 (3.6%) in England, Wales or Ireland, and one in mainland Europe. All but three were of Caucasian origin.

Co-morbidity

Substance misuse

Substance misuse is common is people who develop a psychotic illness (Duke *et al.* 2001), therefore those who misused substances to the detriment of their mental or physical health were included in the study. People were excluded if their psychosis was due to substance intoxication or withdrawal. However, those with multiple episodes of drug induced psychoses, or prolonged episodes thought to have been precipitated by substances were included. It is debatable to what extent substance misuse was causative in an individual's psychosis, but the interaction between substance misuse and other factors in precipitating or exacerbating each individual's psychotic illness is complex. For example, in our original needs assessment study, a relatively common reason for stopping antipsychotic medication intermittently was to take alcohol (unpublished data). Within the 387 subjects 61 were known to misuse alcohol, drugs, or both and a further 15 were probably misusing these substances. This gives 19.6% of subjects probably or definitely using substances to the detriment of their health.

Learning Disability

A pragmatic approach was adopted when including people with mild learning disability. If their mental health care was delivered by general psychiatric services during the study period they were included if they otherwise met inclusion criteria. People resident in the learning disability hospital (which is situated in the study's catchment area) were not included. This was due to the greater severity of the leaning disability in this population, and also because originally many would have been admitted from outside the geographical catchment area of the study. However, the chances of an individual being served by general psychiatric services was greater at the beginning of the inclusion period, and lessened towards the end when specialised services for people with learning disabilities improved. Mild learning disability was present in 14 with a further 9 possible cases giving a total of 5.9% having a definite or likely comorbid learning disability.

Organic Confounder

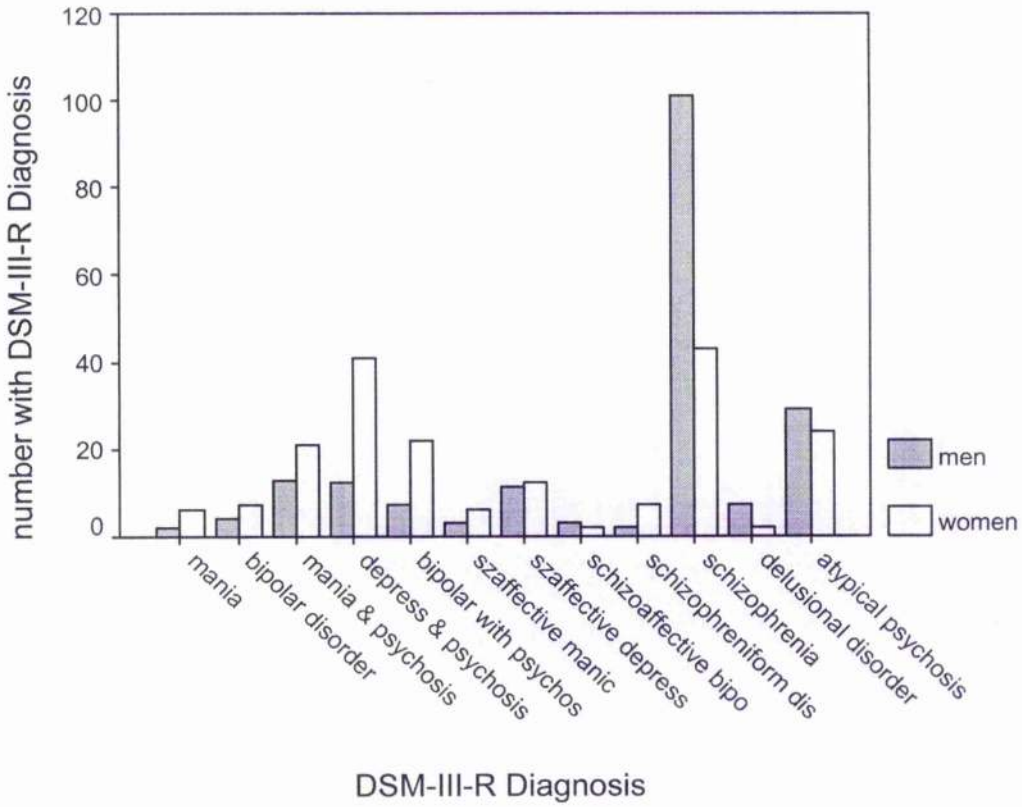
People were excluded from the study if a medical condition was thought to be the sole cause of their psychosis e.g. a subject with psychosis secondary to Levo Dopa medication was excluded. However, subjects were included if their psychosis was enduring but associated with epilepsy. In total 20 (5.2 %) had a medical condition which may have precipitated or exacerbated their psychosis, but was not thought to be solely responsible, so these subjects were included. The various organic confounders in this group were: eight with history of head injury; two with history of head injury and epilepsy; one with a perinatal CVA; one with Grave's disease; one with microcephaly; one subject who developed multiple sclerosis apparently some time after developing psychosis; one with severe thrombocytopaenia and the remaining five with combined substance misuse and epilepsy or head injury.

Diagnoses

For ICD 10 the most frequent diagnosis was "other non organic psychosis", at 29% of subjects, with the next most frequent being undifferentiated schizophrenia at 19% and paranoid schizophrenia at 18.6%. Due to the high number of "other non organic psychosis" generated by OPCRIT for ICD 10, DSM-III-R was used throughout the analyses.

The DSM-III-R diagnoses are illustrated in Figure R1 below .

Figure R1: DSM-III-R diagnoses by gender (n=387)



Characteristics of the Illness

Age at onset

A cumulative age of onset curve is shown in Figure R2a, with a non-cumulative curve displayed in figure R2b . The mean age of onset differed for men and women: 26.8 (SD 9.4) and 30.1 (SD 11.6) respectively (t=-3.076, p=0.002). The age at onset is compared for the latent classes in figure R3a (for explanation of latent classes see section "Latent class analysis later in this chapter). For comparison, the age at onset graphs for affective psychoses and non-affective psychoses are displayed in figure R3b and R3c.

Figure R2a: cumulative age of onset

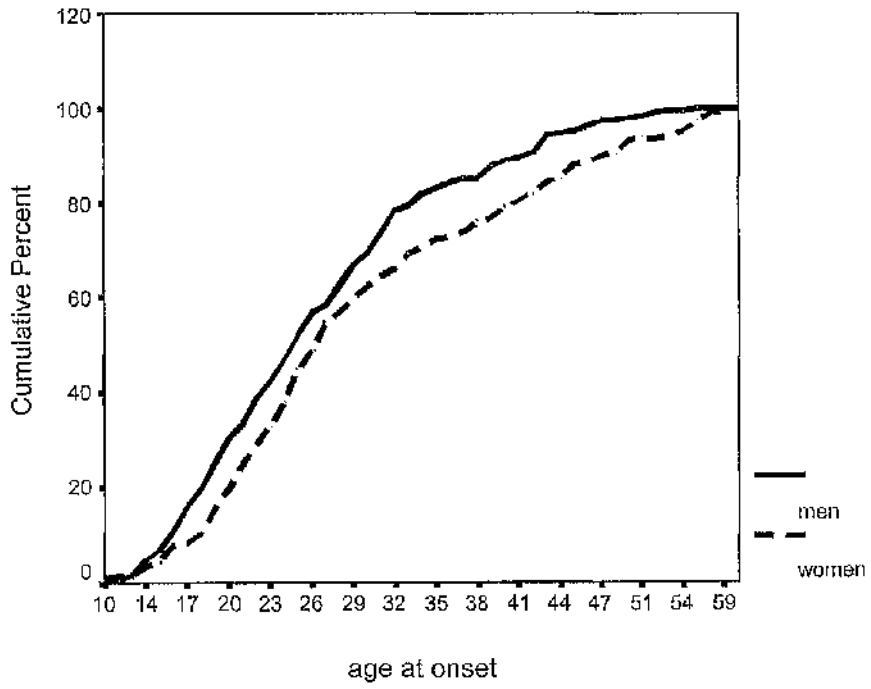


Figure R2b: age at onset by gender

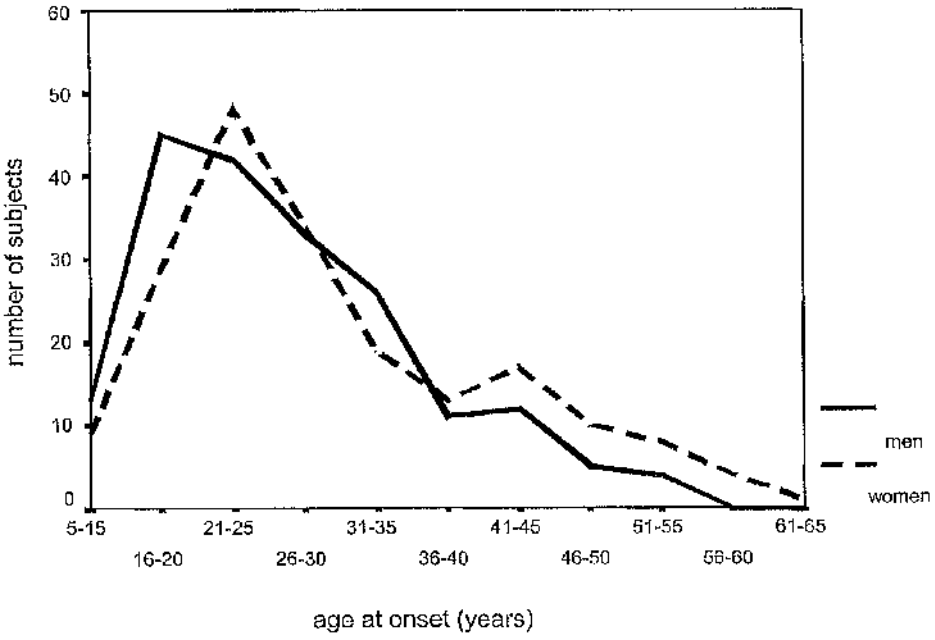


Figure R3a: Age at onset by latent class

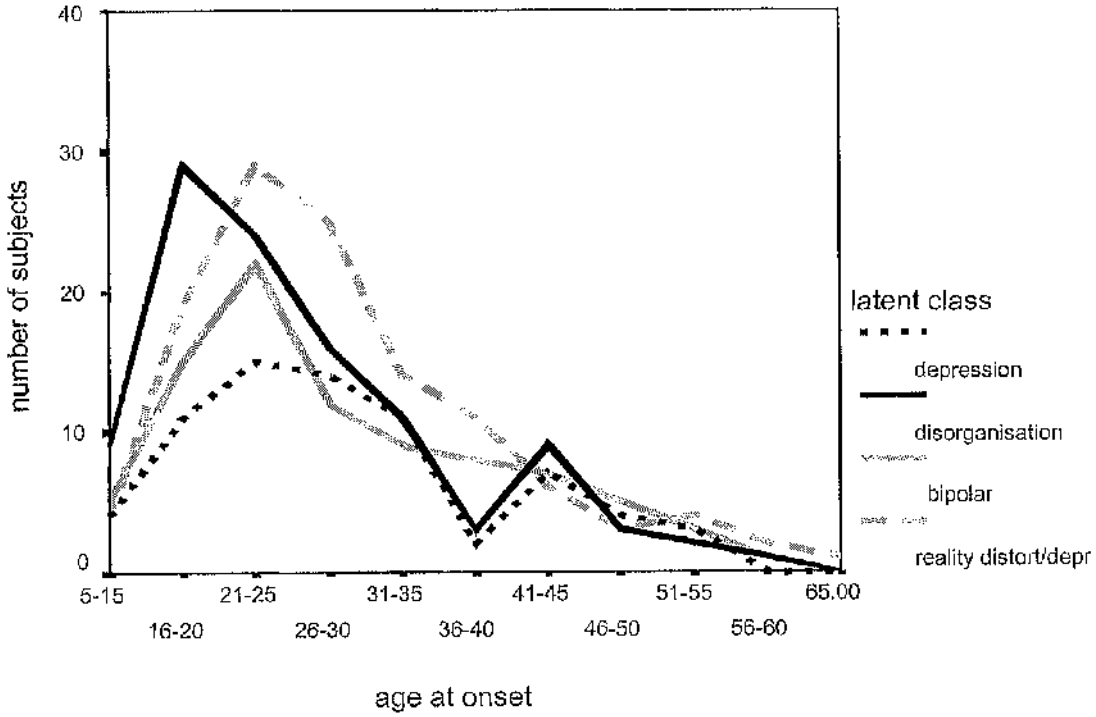
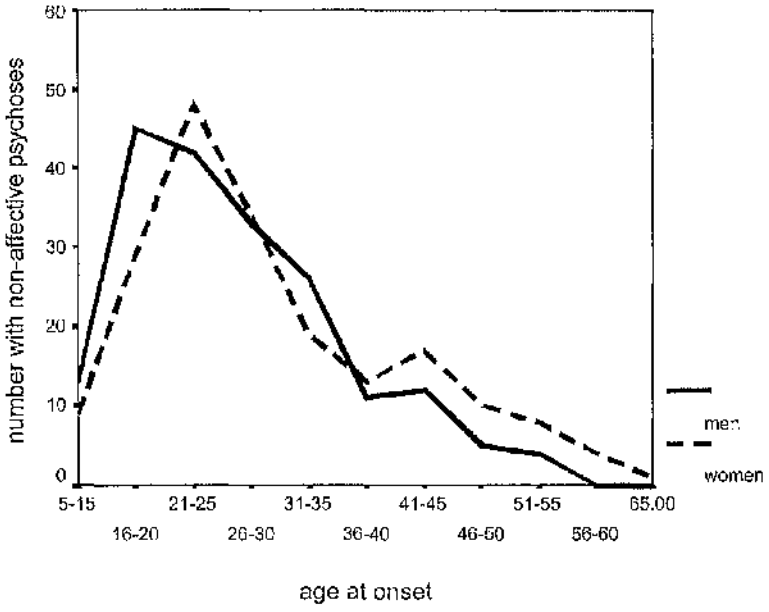
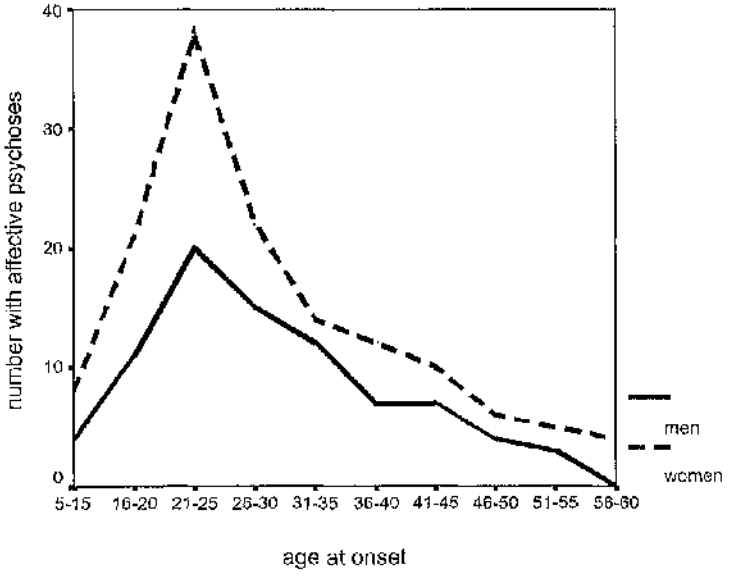


Figure R3b: age at onset by gender for non-affective psychoses*



*Non- affective psychoses are defined as schizophrenia, delusional disorder, schizophreniform disorder and atypical psychoses

Figure R3c: age at onset by gender for affective psychoses*



*Affective psychoses include depression with psychosis, hypomania, mania, mania with psychosis, bipolar with psychosis, schizoaffective mania and schizoaffective depression

Examination of age at onset and family history

The differential age at onset by gender is displayed in table R1 with respect to family history of psychiatric disorder. (Latent classes are described on page 85, and it should be noted that "schizophrenia" includes DSM-III-R schizophrenia, delusional disorder and schizophreniform disorder.) It can be seen that in accordance with the literature men have an earlier age at onset for schizophrenia, but this is statistically significant only in cases with a negative family history of psychiatric disorder. This is also true of all psychoses, and holds true for the disorganisation class but is not seen for either the depression or reality distortion/depression class

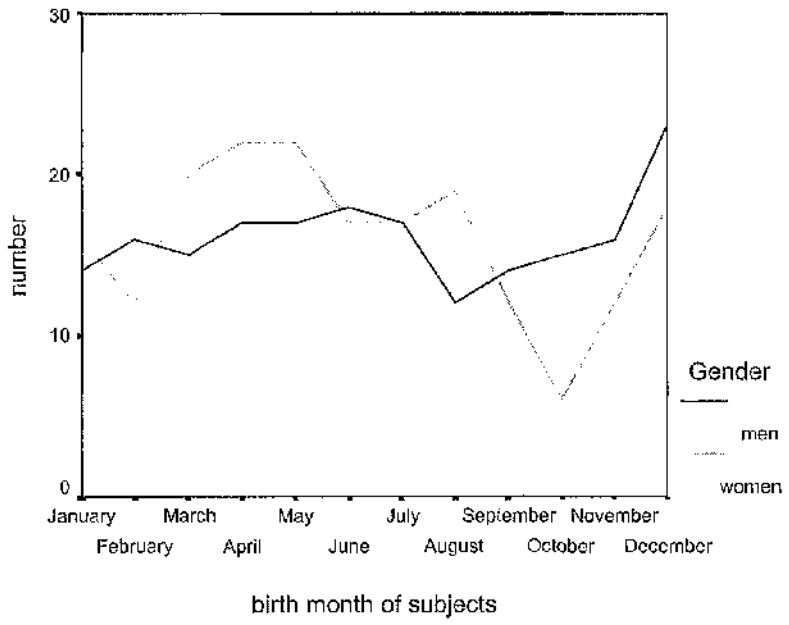
Table R0: Age at onset by family history of psychiatric disorder

Family history in 1st or 2nd degree relative		Age at onset Men	Age at onset Women	Difference in age at onset (years)	Statistical test
		Mean (median, standard error)	Mean (median, standard error)		Mann-Whitney U test
All subjects	Positive (n=129)	26.7 (24, 1.13)	28.8 (26, 1.57)	2.1	Z=0.781 p=0.435
	Negative (n=223)	27.1 (26, 0.91)	31.2 (27.5, 1.06)	4.1	Z=2.606 p=0.009
Schizophrenia	Positive (n=42)	22.2 (20,1.29)	26.1 (26, 3.03)	3.9	Z=1.19 p=0.246
	Negative (n=89)	25.3 (24, 1.05)	31.3 (27, 2.12)	6.0	Z=2.41 P=0.016
Depression class	Positive (n=28)	32.2 (32.5, 3.07)	29.1 (26, 3.41)	-3.1	Z=0.883 p=0.397
	Negative (n=35)	28.2 (29.5, 2.8)	30.6 (28, 2.0)	2.37	Z=0.383 p=0.719
Disorganisation class	Positive (n=24)	20.9 (20, 1.25)	22.5, (22, 3.27)	1.6	Z=0.368 p=0.721
	Negative (n=74)	25.0 (24, 1.29)	32.7 (27, 2.28)	7.7	Z=2.72 p= 0.007
Bipolar class	Positive (n=34)	31.1 (28, 2.89)	31.2 (31, 2.8)	0.1	Z=0.07 p=0.944
	Negative (n=48)	26.33 (23, 2.46)	30.9 (28.5, 1.89)	4.57	Z=1.79 p=0.073
Reality distortion/ depression	Positive (n=43)	26.0 (23, 1.64)	28.1 (25, 2.76)	2.1	Z=0.185, p=0.853
	Negative (n=66)	29.8 (28.5, 1.69)	30.6 (27, 2.25)	0.8	Z=0.282 p=0.78

Season of birth

The distribution of birth month is illustrated in figure R4

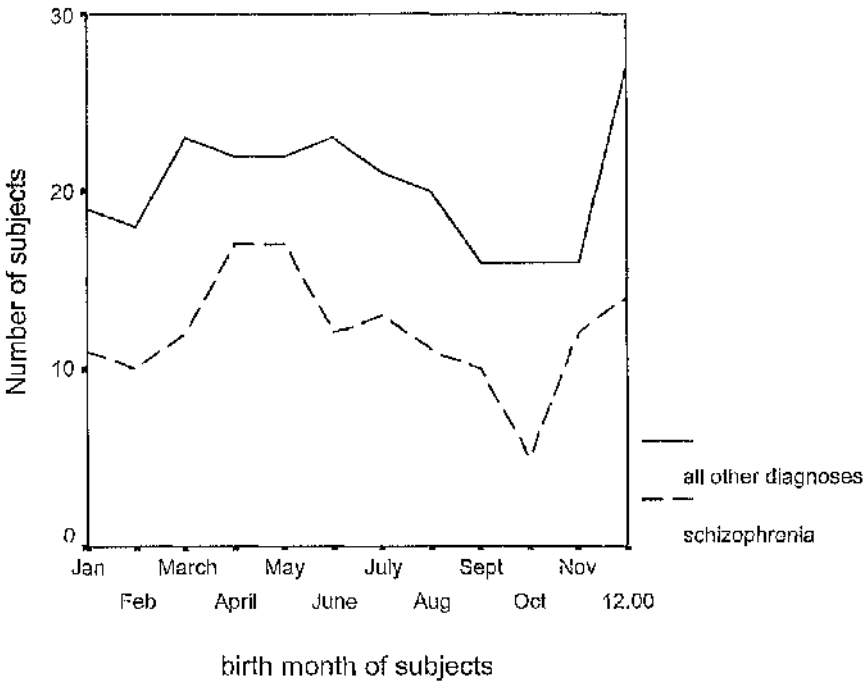
Figure R4: Distribution of month of birth by gender



Winter birth and schizophrenia

No general population information was available to determine if schizophrenia was more common in the winter months. Comparing the birth month of those with schizophrenia with the rest of the study population shows that the pattern for schizophrenia reflects that of the study population as a whole (figure R5).

Figure R5: Distribution of schizophrenia by month of birth



Summer birth and deficit syndrome

Summer birth was defined as March to August. A restricted affect was used as a proxy for the deficit syndrome. Other authors using restricted affect plus lack of dysphoria as a proxy have found an excess of summer births in people with schizophrenia with deficit syndrome thus defined (Kirkpatrick *et al.* 2002). In this study such a definition resulted in very small numbers, but having a broader proxy for the deficit syndrome highlighted some interesting trends as seen in table R1. While the findings by other authors may suggest relaxing the stringency of the p value because of prior evidence for a hypothesis that the defict syndrome is more common in people with schizophrenia who are summer born, the values for two sided p values are reported, in keeping with analyses elsewhere in the thesis.

Table R1: Season of birth* by restricted affect (as proxy for deficit syndrome)

	Season of birth	N (%) with restricted affect	Statistical test
All subjects			
	winter	56 (40%)	$\chi^2(1)=2.40$
	summer	84 (60%)	p=0.137
Schizophrenia			
	winter	24 (33.3%)	$\chi^2(1)=5.93$
	summer	48 (66.7%)	p= 0.018
Disorganisation class			
	winter	18 (37.5%)	$\chi^2(1)=2.98$
	summer	30 (62.5%)	p=0.119

*Winter birth September – February; summer birth March-August

For those with schizophrenia, 48 (66.7%) of those born in summer had a restricted affect compared with 24 (33.3%) of those born outwith the summer ($\chi^2(1)=5.93$, p=0.018). For the population as a whole there was no significant difference in season of birth and restricted affect, but there was a trend towards summer birth being more likely in those with a restricted affect. None of the latent classes had a statistically significant association between restricted affect and season of birth. For latent class two, of those born within summer, 30 (62.5%) had a restricted affect, compared with18 (37.5%) of those born in winter ($\chi^2(1)=2.98$, p=0.084 two sided).

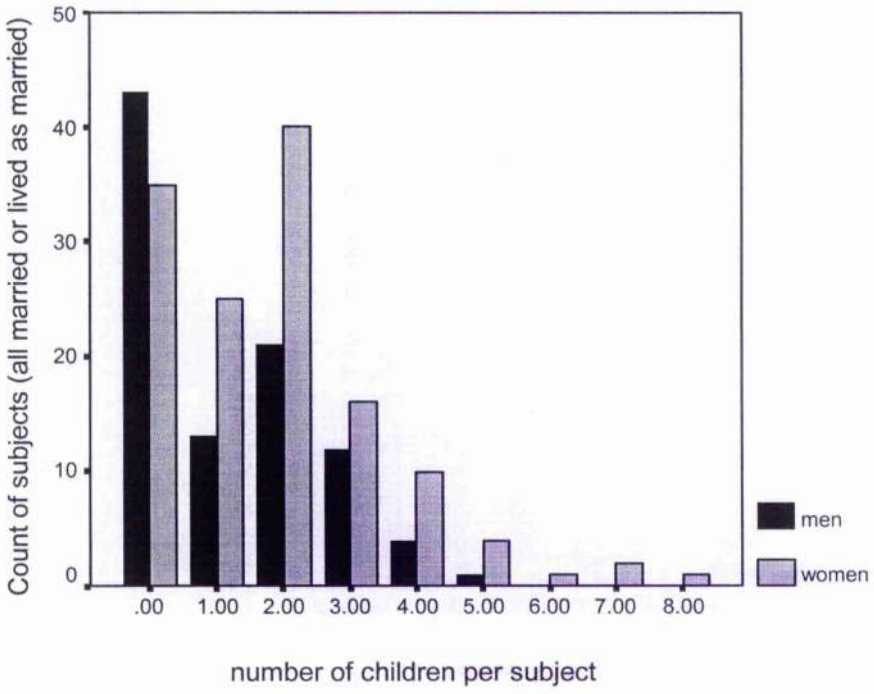
Fertility

The sexes differ sharply with respect to fertility. Of men, only 56 (28.9%) were fertile, compared to 112 (58%) of women ($\chi^2(1)=33.5$, p<0.001). Likewise, of those who marry or have lived as married: only 94 (48%) were men, compared to 134 (69%) of women ($\chi^2(1)=17.6$, p<0.001).

Of subjects who were single, five men and 13 women were fertile. Even when married or lived as married the sexes differed with respect to fertility. Thus 43 (45.7%) of such men were infertile, compared with 35 (26.1%) of women ($\chi^2(1)=9.45$, p=0.003). For those who were fertile, (56 men and 112 women) the mean number of children was not significantly

different: 2.12, median 2.0, range 0 – 5 for men and 2.38, median 2.0, range 1 – 8 for women (Z= -0.43, p=0.665, Mann-Whitney U test).

Figure R6: Fecundity of subjects who were married or lived as married



Other Illness Characteristics

Tables R2a and R2b display the outcomes for variables grouped together as premorbid characteristics, forensic history and employment, and illness course and treatment. Values for men and women are compared. Table R2c lists employment and table R2d displays the occurrences of deliberate self harm. Marital status is shown in table R2e and forensic history shown in R2f.

Thus table R2a shows that men are more compromised in terms of premorbid functioning, with table R2b revealing that men are more likely to have an insidious onset, and more likely to have the poorest outcome. There is no significant difference between the sexes for deliberate self harm, receiving electroconvulsive therapy or detention under the Mental Health Act.

Table R2a: Premorbid characteristics, forensic history, and employment

	Men (n=194) (%)	Women (n=193) (%)	Statistical Tests
poor premorbid social adjustment (n=371)	29 16%	8 4%	$\chi^2(1)=13.9$ P<0.001
pre-morbid personality disorder (n=371)	19 10.3%	6 3.2%	$\chi^2(1)=7.5$ P=0.006
Poor work record prior to illness (n=365)	40 22.2%	10 5.4%	$\chi^2(1)=22.6$ P<0.001
Unemployed at onset (n=365)	73 41%	36 19.3%	$\chi^2(1)=20.6$ P<0.001
Unemployed at OPCRIT completion (paid or unpaid occupation)	126 64.9%	60 31.1%	$\chi^2(1)=109.9$ P<0.001

Table R2b: Illness course and treatment

		Men	Women	Statistical Test
		n	n	
		%	%	
Onset mode	within 1 week	13	32	$\chi^2(3)=15.6$
(n=249)		10.6%	25.4%	P<0.001
	within 1 month	25	32	
		20.3%	25.4%	
	gradual up to six months	30	31	
		24.4%	24.6%	
	insidious > 6 months	55	31	
		44.7%	24.6%	
course of disorder	single episode	9	14	$\chi^2(3)=19.32$
(n=366)		4.9%	7.7%	P<0.001
	multiple episodes (good recovery in between)	47	77	
		25.5%	42.3%	
	multiple episodes (partial recovery in between)	58	55	
		31.5%	30.2%	
	continuous chronic illness	70	36	
		38.0%	19.8%	
History of deliberate self harm	no	112	114	$\chi^2(1)=0.071$
(n=387)		57.7%	59.1%	NS
	yes	82	79	
		42.3%	40.9%	
ECT ever received	no	146	127	$\chi^2(1)=4.16$
(n=387)		75.3%	65.8%	P=0.041
	yes	48	66	
		24.7%	34.2%	
Ever detained under Mental Health Act	no	89	95	
(n=387)		45.9%	49.2%	$\chi^2(1)=0.434$
	yes	105	98	NS
		54.1%	50.8%	

Table R2c: details of employment at time of OPCRiT completion

	Men	Women
Unemployed	126 (64.9%)	60 (31.1%)
Full-time homemaker	1 (0.5%)	81 (42%)
College/training	7 (3.6%)	6 (3.1%)
Working	23 (11.9%)	18 (9.3%)
Voluntary work	1 (0.5%)	1 (0.5%)
Sheltered work	1 (0.5%)	2 (1%)
Retired	4 (2%)	5 (2.6%)
Sick leave	0	1 (0.5%)

(Data missing for 49 cases)

Table R2d: details of history of Deliberate Self Harm (DSH)

	Men	Women
No history of DSH	112 (57.7%)	113 (58.5%)
Overdose	20 (10.3%)	25 (13%)
Physical	17 (8.8%)	14 (7.3%)
Combination	13 (6.7%)	12 (6.2%)
Violent	16 (8.2%)	7 (3.6%)
Unclear but definite DSH	16 (8.3%)	21 (10.9%)

Key: "overdose" involves taking a large non-therapeutic dose of medication or street drugs; "physical" includes cutting wrists, swallowing hazardous substance eg bleach or attempted drowning; "combination" includes both physical and overdose episodes and "violent" includes attempted hanging or jumping in front of train.

Table R2e: details of marital status

	Men	Women
Single	111 (57.2%)	55(28.5%)
Married or lived as married	40 (20.6%)	91(47.2%)
Divorced	37 (19.1%)	34 (17.6%)
Widowed	1 (0.5%)	9 (4.7%)

Table R2f: details of forensic history

	Men	Women
None known	102 (52.6%)	165 (85.5%)
Police involvement	29 (14.9%)	14 (7.3%)
charged	63 (32.5%)	11 (5.7%)

DSM-III-R diagnoses and "external validators"

The distribution of the various "external validators" on the DSM-III-R diagnoses is summarized in tables R4a-c, which examine in turn: premorbid characteristics; illness and treatment characteristics; use of mental health act, forensic history and substance misuse. The association between DSM-III-R diagnoses and family history are examined in the next section (family history). Since there are 14 different categories which would inevitably result in small cell sizes for comparisons, these have been condensed as shown in table R3 (and hereafter all DSM-III-R diagnoses refer to these condensed categories unless otherwise specified).

Table R3: Condensation of DSM-III-R categories

Short DSM-III-R category	Original DSM-III-R categories
Depression	Major depression and depression with psychosis
Bipolar	Hypomania, mania, bipolar disorder, mania with psychosis, and bipolar with psychosis
Schizoaffective	Schizoaffective manic, schizoaffective depressed and schizoaffective bipolar
Schizophrenia	Schizophrenia, delusional disorder and schizophreniform disorder
Atypical psychosis	Atypical psychosis

Examination of table R4a shows that the sexes are significantly different with respect to DSM-III-R diagnoses. Women are over-represented within the diagnostic categories of unipolar and bipolar depression, with men over-represented in schizophrenia. The earlier age of onset in men appears restricted to schizophrenia. Poor premorbid social adjustment and personality disorder are over-represented in schizophrenia, but season of birth and organic confounder have an even distribution across the diagnostic categories. Table R4b shows that deliberate self harm is over-represented in unipolar psychotic depression. Schizophrenia has the most insidious onset with bipolar disorder having the most abrupt onset. Bipolar disorder and unipolar psychotic depression are significantly less likely to involve rapport difficulties, with those with bipolar disorder being the least likely to deteriorate and having the best outcome, with people suffering from schizophrenia having the worst outcome. Table R4c shows that those with unipolar psychotic depression are least likely to be detained under the Mental Health Act or have forensic involvement. While alcohol use appears uniformly distributed across the diagnostic categories, the use of street drugs is most likely in those with schizophrenia or atypical psychosis and least likely in those with unipolar psychotic depression.

Table R4a: Relationship between premorbid characteristics and DSM-III-R diagnoses (n=387 unless otherwise stated)

Key outcome measures			unipolar n (%)	bipolar n (%)	szaffective n (%)	schizophrenia n (%)	Atypical	Statistical test *
Gender		Male	12 (22.6%)	26 (31.7%)	17 (45.9%)	110 (67.9%)	29 (54.7%)	$\chi^2(4)=48.3$, p<0.001
		Female	41 (77.4%)	56(68.3%)	20 (54.1%)	52 (32.1%)	24 (45.3%)	
Season of birth		Summer (Apr-Sep)	34 (62.4%)	46 (56.1%)	18 (48.6%)	89 (54.9%	26 (49.1%)	$\chi^2(4)=3.19$, p=0.529
		Winter (Oct-Mar)	19 (35.8)	36 (43.9)	19 (51.4%)	73 (45.1%))	27 (50.9%)	
Evidence of poor pre-morbid social adjustment (n=371)		No	47 (94%)	81 (98.8%)	34 (97.1%)	126 (82.9)	45 (86.5%)	$\chi^2(4)=26.6$, p<0.001
		Yes	2 (4%)	1 (1.2%)	1(2.9%)	26 (17.1%)	7 (13.5%)	
Evidence of personality disorder prior to onset of psychosis (n=371)		No	47 (91%)	78 (95.1%)	34 (97.1%)	138 (90.2%)	48 (94.1%)	$\chi^2(4)= 8.6$, p=0.372
		Yes	22 (4%)	4 (5.0%)	11 (2.9%)	15 (9.8%)	3 (5.9%)	
Organic confounder		None	50 (94.4%)	79 (96.3%)	36 (97.3%)	154 (95.1%)	51 (96.2%)	
		Organic confounder	3 (5.7%)	3 (3.7%)	1 (2.7%)	8 (4.9%)	2 (3.8%)	$\chi^2(4)=0.723$, p=0.95
Age at onset	**Males:**	mean/ median	30.1/29.0	30.3/28.0	28.35/25.0	24.73/23.5	29.0/28.0	$\chi^2(4)=3.25$
		standard error	2.66	2.21	2.91	0.79	1.59	p=0.13
	Females:	mean/ median	29.5/27.0	31.36/29.0	24.1/24.5	31.67/27.0	29.63/24.5	$\chi^2(4)=1.82$
		standard error	1.83	1.54	1.17	1.71	2.59	p=0.127

*Tests performed: Chi-squared used on categorical variables, Kruskal Wallis test used on continuous variables. NS indicates a non-significant result

Thus DSM-III-R diagnoses are significantly different with respect to gender, with women having more unipolar and bipolar illness, and more men being affected by schizophrenia, with a significantly earlier age of onset.

Table R4b: Relationship between illness and treatment characteristics and DSM-III-R diagnoses (n=387 unless otherwise stated)

Key outcome measures		unipolar n (%)	bipolar n (%)	sz affective n (%)	schizophrenia n (%)	atypical	Statistical tests
Deliberate Self Harm	No	21 (39.6%)	52 (63.4%)	18 (48.6%)	102 (63%)	33 (62.3%)	$\chi^2(4)=11.7$
	Yes	32 (60.4%)	30 (36.6%)	19 (51.4%)	60 (37%)	20 (37.7%)	p<0.021
Onset Mode	<1 week	4 (13.8%)	19 (36.5%)	3 (15%)	13 (11.8%)	6 (15.8%)	$\chi^2(12)=28.9$
(n=249)	Within 1 month	11 (37.9%)	13 (35%)	6 (30%)	20 (18.2%)	7 (18.4%)	p=0.004
	Gradual up to 6 months	5 (17.2%)	13 (25%)	4 (20%)	28 (25.5%)	11 (28.9%)	
	Insidious > 6 months	9 (31%)	7 (13.5%)	7 (35%)	49 (44.5%)	14 (36.8%)	
Difficult Rapport	No	48 (90.6%)	79 (96.3%)	31 (83.8%)	132 (81.5%)	46 (86.8%)	$\chi^2(4)=11.48$
	Yes	5 (9.4%)	3 (3.7%)	6 (16.2%)	30 (18.5%)	7 (13.2%)	p=0.021
Deterioration (does not regain function after acute episode) n=353	No	29 (59.2%)	52 (67.5%)	15 (42.9%)	47 (31.8%)	24 (54.5%)	$\chi^2(4)=30.97$,
	Yes	20 (40.8%)	25(32.5%)	20 (57.1%)	101 (68.2%)	20 (45.5%)	p<0.001
Course	Single episode (good recovery)		3 (3.9%)		12 (7.9%)	8 (16%)	$\chi^2(12)=74.7$
	Multiple episodes (good recovery in between)	20 (39.2%)	46 (59.7%)	12 (33.3%)	27 (17.8%)	19 (38%)	p<0.001
	Multiple episodes (partial recovery in between)	21 (41.2%)	22 (28.6%)	15 (41.7%)	44 (28.9%)	11 (22%)	
	Continuous chronic illness	10 (19.6%)	6 (7.8%)	9 (25%)	69 (45.4%)	12 (24%)	
ECT ever received	No	29 (54.7%)	54 (65.9%)	17 (45.9%)	130 (80.2%)	43 (81.1%)	$\chi^2(4)=28.2$
	Yes	24 (45.3%)	28 (34.1%)	20 (54.1%)	32 (19.8%)	10 (18.9%)	p<0.001

Table R4c: use of mental health act, substance use, forensic history and DSM-III-R diagnoses

Key outcome measures		unipolar n (%)	bipolar n (%)	Sz affective n (%)	schizophrenia n (%)	atypical	Statistical tests
Ever detained under Mental Health Act	No	37 (69.8%)	37 (45.1%)	17 (45.9%)	67 (41.4%)	26 (49.1%)	$\chi^2(4)=13.3$
	Yes	16 (13.7%)	45 (54.9%)	20 (54.1%)	95 (58.6%)	27 ((50.9%)	P=0.010
Street drugs use ever	No	48 (90.6%)	71 (86.6%)	31 (86.1%)	114 (70.4%)	40 (75.5%)	$\chi^2(4)=15.74$
	yes	5 (9.4%)	11 (13.4%)	5 (13.9%)	48 (29.6%)	13 (24.5%)	P=0.003
Alcohol use	No	38 (71.7%)	58 (70.7%)	24 (66.7%)	99 (61.1%)	30 (56.6%)	$\chi^2(4)=4.92$
	Within limit	15 (28.3%)	24 (29.3%)	12 (33.3%)	63 (38.9%)	23 (43.4%)	P=0.297
Forensic involvement	No	46 (88.5%)	60 (73.2%)	8 (22.2%)	96 (59.6%)	37 (69.8%)	$\chi^2(4)=17.9$
	Yes	6 (11.5%)	22 (26.8%)	28 (77.8%)	65 (40.4%)	16 (30.2%)	P=0.001

Family History

The number of affected relatives would be inflated if all related probands within the epidemiological sample were included. For example taking all 387 probands and counting occurrences of family history of schizophrenia produces a total of 33. However, removal of all but one individual from a group of related individuals reduces the study population to 355 subjects and produces only 19 probands with a family history of schizophrenia. The proband chosen for retention was the first to join the study.

Aggregated data for Family History are shown in table R5.

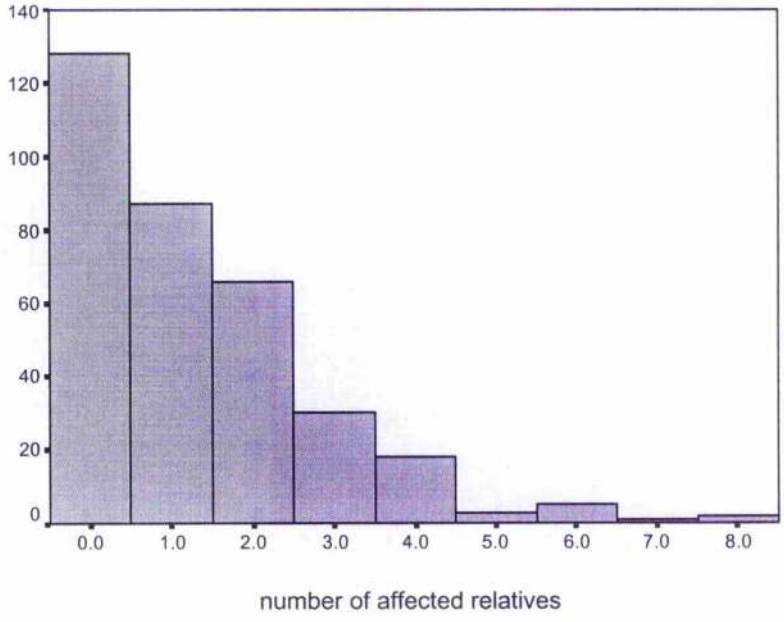
Table R5: family history from OPCRIT and other data

	Men	Women	Total	Statistical Tests
family history of schizophrenia (OPCRIT) (n=371)	12 7.1%	7 4.1%	19 5.6%	$\chi^2(1)=1.49$ P=0.246
family history of other psychiatric disorder (OPCRIT) (n=370)	60 35.7%	57 35.5%	117 34.6%	$\chi^2(1)=0.178$ P=0.732
1st or 2nd or 3rd degree relative with psychosis	31 20%	34 22.2%	65 21.1%	$\chi^2(1)=0.228$ P=0.676
1st or 2nd or 3rd degree relative with neurosis	45 29%	53 34.4%	98 31.7%	$\chi^2(1)=1.03$ P=0.330
1st or 2nd or 3rd degree relative with addiction	27 17.9%	25 16.9%	52 17.4%	NS
1st or 2nd or 3rd degree relative with other psychiatric disorder	42 31.6%	38 26.4%	80 28.9%	$\chi^2(1)=0.907$ P=0.356
1st or 2nd or 3rd degree relative with LD	7 3.9%	15 8.5%	22 6.2%	$\chi^2(1)=3.25$ P=0.056

Family loading for psychiatric disorder

A crude measure of family loading of psychiatric disorder (including all of the above categories except learning disability) was calculated by simple addition of each affected relative (1st, 2nd or 3rd degree). This is illustrated in figure R7

Figure R7: Number of affected relatives per proband*



*n=340: subjects for whom family history was available, and were not related to any other subject in the study

Thus, around one third of probands had no known family history of any psychiatric disorder (128, 37.6%). Around one quarter had only one affected relative (87, 25.6%). There was no significant difference between the sexes.

Family History Additional Data

The aggregated Family History information does not display the various groups of individuals known to be related to each other *within* the population-based sample. Therefore the results of OPCRIT diagnosis and latent classes are listed for each of the individuals within these groups of relatives. One would not expect psychotic disorders to "breed true" but it is of interest to see if the DSM-III-R diagnoses or latent classes more often sort relatives into the same diagnostic category. As a crude measure of how well each diagnostic system identifies homotypic pairs within these relative groups a simple scoring system was used: score 1 for homotypic pairs, 0 for heterotypic pairs (table R6).

Table R6: Comparison of homotypic pairs in related probands using DSM-III-R diagnoses and Latent Classes

Relative 1	Relative 2	Relative 3	Relative 4	Relative 5	Score DSM-	Score Latent
DSM-III-R (latent class)	DSM-III-R (latent class)	DSM-III-R (latent class)	DSM-III-R (latent class)	DSM-II-R (latent class)		Class
Schizophrenia(4)	Schizophrenia (2)	Schizophrenia (2)			3	1
Atypical psychosis (4)	Schizoaffective bipolar (4)	Schizophrenia (2)	Atypical psychosis (4)	Atypical psychosis (4)	3	6
Depression with psychosis (1)	Schizoaffective depression (4)	Schizophrenia (1)			0	1
Schizophrenia (1)	Depression with psychosis (1)	Schizoaffective depression (4)			0	1
Mania with psychosis (4)	Schizophrenia(2)				0	0
Schizoaffective depression (4)	Schizophrenia (3)				0	0
Schizophrenia (4)	Schizophreniform disorder (4)				0	1
Depression with psychosis (1)	Bipolar with psychosis (3)				0	0
Bipolar with psychosis (4)	Mania with psychosis (3)				0	0
Schizoaffective manic (3)	Depression with psychosis (4)				0	0
Atypical psychosis (4)	Mania with psychosis (3)				0	0
Atypical psychosis (2)	Schizophrenia (4)				0	0
Schizophrenia (2)	Schizophrenia (4)				1	0
Schizophrenia (2)	Schizophrenia (4)				1	0
Schizophrenia (2)	Mania with psychosis (3)				0	0
Depression with psychosis (1)	Schizophrenia (1)				0	1
Schizophreniform disorder (4)	Schizophrenia (4)				0	0
Schizoaffective depression (4)	Bipolar with psychosis (3)				0	0
Mania with psychosis (3)	Schizophrenia(4)				0	0
Schizophrenia (4)	Schizophrenia (2)				1	0
Schizophrenia (4)	Schizophrenia (2)				1	0
Schizophrenia (2)	Mania with psychosis (4)				0	0
Mania with psychosis (3)	Mania with psychosis (3)				1	1
Depression with psychosis (1)	Depression with psychosis (4)				1	0
Bipolar with psychosis (3)	Schizopheniform disorder (2)				0	0
Bipolar with psychosis (2)	Schizoaffective depression (4)				0	0
Bipolar with psychosis (3)	Delusional disorder (1)				0	0
Atypical psychosis (1)	Mania with psychosis (3)				0	0
Depression (1)	Bipolar disorder(1)				0	1
Atypical (2)	Depression with psychosis (1)				0	0
Schizophrenia (2)	Schizophrenia (4)	**Total score for homotypy**	**DSM–III-R =16**	**Latent class = 20**	1	0
Atypical (1)	Schizoaffective depression (4)				0	0
Depression (1)	Bipolar with psychosis (3)				0	0

Family history and DSM-III-R diagnoses

The distribution of various measurements of family history with respect to DSM-III-R diagnoses are shown inTable R7.

Table R7: Family History and DSM-III-R diagnoses

Key outcome measures		unipolar n (%)	bipolar n (%)	Sz affective n (%)	schizophrenia n (%)	atypical	Statistical tests
Fertility	No children	11 (20.8%)	29 (35.4%)	16 (43.2%)	115 (71%)	29 (54.7%)	$\chi^2(4)=54.5, p<0.001$
	At least one child	42(79.2%)	53 (64.6%)	21 (56.8%)	47 (29%)	24 (45.3%)	
Married or lived as married	No	11 (20.8%)	18 (22%)	12 (32.4%0	91 (56.2%)	27 (50.9%)	$\chi^2(4)=40.0, p<0.001$
	Yes	42 (79.2%)	64 (78%)	25(67.6%)	71 (43.8%)	26(49.1%)	
History of schizophrenia in 1st or 2nd degree relative (n=339)	No	48 (98%)	69 (98.6%)	129 (91.5%)	129 91.5%)	42 (91.3%)	$\chi^2(4)=7.0, p=0.133$
	yes	1 (2%)	1 (1.4%)	12 (8.5%)	12 (8.5%)	4 (8.7%)	
History of other disorder in 1st or 2nd degree relative (N=338)	No	26 (54.2%)	40 (57.1%)	18 (52.9%)	103 (73.6%)	34 (73.9%)	$\chi^2(4)=12.72, p=0.012$
	Yes	22 (45.8%)	30 (42.9%)	16 (47.1%)	37 (26.4%)	12 26.1%)	
History of psychosis in !st 2nd or 3rd degree relative (n=300)	No	37 (86%)	49 (73%)	26 (86.7%)	99 (81.1%)	32 84.2%)	$\chi^2(4)=4.29, p=0.371$
	yes	6 (14%)	18 (27%)	4 (13.3%)	23 (18.9%)	6 (15.8%)	
History of neurosis in 1st 2nd or 3rd degree relative (N=260)	No	27 (60%)	46 (68.7%)	21 (63.6%)	90 (71.4%)	27 (7.1%)	$\chi^2(4)=2.47, p=0.653$
	yes	18 (40%)	21 (31.3%)	12 (36.4%)	36 (28.6%)	11 (28.9%)	
History of addiction in 1st 2nd or 3rd degree relative (N=355)	No	35 (81.4%)	51 (79.7%)	26 (83.9%)	106 (86.2%)	29 (76.3%)	$\chi^2(4)=2.60, p=0.632$
	Yes	8 (18.6%)	13 (20.3%)	5 (16.1%)	17 (13.8%)	9 (23.7%)	
History of other disorder in 1st 2nd or 3rd degree relative (n=355)	No	28 (66.7%)	33 (55%)	16 (57.1%)	91 (82%)	29 (80.6%)	$\chi^2(4)=18.6$ $p<0.001$
	Yes	14 (33.3%	27 (45%)	12 (42.9%)	20 (18%)	7 (17.4%)	
Any family history of psychiatric disorder (n=355)	No	33 (68.8%)	52 (72.2%)	24 (68.6%)	77 (55.4%)	26 (56.5%)	$\chi^2(4)=7.93, p=0.094$
	Yes	15 (31.3%)	20 (27.8%)	11 (31.4%)	62 (44.6%)	20 (43.5%)	

Principal Components Analysis

62 OPCRIT items relating to symptoms were entered into a principal components analysis. This was run under four conditions: firstly, the items were left without dichotomisation; secondly the items were dichotomised as necessary (by both conservative and non-conservative restraints); thirdly the principal components analysis was run separately for men and women and lastly it was re-run extracting an increased number of factors.

Principal components analysis using non-dichotomised data

Principal components analysis was run using non-dichotomised scores. Communalities are shown in table R8a (overleaf). The number of factors to be extracted was indicated by a scree test (figure R7), and the variance explained up to one eigenvalue is presented in table R8b. The principal components analysis was repeated extracting four factors, with the unrotated solution illustrated in table R8c. Varimax rotation was used to produce a rotated solution as shown in table R8d. Factor loadings of >0.3 are deemed significant and are shown bold.

Figure R7: Scree plot of eigenvalues of Principal Components (non-dichotomised items)

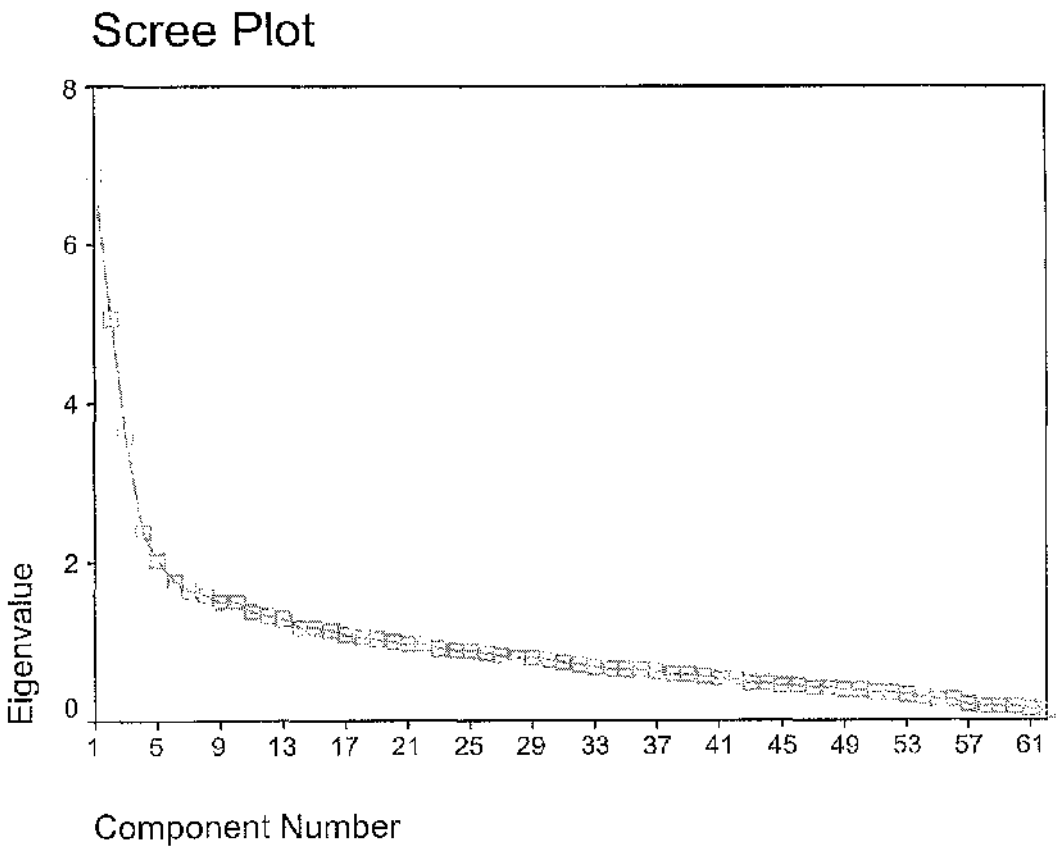


Table R8a: Communalities of 62 non dichotomised items of principal component analysis

	Initial	Extraction
Excessive activity	1.000	.780
Pressured speech	1.000	.715
Elevated mood	1.000	.757
Thoughts racing	1.000	.703
Reduced need for sleep	1.000	.730
Increased self-esteem	1.000	.757
Recklessness	1.000	.601
Increased sociability	1.000	.534
Distractibility	1.000	.527
Grandiose delusions	1.000	.732
Irritable mood	1.000	.719
Thought echo	1.000	.611
Weight gain	1.000	.723
Persecutory, jealous delusions and hallucinations	1.000	.748
Delusions, hallucinations one week	1.000	.785
Widespread delusions	1.000	.693
Well organised delusions	1.000	.617
Abusive/accusatory/persecutory voices	1.000	.618
Persecutory delusions	1.000	.617
Delusions of passivity	1.000	.499
Delusions of influence	1.000	.522
Bizarre delusions	1.000	.480
Non affective hallucinations any mode	1.000	.581
Third person auditory hallucinations	1.000	.575
Thought insertion	1.000	.501
Thought broadcast	1.000	.639
Thought withdrawal	1.000	.564
Running commentary voices	1.000	.596
Dysphoria	1.000	.739
Loss of pleasure	1.000	.700
Poor appetite	1.000	.573
Suicidal ideation	1.000	.593
Initial insomnia	1.000	.752
Loss of energy	1.000	.555
Poor concentration	1.000	.614
Excessive self-reproach	1.000	.730
Relationship psychotic/affective	1.000	.596
Slowed activity	1.000	.520
Middle insomnia	1.000	.780
Early morning wakening	1.000	.589
Diurnal variation	1.000	.592
Weight loss	1.000	.631
Diminished libido	1.000	.717
Delusions of guilt	1.000	.684
Excessive sleep	1.000	.687
Agitated activity	1.000	.637
Nihilistic delusions	1.000	.653
Increased appetite	1.000	.696
Positive formal thought disorder	1.000	.620
Restricted affect	1.000	.604
Rapport	1.000	.599
Inappropriate affect	1.000	.687
Blunted affect	1.000	.574
Speech difficult to understand	1.000	.670
Negative formal thought disorder	1.000	.658
Catatonia	1.000	.595
Bizarre behaviour	1.000	.614
Incoherent	1.000	.661
Lack of insight	1.000	.530
Other auditory hallucinations	1.000	.752
Other primary delusions	1.000	.503
Primary delusional perception	1.000	.609

Table R8b Variance Explained up to one eigenvalue for non-dichotomised items

	Initial Eigenvalues			Extraction Sums of Squared Loadings		
Component	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	6.883	11.102	11.102	6.883	11.102	11.102
2	5.044	8.136	19.237	5.044	8.136	19.237
3	3.580	5.774	25.011	3.580	5.774	25.011
4	2.390	3.856	28.867	2.390	3.856	28.867
5	2.032	3.277	32.143	2.032	3.277	32.143
6	1.771	2.857	35.001	1.771	2.857	35.001
7	1.662	2.680	37.681	1.662	2.680	37.681
8	1.599	2.579	40.259	1.599	2.579	40.259
9	1.495	2.411	42.670	1.495	2.411	42.670
10	1.487	2.398	45.068	1.487	2.398	45.068
11	1.396	2.252	47.320	1.396	2.252	47.320
12	1.330	2.145	49.465	1.330	2.145	49.465
13	1.300	2.097	51.562	1.300	2.097	51.562
14	1.174	1.893	53.455	1.174	1.893	53.455
15	1.169	1.886	55.342	1.169	1.886	55.342
16	1.140	1.839	57.181	1.140	1.839	57.181
17	1.082	1.746	58.927	1.082	1.746	58.927
18	1.061	1.711	60.637	1.061	1.711	60.637
19	1.041	1.679	62.316	1.041	1.679	62.316
20	1.001	1.615	63.931	1.001	1.615	63.931

Table R8c: Unrotated component matrix for non-dichotomised items

	Principal component loadings			
	Mania	Reality distortion	Depression	Disorganisation
Excessive activity	.748	.390	.133	-.049
Pressured speech	.672	.432	.197	-.073
Elevated mood	.704	.365	.253	-.038
Thoughts racing	.655	.448	.170	-.100
Reduced need for sleep	.723	.343	.101	-.109
Increased self-esteem	.369	.528	.297	-.027
Recklessness	.584	.313	.099	-.062
Increased sociability	.453	.414	.170	.041
Distractibility	.412	.340	.199	-.057
Grandiose delusions	.171	.562	.264	-.019
Irritable mood	.386	.157	-.051	-.031
Thought echo	-.156	.024	.018	-.013
Weight gain	.059	.022	.087	-.028
Persecutory, jealous delusions and hallucinations	-.586	.179	.387	-.241
Delusions, hallucinations one week	-.544	.200	.396	-.211
Widespread delusions	-.493	.295	.278	-.216
Well organised delusions	-.432	.360	.289	-.121
Abusive/accusatory/persecutory voices	-.399	-.055	.320	-.254
Persecutory delusions	-.469	.185	.229	-.133
Delusions of passivity	-.387	.201	.325	-.061
Delusions of influence	-.327	.223	.231	-.141
Bizarre delusions	-.328	.306	.188	-.091
Non affective hallucinations any mode	-.392	.217	.109	-.063
Third person auditory hallucinations	-.335	-.028	.224	-.150
Thought insertion	-.233	.096	.170	-.262
Thought broadcast	-.215	.103	.204	-.187
Thought withdrawal	-.240	.144	.188	-.138
Running commentary voices	-.225	-.006	.031	-.224
Dysphoria	.276	-.576	.493	.070
Loss of pleasure	.253	-.562	.477	.092
Poor appetite	.155	-.400	.396	.047
Suicidal ideation	.015	-.399	.365	-.043
Initial insomnia	.112	-.304	.396	.065
Loss of energy	.276	-.366	.199	.194
Poor concentration	.194	-.418	.225	.006
Excessive self-reproach	-.038	-.298	.406	-.074
Relationship psychotic/affective	.344	-.097	.409	-.006
Slowed activity	.165	-.174	.357	.208
Middle insomnia	.032	-.161	.435	.046
Early morning wakening	.207	-.281	.236	-.029
Diurnal variation	.192	-.271	.173	.040
Weight loss	.068	-.225	.234	.156
Diminished libido	.054	-.207	.201	.116
Delusions of guilt	-.140	-.188	.287	-.156
Excessive sleep	.129	-.137	.125	.093
Agitated activity	.106	-.226	.066	.064
Nihilistic delusions	-.021	-.160	.139	-.031
Increased appetite	.168	-.098	.118	-.014
Positive formal thought disorder	-.264	.343	.206	.402
Restricted affect	-.304	.103	.187	.502
Rapport	-.199	.019	-.031	.574
Inappropriate affect	-.134	.331	.144	.408
Blunted affect	-.224	.102	.057	.481
Speech difficult to understand	-.057	.355	.125	.350
Negative formal thought disorder	-.235	.121	.043	.371
Catatonia	-.194	.171	.143	.310
Bizarre behaviour	-.200	.334	.180	.196
Incoherent	-.053	.266	.101	.284
Lack of insight	-.161	.336	.068	.116
Other auditory hallucinations	-.185	.179	.095	.135
Other primary delusions	-.088	-.050	.122	.179
Primary delusional perception	-.067	.124	.050	.048

Table R8d: Rotated component matrix for non-dichotomised items

	Principal component loadings			
	Mania	Reality distortion	Depression	Disorganisation
Excessive activity	**.816**	-.248	.009	-.068
Pressured speech	**.813**	-.143	.008	-.036
Elevated mood	**.809**	-.168	.103	-.027
Thoughts racing	**.805**	-.130	-.029	-.055
Reduced need for sleep	**.767**	-.235	.001	-.137
Increased self-esteem	**.685**	.104	-.042	.147
Recklessness	**.644**	-.183	-.006	-.071
Increased sociability	**.622**	-.083	-.031	.108
Distractibility	**.572**	-.017	.013	.015
Grandiose delusions	**.542**	.207	-.118	.207
Irritable mood	**.354**	-.204	-.054	-.085
Thought echo	-.088	.119	-.040	.046
Weight gain	.089	.032	.057	-.011
Persecutory, jealous delusions and hallucinations	-.138	**.741**	-.003	.117
Delusions, hallucinations one week	-.097	**.712**	.005	.142
Widespread delusions	-.043	**.646**	-.130	.132
Well organised delusions	.030	**.588**	-.135	.223
Abusive/accusatory/persecutory voices	-.170	**.529**	.137	-.050
Persecutory delusions	-.121	**.532**	-.077	.142
Delusions of passivity	-.031	**.504**	.011	.210
Delusions of influence	.004	**.461**	-.070	.110
Bizarre delusions	.032	**.438**	-.146	.176
Non affective hallucinations any mode	-.099	**.394**	-.157	.163
Third person auditory hallucinations	-.155	**.394**	.081	.008
Thought insertion	-.011	**.392**	-.031	-.081
Thought broadcast	.007	**.365**	.005	-.011
Thought withdrawal	.002	**.360**	-.031	.049
Running commentary voices	-.120	**.262**	-.059	-.123
Dysphoria	.005	-.099	**.795**	-.120
Loss of pleasure	-.011	-.101	**.772**	-.093
Poor appetite	-.004	-.016	**.582**	-.061
Suicidal ideation	-.100	.096	**.514**	-.107
Initial insomnia	.021	.029	**.515**	.002
Loss of energy	.014	-.260	**.468**	-.004
Poor concentration	-.040	-.119	**.472**	-.155
Excessive self-reproach	-.058	.196	**.462**	-.069
Relationship psychotic/affective	.325	-.011	**.433**	-.041
Slowed activity	.104	-.056	**.438**	.149
Middle insomnia	.068	.151	**.431**	.072
Early morning wakening	.060	-.065	**.390**	-.134
Diurnal variation	.025	-.121	**.346**	-.082
Weight loss	-.030	-.053	**.352**	.083
Diminished libido	-.035	-.039	**.306**	.052
Delusions of guilt	-.092	.265	.271	-.098
Excessive sleep	.038	-.096	.221	.021
Agitated activity	-.049	-.126	.225	-.046
Nihilistic delusions	-.060	.058	.192	-.048
Increased appetite	.101	-.060	.184	-.068
Positive formal thought disorder	.036	.181	-.065	**.594**
Restricted affect	-.157	.076	.080	**.595**
Rapport	-.219	-.168	.011	**.542**
Inappropriate affect	.099	.060	-.072	**.544**
Blunted affect	-.143	-.035	.002	**.523**
Speech difficult to understand	.169	.037	-.093	**.478**
Negative formal thought disorder	-.129	.023	-.040	**.436**
Catatonia	-.027	.097	.000	**.416**
Bizarre behaviour	.096	.224	-.096	**.393**
Incoherent	.119	.028	-.063	**.381**
Lack of insight	.097	.178	-.182	.288
Other auditory hallucinations	-.009	.153	-.065	.257
Other primary delusions	-.076	.020	.128	.186
Primary delusional perception	.039	.081	-.050	.119

Significant values are shown in bold

Principal Components analysis using dichotomised scores

The principal components analysis was repeated as above, using dichotomised items. The scree test again indicated that four components should be extracted, accounting for 27.9% of the variance. The rotated component matrix is shown in table R9. Dichotomised data produced the same factors, accounting for slightly less of the variance (27.9% vs 28.9%). Using conservatively dichotomised scores (for changed items see table M4) did not improve the variance accounted for but produced the same four factors. Since dichotomisation introduces error and loss of information, henceforth the results of the principal components analysis are those of the non-dichotomised data.

Selection of five factors

Although the scree test appears quite clear in indicating selection of four factors, it was of interest to consider the effect of choosing 5 factors. Here 32% of the variance is accounted for, but the third and fourth factors appear to be fragments of the original third factor, and do not appear to be so clinically recognisable (Table R10).

Principal components analysis for each gender separately

The principal components analysis was repeated separately for men and women, producing very similar factors (see Tables R11a and R11b).

Table R9: Rotated Component Matrix for dichotomised items

	Principal component loadings			
	Mania	Reality distortion	Depression	Disorganisation
Excessive activity	**.798**	-.234	.043	-.054
Pressured speech	**.772**	-.088	.024	.018
Elevated mood	**.772**	-.122	.153	.007
Thoughts racing	**.777**	-.074	.008	**-.002**
Reduced need for sleep	**.757**	-.208	.050	-.129
Increased self-esteem	**.662**	.115	**-.054**	.135
Recklessness	**.598**	-.175	-.006	-.086
Increased sociability	**.658**	-.101	-.025	.025
Distractibility	**.522**	.003	.032	-.023
Grandiose delusions	**.545**	.228	-.111	.203
Irritable mood	**.349**	-.135	.029	**-.045**
Thought echo	-.090	.116	.007	.063
Weight gain	.135	.003	.116	.053
Persecutory, jealous delusions and hallucinations	-.136	**.738**	.065	.124
Delusions, hallucinations one week	-.101	**.708**	.054	.145
Widespread delusions	-.052	**.651**	-.138	.124
Well organised delusions	.030	**.596**	-.146	.209
Abusive/accusatory/persecutory voices	-.178	**.518**	.174	-.047
Persecutory delusions	-.119	**.538**	**-.037**	.143
Delusions of passivity	-.015	**.511**	.020	.196
Delusions of influence	-.007	**.466**	-.059	.099
Bizarre delusions	.056	**.450**	-.166	.165
Non affective hallucinations any mode	-.100	**.409**	-.140	.165
Third person auditory hallucinations	-.172	**.384**	.115	.015
Thought insertion	-.013	**.394**	-.018	-.090
Thought broadcast	-.001	**.366**	-.030	**-.030**
Thought withdrawal	.009	**.361**	-.045	.033
Running commentary voices	-.120	**.266**	.003	-.109
Dysphoria	.038	-.026	**.736**	-.106
Loss of pleasure	.014	-.045	**.729**	-.092
Poor appetite	.025	.015	**.537**	-.063
Suicidal ideation	**-.057**	.126	**.463**	-.033
Initial insomnia	.074	.140	**.546**	.092
Loss of energy	.051	-.249	**.442**	.027
Poor concentration	-.025	-.086	**.404**	-.143
Excessive self-reproach	-.057	.160	**.460**	-.001
Relationship psychotic/affective	.327	-.021	**.440**	-.067
Slowed activity	.081	-.068	**.457**	.123
Middle insomnia	.077	.151	**.484**	.074
Early morning wakening	.032	-.080	**.340**	-.119
Diurnal variation	.028	-.138	**.319**	-.094
Weight loss	-.014	-.052	**.402**	.069
Diminished libido	-.027	-.055	.290	.051
Delusions of guilt	-.105	.240	.275	-.084
Excessive sleep	.062	-.083	.246	.034
Agitated activity	-.032	-.054	.217	-.016
Nihilistic delusions	-.064	.044	.156	-.056
Increased appetite	.114	-.066	.165	-.059
Positive formal thought disorder	.045	.190	-.078	**.585**
Restricted affect	**-.109**	.076	.120	**.616**
Rapport	**-.195**	-.164	.044	**.564**
Inappropriate affect	.120	.068	-.039	**.544**
Blunted affect	-.141	-.036	.007	**.537**
Speech difficult to understand	.200	.054	-.082	**.463**
Negative formal thought disorder	-.121	.028	-.030	**.440**
Catatonia	-.013	.103	-.005	**.410**
Bizarre behaviour	**.115**	.239	-.066	**.383**
Incoherent	.132	.034	-.054	**.371**
Lack of insight	.088	.180	-.237	.276
Other auditory hallucinations	-.001	.162	-.057	.257
Other primary delusions	-.100	.011	.105	.181
Primary delusional perception	.037	.094	-.060	.098

Significant values are shown in bold

Table R10: Rotated Component Matrix for non-dichotomised items with five components extracted

	Component				
	1	2	3	4	5
Excessive activity	**.839**	.006	-.114	-.167	-.057
Pressured speech	**.823**	.013	-.072	-.056	-.036
Elevated mood	**.822**	.106	-.078	-.091	-.024
Thoughts racing	**.812**	-.022	-.082	-.027	-.059
Reduced need for sleep	**.789**	-.003	-.104	-.169	-.125
Increased self-esteem	**.654**	-.010	-.070	.310	.105
Recklessness	**.659**	-.007	-.090	-.114	-.064
Increased sociability	**.636**	-.030	.000	-.050	.111
Distractibility	**.573**	.021	-.002	.034	.007
Grandiose delusions	**.499**	-.078	-.043	**.427**	.153
Irritable mood	**.369**	-.058	-.130	-.129	-.076
Thought echo	-.063	-.059	.287	-.138	.072
Weight gain	.108	.044	.168	-.130	.009
Persecutory, jealous delusions and	-.160	.003	**.713**	.313	.101
Delusions, hallucinations one week	-.114	.009	**.707**	.284	.130
Widespread delusions	-.123	-.079	**.223**	**.720**	.054
Well organised delusions	-.044	-.086	**.192**	**.684**	.148
Abusive/accusatory/persecutory voices	-.180	.133	**.563**	**.139**	-.051
Persecutory delusions	-.180	-.042	**.230**	**.536**	.086
Delusions of passivity	-.042	.014	**.502**	**.212**	.200
Delusions of influence	-.039	-.044	.255	**.414**	.069
Bizarre delusions	-.010	-.117	.221	**.430**	.132
Non affective hallucinations any mode	-.086	-.169	**.513**	.037	.176
Third person auditory hallucinations	-.158	.075	**.443**	.079	.012
Thought insertion	-.008	-.039	**.475**	.055	-.074
Thought broadcast	-.009	.012	**.324**	.184	-.024
Thought withdrawal	-.007	-.028	**.353**	.152	.041
Running commentary voices	-.090	-.087	**.497**	-.172	-.088
Dysphoria	.004	**.787**	-.042	-.153	-.109
Loss of pleasure	-.006	**.761**	-.014	-.184	-.077
Poor appetite	-.017	**.585**	-.053	-.004	-.067
Suicidal ideation	-.130	**.526**	-.029	.126	-.126
Initial insomnia	.000	**.524**	-.053	.074	-.012
Loss of energy	.034	**.452**	-.133	-.262	.021
Poor concentration	-.026	**.457**	-.001	-.217	-.133
Excessive self-reproach	-.101	**.484**	-.004	.254	-.103
Relationship psychotic/affective	.306	**.447**	-.085	.080	-.058
Slowed activity	.111	**.433**	.010	-.094	.158
Middle insomnia	.046	**.442**	.070	.134	.055
Early morning wakening	.071	**.379**	.037	-.162	-.117
Diurnal variation	.047	**.328**	.034	-.237	-.056
Weight loss	-.032	**.350**	-.049	-.040	.085
Diminished libido	-.023	**.295**	.050	-.127	.068
Delusions of guilt	-.138	**.295**	**.041**	.311	-.136
Excessive sleep	.055	.208	.014	-.161	.039
Agitated activity	-.053	.226	-.155	-.038	-.047
Nihilistic delusions	-.079	.202	-.036	**.103**	-.063
Increased appetite	.119	.170	.065	-.164	-.048
Positive formal thought disorder	.019	-.048	.057	.263	**.569**
Restricted affect	-.151	.078	.094	.044	**.597**
Rapport	-.179	-.013	.020	-.240	**.577**
Inappropriate affect	.106	-.070	.074	.070	**.542**
Blunted affect	-.129	-.005	.015	-.035	**.532**
Speech difficult to understand	.157	-.077	-.063	.186	**.458**
Negative formal thought disorder	-.129	-.037	-.008	.071	**.432**
Catatonia	-.022	.000	.116	.052	**.416**
Bizarre behaviour	.075	-.077	.092	.278	**.365**
Incoherent	.129	-.065	.072	.012	**.384**
Lack of insight	.060	-.151	-.059	.369	.244
Other auditory hallucinations	.021	-.085	.343	-.121	.284
Other primary delusions	-.088	.137	-.060	.097	.174
Primary delusional perception	.048	-.056	.145	-.021	.126

Significant values shown in bold

R11a: Rotated Component Matrix for men (non-dichotomised data)

	Principal component loadings			
	Mania	Reality distortion	Depression	Disorganisation
Excessive activity	**.799**	-.216	.025	-.035
Pressured speech	**.765**	-.121	.026	.043
Elevated mood	**.762**	-.151	.151	.037
Thoughts racing	**.802**	-.061	.022	.022
Reduced need for sleep	**.681**	-.209	.047	-.135
Increased self-esteem	**.747**	.081	-.024	.142
Recklessness	**.664**	-.221	.102	-.010
Increased sociability	**.557**	.005	.006	.086
Distractibility	**.558**	-.058	.054	-.015
Grandiose delusions	**.607**	.177	-.184	.215
Irritable mood	**.401**	-.332	.088	-.114
Thought echo	-.126	.067	.086	.154
Weight gain	.018	.061	.077	-.062
Persecutory, jealous delusions and hallucinations	-.171	**.756**	.059	.108
Delusions, hallucinations one week	-.170	**.739**	.110	.099
Widespread delusions	.108	**.665**	-.040	.071
Well organised delusions	.093	**.605**	-.125	.234
Abusive/accusatory/persecutory voices	-.214	**.570**	.141	-.047
Persecutory delusions	-.094	**.499**	.113	.097
Delusions of passivity	-.073	**.486**	-.042	.217
Delusions of influence	.071	**.556**	-.073	.065
Bizarre delusions	.088	**.406**	-.190	.111
Non affective hallucinations any mode	-.240	**.433**	-.123	.072
Third person auditory hallucinations	-.174	**.345**	.115	.123
Thought insertion	-.070	**.353**	-.010	-.121
Thought broadcast	.008	**.370**	.029	-.105
Thought withdrawal	-.070	.255	-.006	.100
Running commentary voices	-.163	.184	.071	-.082
Dysphoria	.026	-.032	**.806**	-.150
Loss of pleasure	.051	-.065	**.755**	-.098
Poor appetite	.078	.028	**.524**	-.106
Suicidal ideation	-.054	.115	**.377**	-.148
Initial insomnia	-.111	.028	**.615**	-.021
Loss of energy	.002	-.208	**.445**	.103
Poor concentration	-.107	-.084	**.440**	-.183
Excessive self-reproach	.010	.221	**.408**	-.077
Relationship psychotic/affective	.370	-.048	**.391**	-.053
Slowed activity	.128	-.001	**.421**	.335
Middle insomnia	-.074	.141	**.474**	.050
Early morning wakening	.083	.017	**.417**	-.043
Diurnal variation	-.036	-.170	.209	-.076
Weight loss	.083	-.161	.353	.181
Diminished libido	-.027	-.066	.240	.069
Delusions of guilt	-.085	.240	.312	-.092
Excessive sleep	-.005	-.087	**.104**	-.050
Agitated activity	.079	-.027	.219	-.213
Nihilistic delusions	-.123	.031	.076	-.189
Increased appetite	.093	.047	.171	.092
Positive formal thought disorder	.071	.275	-.132	**.510**
Restricted affect	-.167	.096	.083	**.608**
Rapport	-.269	-.142	.071	**.624**
Inappropriate affect	.167	.135	-.222	**.471**
Blunted affect	-.174	-.045	.124	**.624**
Speech difficult to understand	.179	.048	-.147	**.444**
Negative formal thought disorder	-.140	.090	.084	**.367**
Catatonia	.013	.110	-.002	**.338**
Bizarre behaviour	.129	.156	-.196	**.378**
Incoherent	.144	-.054	-.033	**.392**
Lack of insight	.156	.166	-.146	**.349**
Other auditory hallucinations	-.121	.224	-.107	.189
Other primary delusions	-.214	-.040	.137	.081
Primary delusional perception	.024	.118	-.138	.163

Significant values shown in bold

R11b: Rotated Component Matrix for women (non-dichotomised data)

	Principal component loadings			
	Mania	Reality distortion	Depression	Disorganisation
Excessive activity	**.825**	-.255	.003	-.016
Pressured speech	**.850**	-.127	.010	-.046
Elevated mood	**.835**	-.166	.106	-.039
Thoughts racing	**.808**	-.141	-.070	-.080
Reduced need for sleep	**.829**	-.234	-.025	-.087
Increased self-esteem	**.670**	.147	.058	.043
Recklessness	**.634**	-.165	-.036	-.048
Increased sociability	**.654**	-.127	-.061	.158
Distractibility	**.575**	.046	-.012	.061
Grandiose delusions	**.555**	.306	.076	.005
Irritable mood	**.327**	-.065	-.170	.030
Thought echo	-.012	.192	-.138	-.125
Weight gain	.108	-.020	.018	.126
Persecutory, jealous delusions and hallucinations	-.134	**.663**	-.009	.220
Delusions, hallucinations one week	-.066	**.624**	-.048	.249
Widespread delusions	-.163	**.658**	-.178	.087
Well organised delusions	-.028	**.614**	-.121	.085
Abusive/accusatory/persecutory voices	-.148	**.433**	.200	-.033
Persecutory delusions	-.145	**.555**	-.212	.134
Delusions of passivity	.010	**.526**	.143	.118
Delusions of influence	-.094	**.426**	-.124	.047
Bizarre delusions	-.038	**.475**	-.102	.253
Non affective hallucinations any mode	.033	**.290**	-.164	.356
Third person auditory hallucinations	-.183	**.406**	.064	.007
Thought insertion	.051	**.412**	-.026	-.026
Thought broadcast	.026	**.327**	.040	.042
Thought withdrawal	.047	**.496**	-.033	-.013
Running commentary voices	-.062	**.306**	-.117	-.121
Dysphoria	-.084	-.210	**.768**	-.049
Loss of pleasure	-.127	-.163	**.786**	-.034
Poor appetite	-.117	-.066	**.602**	-.009
Suicidal ideation	-.165	.075	**.576**	-.080
Initial insomnia	.124	-.009	**.433**	.034
Loss of energy	-.018	-.322	**.434**	-.047
Poor concentration	.001	-.209	**.494**	-.123
Excessive self-reproach	-.137	.197	**.474**	-.123
Relationship psychotic/affective	.245	.056	**.445**	.028
Slowed activity	.039	-.075	**.405**	.022
Middle insomnia	.152	.145	**.391**	.135
Early morning wakening	.020	-.143	**.377**	-.208
Diurnal variation	.036	-.102	**.397**	-.070
Weight loss	-.155	.057	**.336**	-.032
Diminished libido	-.084	-.022	**.334**	-.079
Delusions of guilt	-.124	.275	.220	-.183
Excessive sleep	.064	-.083	.279	.086
Agitated activity	-.183	-.203	.145	.176
Nihilistic delusions	-.026	.084	.248	.093
Increased appetite	.090	-.134	.181	-.049
Positive formal thought disorder	-.001	.096	-.020	**.633**
Restricted affect	-.152	.075	.086	**.539**
Rapport	-.169	-.197	-.045	**.432**
Inappropriate affect	.039	.010	.066	**.601**
Blunted affect	-.100	-.029	-.164	**.299**
Speech difficult to understand	.158	.078	-.046	**.484**
Negative formal thought disorder	-.121	-.026	-.197	**.448**
Catatonia	-.057	.105	-.001	**.507**
Bizarre behaviour	.055	.331	-.001	**.333**
Incoherent	.087	.113	-.058	**.431**
Lack of insight	.049	.239	-.232	.124
Other auditory hallucinations	.093	.084	-.035	**.391**
Other primary delusions	.072	.097	.126	.241
Primary delusional perception	.052	.033	.060	.026

Significant values shown in bold

Description of factors

Factor 1 accounting for 11.1% of the variance loads on items commonly occurring in a manic upswing, therefore this factor is called "mania". The second factor, accounting for 8.1% of the variance loads highly on delusions and hallucinations, as well as disorders of thought possession. Running commentary voices, another Schneiderian first rank symptom has its highest loading on this factor, but does not quite reach significance. This factor is named "reality distortion". The third factor, accounting for 5.8% of the variance loads highly on symptoms common in depressive illness and so is named "depression". The final factor, accounting for 3.9% of the variance loads highly on thought disorder, catatonia, blunting of affect and rapport problems in addition to bizarre behaviour and so is named "disorganisation".

The factors are complex, with each loading a minimum of 10 items. In addition, items do not load highly on more than one factor (a reflection of varimax rotation in aiming for simple structure (Kline 1994). However the factor analysis accounts for only 28.9% of the variance.

Latent Class Analysis

The best latent class model contained four classes and placed 19% of the sample in class one, 28% in class two, 23% in class three and 30% in class four. The conditional probabilities (which are analogous to principal component loadings) are shown in Table R12. The highest probabilities for each item are shown bold, although >0.5 is considered significant. Class one has high conditional probabilities on items commonly associated with depression, and is named "depression". Class two scores highly on items such as thought disorder, poor rapport, affective blunting, bizarre behaviour and bizarre delusions and is named "disorganisation". Class three has high conditional probabilities for items associated with a bipolar upswing and so is named "mania". Class four has the highest conditional probabilities for positive symptoms, but also scores highly on items associated with depression, and so is named "reality distortion/depression". The latent class conditional probabilities are shown in table R12, with the principal component loadings of the principal components analysis shown for comparison.

Table R12: Latent classes and principal components

	Principal component loadings				Latent class conditional probabilities			
	Mania	Reality distortion	Depression	Disorganisation	one	two	three	four
Excessive activity	**.816**	-.248	.009	-.068	.12	.04	**.94**	.07
Pressured speech	**.813**	-.143	.008	-.036	.18	.18	**.90**	.17
Elevated mood	**.809**	-.168	.103	-.027	.19	.08	**.86**	.13
Thoughts racing	**.805**	-.130	-.029	-.055	.10	.15	**.86**	.13
Reduced need for sleep	**.767**	-.235	.001	-.137	.13	.01	**.88**	.10
Increased self-esteem	**.685**	.104	-.042	.147	.07	.19	**.64**	.22
Recklessness	**.644**	-.183	-.006	-.071	.03	.03	**.50**	.02
Increased sociability	**.622**	-.083	-.031	**.108**	.14	.13	**.77**	.16
Distractibility	**.572**	-.017	.013	.015	.03	.05	.38	.06
Grandiose delusions	**.542**	.207	-.118	.207	.03	.18	**.41**	.16
Irritable mood	**.354**	-.204	-.054	-.085	.28	.07	**.50**	.19
Thought echo	-.088	.119	-.040	.046	.03	**.05**	.02	.03
Weight gain	.089	.032	.057	-.011	.06	.07	**.15**	.08
Persecutory, jealous delusions and hallucinations	-.138	**.741**	-.003	.117	.06	.53	.21	**.80**
Delusions, hallucinations one week	-.097	**.712**	.005	.142	.08	.60	.32	**.88**
Widespread delusions	-.043	**.646**	-.130	.132	.23	**.71**	.40	**.84**
Well organised delusions	.030	**.588**	-.135	.223	.09	.56	.31	**.63**
Abusive/accusatory/persecutory voices	-.170	**.529**	.137	-.050	.21	.38	.19	**.66**
Persecutory delusions	-.121	**.532**	-.077	.142	.49	.80	.56	**.93**
Delusions of passivity	-.031	**.504**	.011	.210	.04	.24	.13	**.43**
Delusions of influence	.004	**.461**	-.070	.110	.16	.48	.33	**.62**
Bizarre delusions	.032	**.438**	-.146	.176	.11	**.40**	.22	.38
Non affective hallucinations any mode	-.099	**.394**	-.157	.163	.02	.37	.10	**.41**
Third person auditory hallucinations	-.155	**.394**	.081	.008	.08	.20	.05	**.37**
Thought insertion	-.011	**.392**	-.031	-.081	.02	.09	.05	**.20**
Thought broadcast	.007	**.365**	.005	-.011	.04	.10	.05	.22
Thought withdrawal	.002	**.360**	-.031	.049	.01	.11	.02	**.13**
Running commentary voices	-.120	**.262**	-.059	-.123	.01	.10	.01	**.19**
Dysphoria	.005	-.099	**.795**	-.120	**.96**	.09	.68	.91
Loss of pleasure	-.011	-.101	**.772**	-.093	**.87**	.14	.61	.87
Poor appetite	-.004	-.016	**.582**	-.061	**.56**	.12	.33	.49
Suicidal ideation	-.100	.096	**.514**	-.107	**.59**	.26	.40	*.66*
Initial insomnia	.021	.029	**.515**	.002	**.50**	.12	.28	.36
Loss of energy	.014	-.260	**.468**	-.004	**.56**	.03	.31	.28
Poor concentration	-.040	-.119	**.472**	-.155	**.72**	.19	.36	.49
Excessive self-reproach	-.058	.196	**.462**	-.069	**.23**	.01	.08	*.30*
Relationship psychotic/affective	.325	-.011	**.433**	-.041	.65	.02	**.70**	.10
Slowed activity	**.104**	-.056	**.438**	.149	**.18**	.04	.14	.12
Middle insomnia	.068	.151	**.431**	.072	**.56**	.39	.62	*.71*
Early morning wakening	.060	-.065	**.390**	-.134	**.27**	.04	.22	.23
Diurnal variation	.025	-.121	**.346**	-.082	**.26**	.01	.11	.12
Weight loss	-.030	-.053	**.352**	.083	**.49**	.12	.30	.40
Diminished libido	-.035	-.039	**.306**	.052	**.17**	.03	.06	.09
Delusions of guilt	-.092	.265	.271	-.098	.08	.03	.01	**.18**
Excessive sleep	.038	-.096	.221	.021	**.11**	.02	.09	.06
Agitated activity	-.049	-.126	.225	-.046	**.34**	.09	.17	.14
Nihilistic delusions	-.060	.058	.192	-.048	**.12**	.02	.05	.07
Increased appetite	.101	-.060	.184	-.068	.07	.01	**.08**	.05
Positive formal thought disorder	.036	.181	-.065	**.594**	.15	**.37**	.20	.27
Restricted affect	-.157	.076	.080	**.595**	.32	**.44**	.22	.42
Rapport	-.219	-.168	.011	**.542**	.07	**.18**	.17	.14
Inappropriate affect	.099	.060	-.072	**.544**	.15	**.45**	.36	.31
Blunted affect	-.143	-.035	.002	**.523**	.01	**.10**	0	.08
Speech difficult to understand	.169	.037	-.093	**.478**	.12	.22	**.26**	.10
Negative formal thought disorder	-.129	.023	-.040	**.436**	.10	**.20**	.04	.14
Catatonia	-.027	.097	.000	**.416**	0	**.13**	.06	.10
Bizarre behaviour	.096	.224	-.096	**.393**	.30	**.59**	.54	.57
Incoherent	.119	.028	-.063	**.381**	.01	.06	**.09**	.04
Lack of insight	.097	.178	-.182	.288	.38	**.79**	.67	.62
Other auditory hallucinations	-.009	.153	-.065	.257	.10	**.34**	.26	.33
Other primary delusions	-.076	.020	.128	.186	.05	.10	.07	**.16**
Primary delusional perception	.039	.081	-.050	.119	0	**.05**	0	.04

For principal components, significant values are shown in bold. For conditional probabilities, the highest probability is shown in bold, other values may be significant

Correspondence between the principal components analysis and latent class analysis

The analyses were compared in two ways. Firstly correlations were run between the component loadings and the conditional probabilities. The Spearman Rho values (all with n=62 since there were 62 loading items) significant beyond the 0.001 level were :

Mania to latent class three	0.572
Reality distortion to latent class two	0.600
Reality distortion to latent class four	0.490
Depression to latent class one	0.483
Depression to latent class two	-0.499
Disorganisation to latent class two	0.551

The values of all correlations in the analysis are shown in table R13

Table R13: Correlations between Principal Components Analysis factor scores and Latent class probabilities

	Principal component	Correlation coefficient	significance
Latent class one	Mania	0.044	0.732
	Reality distortion	-0.286*	0.024
	Depression	0.483**	<0.001
	Disorganization	-0.289*	0.023
Latent class two	Mania	-0.274*	0.031
	Reality distortion	0.600**	<0.001
	Depression	-0.499**	<0.001
	Disorganization	0.551**	<0.001
Latent class three	Mania	0.572**	<0.001
	Reality distortion	-0.312*	0.014
	Depression	-0.012	0.924
	Disorganization	-0.141	0.274
Latent class four	Mania	-0.379*	0.002
	Reality distortion	0.490**	0.001
	Depression	0.002	0.988
	Disorganization	0.049	0.704

*Correlation is significant at the 0.05 level ** Correlation is significant at the 0.01 level

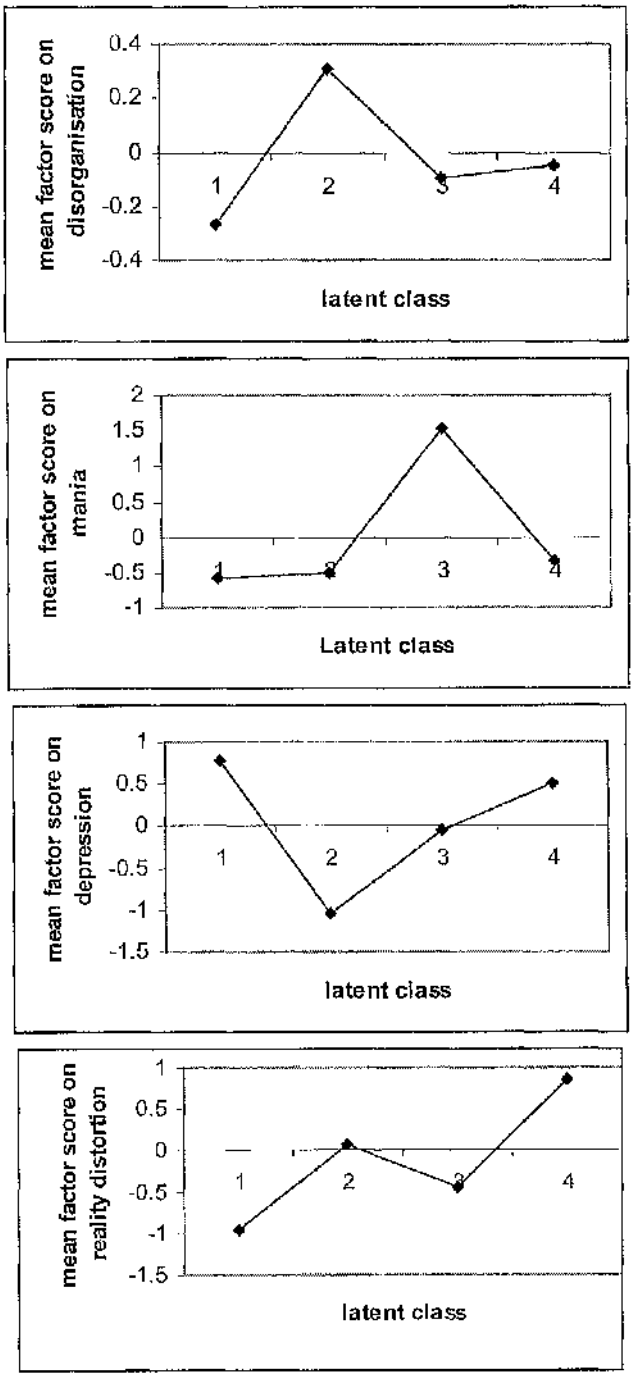
Secondly, the mean values of the principal component scores for the latent classes were compared using one-way ANOVAs followed by the Scheffé test. The overall F values are all significant at the 0.001 level or better. On mania class three differs from all the other classes. On reality distortion all the groups differ from each other. On depression classes one and four are not significantly different, but classes two and three differ from all the rest. Finally, on disorganisation, class two is different from class one. All these *post hoc* comparisons are significant beyond the 0.005 level (Table R14). Thus there is good correspondence between class two and the disorganisation factor and between class three and mania. Subjects in class four and class one score high on depression. Those in class four also score highly on reality distortion. This is illustrated in Figure R8.

Table R14: mean principal components scores for the latent classes

Dependent Variable	Latent class	Latent class	Mean Difference	Significance.	95% Confidence Interval	
					Lower	Upper
mania	one	2.000	-0.084	0.800	-0.319	0.151
		3.000	-2.118	**<0.001**	-2.364	-1.872
		4.000	-0.257	0.021	-0.488	-0.027
	two	1.000	0.084	0.800	-0.151	0.319
		3.000	-2.034	**<0.001**	-2.257	-1.811
		4.000	-0.174	0.135	-0.380	0.032
	three	1.000	2.118	**<0.001**	1.872	2.364
		2.000	2.034	**<0.001**	1.811	2.257
		4.000	1.860	**<0.001**	1.642	2.079
	four	1.000	0.257	0.021	0.027	0.488
		2.000	0.174	0.135	-0.032	0.380
		3.000	-1.860	**<0.001**	-2.079	-1.642
reality distortion	one	2.000	-1.024	**<0.001**	-1.342	-0.706
		3.000	-0.517	**<0.001**	-0.851	-0.184
		4.000	-1.815	**<0.001**	-2.127	-1.502
	two	1.000	1.024	**<0.001**	0.706	1.342
		3.000	0.506	**<0.001**	0.204	0.809
		4.000	-0.791	**<0.001**	-1.070	-0.512
	three	1.000	0.517	**<0.001**	0.184	0.851
		2.000	-0.506	**<0.001**	-0.809	-0.204
		4.000	-1.297	**<0.001**	-1.593	-1.001
	four	1.000	1.815	**<0.001**	1.502	2.127
		2.000	0.791	**<0.001**	0.512	1.070
		3.000	1.297	**<0.001**	1.001	1.593
depression	one	2.000	1.817	**<0.001**	1.514	2.121
		3.000	0.836	**<0.001**	0.518	1.153
		4.000	0.274	0.085	-0.024	0.571
	two	1.000	-1.817	**<0.001**	-2.121	-1.514
		3.000	-0.982	**<0.001**	-1.270	-0.693
		4.000	-1.544	**<0.001**	-1.810	-1.278
	three	1.000	-0.836	**<0.001**	-1.153	-0.518
		2.000	0.982	**<0.001**	0.693	1.270
		4.000	-0.562	**<0.001**	-0.844	-0.280
	four	1.000	-0.274	0.085	-0.571	0.024
		2.000	1.544	**<0.001**	1.278	1.810
		3.000	0.562	**<0.001**	0.280	0.844
disorganisation	one	2.000	-0.578	**0.002**	-0.996	-0.161
		3.000	-0.174	0.740	-0.612	0.263
		4.000	-0.221	0.515	-0.631	0.189
	two	1.000	0.578	**0.002**	0.161	0.996
		3.000	0.404	0.045	0.007	0.801
		4.000	0.357	0.059	-0.009	0.724
	three	1.000	0.174	0.740	-0.263	0.612
		2.000	-0.404	0.045	-0.801	-0.007
		4.000	-0.046	0.990	-0.435	0.343
	four	1.000	0.221	0.515	-0.189	0.631
		2.000	-0.357	0.059	-0.724	0.009
		3.000	0.046	0.990	-0.343	0.435

the mean differences significant at the 0.005 level are shown in bold

Figure R8: The correspondence between latent classes and mean values of the principal components scores



Validation of the dimensions and classes

Relationship between Factor scores and external variables

Initially the relationship between factor scores and the external variables was explored by determining correlation co-efficients specifically Pearson Moment for continuous variables and Spearman Rho for categorical variables. This univariate analysis indicated which of the variables of interest correlated with the factors (Table R15), indicating which items should be selected for multivariate analysis. Multiple regression analysis was used to determine the effects of the factor scores on the age of onset, fertility and deliberate self-harm. In addition to the four factor scores, other variables known to influence these outcome variables were added to the model as detailed below. Logistic regression was used to analyse fertility and deliberate self harm and the results for statistically significant variables are shown in Table R16.

Table R15: Correlation coefficients between factor scores and variables of interest

(Pearson correlation for continual variables and Spearman Rho values for categorical variables)

Variable	Principal Components			
	Mania	Reality distortion	Depression	Disorganisation
Age at onset	-0.005	-0.061	0.06	**-.270****
Onset mode	**-0.263****	-0.036	-0.025	**0.228****
Female sex	**0.116***	**-0.129***	**0.174****	**-0.126***
single	**-0.164***	0.106*	**-0.200****	**0.143****
Poor social adjustment	**-0.180****	-0.05	**-0.42****	**0.165****
Premorbid personality disorder	-0.087	-0.064	-0.013	0.083
Family history of sz	-0.086	0.066	-0.025	0.071
Family history of other psychiatric disorder	0.071	-0.0653	**0.121***	-.023
Course of disorder	-0.126	**0.110***	0.019	**0.309****
ECT ever	**0.129***	0.017	**0.230****	**0.237****
Ever detained	**0.168****	**0.209***	**-0.123***	**0.210****
DSH	-0.024	0.086	**0.286****	0.020
Fertility	**0.129***	-0.077	**0.223****	**-0.223****
Time ill	0.091	**-0.107***	**0.150****	**0.238****
Offspring	**0.146****	-0.068	**0.251****	**-0.221****
Family total affected	0.068	-0.045	0.088	**-0.126***
Psychosis family history	0.011	-0.006	0.021	-0.016
Neurosis family history	0.059	0.028	0.068	**-0.174****
Forensic history	-0.047	**-0.144****	**0.158****	**-0.165****
FH addiction	0.012	-.084	0.042	-0.044
FH other disorder	0.099	-0.062	0.073	-0.027
FH suicide	-0.012	-0.060	0.026	-0.08
Learning disability	-0.084	-0.097	**-0.141****	-0.010
FH learning disability	0.032	-0.040	-0.068	**-0.145***

*indicates p value significant at 0.05 level and ** indicates p value significant at 0.01 level, both shown in bold

Regression Analysis

Relationship between factors and age at onset

Outcome	Predictor	Coefficient	P
Age at onset			
	Female gender	2.253	0.038
	Mania	-0.1015	0.846
	Reality distortion	-0.4910	0.352
	Depression	0.5956	0.260
	Disorganisation	-2.6858	<0.001

Interpretation: Gender and disorganisation are significant in the logistic regression model. The age of onset is significantly lower for males than females (mean age of onset for males is 26.8 years and for females, 30.1 years). The effect of disorganisation is that as the scores increase, the age at onset decreases.

Relationship between factors and DSH

Outcome	Variable	P-value	Odds ratio	95% CI
DSH	Female gender	0.434	0.84	0.54, 1.31
	Time ill	0.487	1.01	0.99,1.03
	Mania	0.206	0.87	0.70, 1.08
	Reality distortion	0.112	1.19	0.96, 1.48
	Depression	<0.001	1.82	1.45, 2.29
	Disorganisation	0.886	0.98	0.79, 1.23

Interpretation: The only variable having a significant effect on DSH is depression. As the depression scores increase, the odds of DSH increase.

Relationship between factors and fertility

Outcome	Variable	P-value	Odds ratio	95% CI
Fertility	Female gender	0.001	2.20	1.40, 3.44
	Age of onset (years)	<0.001	1.04	1.02, 1.07
	Mania	0.012	1.33	1.07, 1.66
	Reality distortion	0.449	0.92	0.73, 1.15
	Depression	<0.001	1.50	1.20, 1.89
	Disorganisation	0.016	0.75	0.59, 0.95

Interpretation: Gender, age at onset, mania, depression and disorganisation are all significantly associated with fertility. Females are more likely to have had children. As age of onset increases by each year, the odds of having children increase. As mania and depression scores increase the odds of having children increase and as disorganisation scores increase the odds of having had children decrease.

Analysis of fertility for each gender separately: men

Outcome	Variable	P-value	Odds ratio	95% CI
Fertility	Age of onset	0.003	1.06	1.02, 1.10
	Mania	0.049	1.40	1.0, 1.96
	Reality distortion	0.511	0.90	0.65, 1.24
	Depression	0.050	1.41	1.0, 1.99
	Disorganisation	0.079	0.74	0.53, 1.04

Interpretation: For men the significant variables associated with fertility are age of onset, mania and depression. As age of onset increases, the odds of having had children increases. As mania and depression scores increase, the odds of having had children increase.

Analysis of fertility for each gender separately: women

Outcome	Variable	P-value	Odds ratio	95% CI
Fertility	Age of onset	0.025	1.03	1.0,1.06
	Mania	0.109	1.28	0.95, 1.72
	Reality distortion	0.758	0.95	0.69, 1.31
	Depression	0.006	1.56	1.14, 2.13
	Disorganisation	0.131	0.77	0.55, 1.08

Interpretation: For females the significant variables associated with fertility are age of onset and depression. As age of onset increases, the odds of having had children increases. As depression scores increase, the odds of having had children increase.

Table R16: Summary of logistic regression analysis results

Outcome	Variable	P-value	Odds ratio	95% CI
Fertility	Gender	0.001	2.20	(1.40, 3.44)
	Age of onset	<0.001	1.04	(1.02, 1.07)
	Factor 1 (Mania)	0.012	1.33	(1.07, 1.66)
	Factor 3 (Depression)	<0.001	1.50	(1.20, 1.89)
	Factor 4 (Disorganisation)	0.016	0.75	(0.59, 0.95)
Deliberate self- harm	Factor 3 (Depression)	<0.001	1.82	(1.45, 2.29)

Summary of regression analysis

Age at onset

Since the age at onset is known to differ between males and females, gender was included as a possible predictor in the multiple regression model along with the factor scores. Gender ($p=0.038$) and the disorganisation factor ($p<0.001$) were found to be significant in predicting the age of onset with the average age of onset of illness for males being 26.7 years and 30.1 years for females. For every one unit increase in the disorganisation factor scores, there was a decrease in age at onset of 2.7 years.

Fertility

The logistic regression model for fertility included gender and age of onset as possible predictors in addition to the factor scores. Gender, age at onset and factors mania, depression and disorganisation were significantly associated with fertility. Females are more likely to have had children and the odds of having had children increase slightly with age. The mania and depression factors are associated with increasing fertility and the disorganisation factor is associated with decreasing fertility.

Deliberate Self Harm

The relationship between deliberate self-harm and factor scores was investigated using logistic regression with gender and length of time ill included in the model. The depression factor was the only significant variable where the odds of DSH increased by 1.82 as the factor score increased by one unit. Note that there is a potential confounder in comparing the factor scores with evidence of DSH since OPCRIT item 43 scores for suicidal ideation, and the two items of information may be considered paraphrases of each other. However the definitions are not exactly the same as OPCRIT allows coding of such behaviour only during an episode of illness. Also, this item scores positively even if no DSH occurs but suicidal ideation is present. Thus not everyone who was considered to have scored positively for DSH scored positively on OPCRIT for suicidal ideation, and vice versa. To be certain that the association between the factor scores and DSH was not confounded by this, the principal components analysis was re-run omitting OPCRIT suicidal ideation, and correlations between the factors repeated. The factor loadings were very similar and the same positive correlation was found between factor 2 (depression) and DSH.

Relationship between latent classes and external variables

The relationship between the four latent classes and variables of interest were explored initially using a simple measure of association, χ^2 (and using Fisher's exact test when necessary). The results of associations between the latent classes and premorbid characteristics are shown in table R17a, with the relationship between latent classes and family history and reproduction shown in table R17b. Results relating to the relationship between illness characteristics and latent classes are shown in table R17c, with forensic history, substance misuse and use of the Mental Health Act in table R17d.

Age of onset

There was no difference between the latent classes in age of onset for women, but there was a clear difference for men with the disorganisation class having a much earlier age of onset (mean of 23.8 years compared to 31 years in women). Indeed it is this latent class which appears to almost completely account for the difference in age of onset between the sexes.

Gender

The latent classes reveal that women are over-represented in the depression and bipolar classes and the disorganisation class is predominantly male with the reality distortion/depression class more evenly distributed.

Fertility

Within the latent classes there is a significant difference in fertility, with the disorganisation class being the least fertile.

Deliberate self harm (DSH)

Members of both the depression and the reality distortion/depression classes are likely to have harmed themselves, with members of the disorganisation class being the least likely to have done so.

Table R17a: Relationship between premorbid characteristics and latent classes

Key outcome measures			Depression n (%)	Disorganisation n (%)	Bipolar n (%)	Reality Distortion/ Depression n (%)	Statistical tests*
Gender		Male	29 (40%)	69 (64%)	32 (37%)	64 (54%)	$\chi^2(3)=18.2$ p<0.001
		Female	44 (60%)	39 (36%)	55 (63%)	55 (46%)	
Season of birth		Summer (Apr-Sep)	38 (52%)	56 (52%)	46 (53%)	64 (54%)	$\chi^2(3)=0.100$ p=0.992
		Winter (Oct-Mar)	35 (48%)	52 (48%)	41 (47%)	55 (46%)	
Evidence of poor pre-morbid social adjustment		No	61 (88%)	84 (84%)	83 (97%)	105 (91%)	$\chi^2(3)=8.5$ p=0.037
		Yes	8 (12%)	16 (16%)	3 (3%)	10 (9%)	
Evidence of personality disorder prior to onset of psychosis		No	63 (91%)	90 (91%)	81 (94%)	111 (96%)	NS
		Yes	6 (9%)	9 (9%)	5 (6%)	5 (4%)	
Confounders		None	58 (81%)	78 (74%)	76 87%)	86 (73%)	NS
		Organic confounder	3 (4%)	8 (8%)	4 (5%)	5 (4%)	
		Substance misuse	11 (15%)	19 (18%)	7 (8%)	27 (23%)	
Age at onset	**Males:**	mean/ median	29.5/29.5	23.8/23.0	28.0/25.5	28.3/28.0	H=11.49 p=0.009
		standard error	1.93	0.97	1.87	1.14	
	Females:	mean/ median	29.3/27.0	31.0/27.0	30.1/27.0	30.0/27.0	NS
		standard error	1.68	1.95	1.53	1.62	

*Tests performed: χ^2 test on categorical variables, Kruskal-Wallis test used on continuous variables, NS indicates a non-significant result at the 5% level

Table R17b: Relationship between family history and latent classes

Key outcome measures		Depression n (%)	Disorganisation n (%)	Bipolar n (%)	Reality Distortion/ Depression n (%)	Statistical tests
Fertility	No children	29 (40%)	77 (71%)	34 (39%)	60 (50%)	$\chi^2(3)=26.4$, p<0.001
	At least one child	44 (60%)	31 (29%)	53 61%)	59 (50%)	
Married or lived as married	No	23 (32%)	66 (61%)	21 (24%)	49 (41%)	$\chi^2(3)=31.0$, P<0.001
	Yes	50 (68%)	42 (39%)	66 (76%)	70 (59%)	
History of schizophrenia in 1st or 2nd degree relative	No	66 (92%)	93 (92%)	77 (96%)	102 (86%)	NS
	yes	6 (8%)	8 (8%)	3 (4%)	16 (14%)	
History of other disorder in 1st or 2nd degree relative	No	40 (55%)	72 (73%)	44 (54%)	79 (68%)	$\chi^2(3)=9.8$, P=0.020
	Yes	33 (45%)	27 (27%)	37 (46%)	38 (32%)	
History of psychosis in 1st Or 2nd or 3rd degree relative (n=300)	No	47 (81%)	68 (85%)	55 (76.4%)	73 (81.1%)	$\chi^2(3)=1.83$, P=0.615
	yes	11 (19%)	12 (15%)	17 (23.6%)	17 (18.9%)	
History of neurosis in 1st or 2nd or 3rd degree relative(n=309)	No	33 (57.9%)	64 (74.4%)	50 (68.5%)	64 (68.8%)	$\chi^2(3)=4.35$, p=0.228
	yes	24 (42.1%)	22 (22.4%)	23 (31.5%0	29 (31.2%)	
History of addiction in 1st Or 2nd or 3rd degree relative (n=299)	No	45 (81.8%)	68 (81.1%)	55 (80.9%)	79 (85.9%)	$\chi^2(3)=1.006$, p=0.811
	yes	10 (18.2%)	16 (19%)	13 (19.1%)	13 (14.1%)	
History of other psychiatric disorder in 1st 2nd or 3rd degree relative (n=277)	No	35 (68.6%)	57 (80.3%)	41 (61.2%)	64 (72.7%)	$\chi^2(3)=6.38$, p= 0.093
	Yes	16 (31.4%)	14 (19.7%)	26 (38.8%)	24 (27.3%)	

Table R17c: Relationship between illness and treatment characteristics and latent classes

Key outcome measures		Depression n (%)	Disorganisation n (%)	Bipolar n (%)	Reality Distortion/ Depression n (%)	Statistical tests
Deliberate Self Harm	No	36 (49%)	82 (76%)	55 (63%)	53 (45%)	$\chi^2(3)=26.3$, $p<0.001$
	Yes	37 (51%)	26 (24%)	32 (37%)	66 (55%)	
Onset Mode	<1 week	5 (11%)	10 (15%)	20 (38%)	10 (12%)	$\chi^2(3)=30.3$, $p<0.001$
	Within 1 month	9 (20%)	11 (16%)	14 (26%)	23 (28%)	
	Gradual up to 6 months	13 (30%)	13 (19%)	11 (21%)	24 (29%)	
	Insidious > 6 months	17 (39%)	34 (50%)	8 (15%)	26 (31%)	
Difficult Rapport	No	63 (86%)	87 (81%)	81 (94%)	103 (87%)	NS
	Yes	10 (14%)	20 (19%)	5 (6%)	16 (13%)	
Deterioration (does not regain function after acute episode)	No	37 (56%)	37 (37%)	51 (62%)	42 (40%)	$\chi^2(3)=15.8$, $p=0.001$
	Yes	29 (44%)	62 (63%)	31 (38%)	64 (60%)	
Course	Single episode (good recovery)	2 (3%)	12 (12%)	3 (4%)	6 (5%)	$\chi^2(3)=47.6$, $p<0.001$
	Multiple episodes (good recovery in between)	26 (38%)	21 (21%)	47 (56%)	30 (26%)	
	Multiple episodes (partial recovery in between)	26 (38%)	25 (25%)	23 (28%)	39 (34%)	
	Continuous chronic illness	14 (21%)	42 (42%)	10 (12%)	40 (35%)	
ECT ever received	No	53 (73%)	88 (81%)	55 (62%)	78 (66%)	$\chi^2(3)=10.8$, $p=0.013$
	Yes	20 (27%)	20 (19%)	33 (38%)	41 (34%)	

Table R17d Relationship between use of mental health act, forensic history, substance misuse and latent classes

Key outcome measures		Depression n (%)	Disorganisation n (%)	Bipolar n (%)	Reality Distortion/ Depression n (%)	Statistical tests
Ever detained under Mental Health Act	No	54 (74%)	43 (40%)	35 (40%)	52 (44%)	$\chi^2(3)=25.6$, p=0.013
	Yes	19 (26%)	65 (60%)	52 (60%)	67 (56%)	
Forensic involvement	No	61 (85%)	64 (60%)	62 (71%)	80 (68%)	$\chi^2(3)=12.9$, p=0.005
	Yes	11 (9%)	43 (37%)	25 (21%)	38 (32%)	
Street drug exposure	Never	63 (86.3%)	78 (72.2%)	72 (82.8%)	91 (77.1%)	$\chi^2(3)=6.26$, p=0.100
	Used sometime	10 (13.7%)	30 (27.8%)	15 (17.2%)	27 (22.9%)	
Alcohol use	None	51 (69.9%)	71 (65.7%)	63 (72.4%)	64 (54.2%)	$\chi^2(3)=8.8$, p=0.032
	Within limit	22 (30.1%)	37 (34.3%)	24 (27.6%)	54 (45.8%)	

Logistic Regression Analysis

In an attempt to quantify these observed effects, while correcting for confounding variables, multivariate analysis was performed. Nominal logistic regression was applied to the data with latent class as the outcome to determine the effects of probable predictor variables while correcting for other confounding variables. From Tables R17a, R17b, R17c and R17d the following variables were selected for inclusion in the logistic regression model: age of onset, gender, fertility, DSH, onset mode, evidence of poor premorbid social adjustment, history of other disorder in 1st or 2nd degree relative, deterioration, course and ECT ever received. Key comparisons of these variables with latent class 1 (depression) are given in Table R18 below:

Table R18: Nominal logistic regression analysis comparing latent classes

Comparison	Variable	Odds ratio	95% CI	P-value
Depression vs Reality distortion/depression	Female gender	2.41	(0.91, 6.38)	0.078
	Social isolation	5.27	(1.26, 21.97)	0.023
Depression vs Bipolar	DSH	2.95	(0.97, 8.98)	0.057
	Social isolation	10.09	(0.93, 109.75)	0.058
Depression vs Disorganisation	Female gender	4.89	(1.62, 14.75)	0.005
	Fertility	2.87	(0.88, 9.38)	0.081
	DSH	4.60	(1.52, 13.88)	0.007
	Social Isolation	5.15	(1.27, 20.79)	0.022

Depression vs reality distortion/depression

Men are approximately 2.5 times more likely to be in the reality distortion/disorganisation class compared to the depression class. Subjects in the reality distortion/disorganisation class are about five times more likely to be socially isolated prior to illness onset compared with those in the depression class.

Depression vs bipolar

The risk of a person harming themselves is almost three times less likely in the bipolar class compared to the depression class. The odds ratio for premorbid social isolation indicates that people in the bipolar class are almost ten times less likely to have been socially isolated compared to the depression class prior to the onset of their illness.

Depression vs disorganisation

Men are almost five times more likely to be in the disorganisation class than the depression class. Subjects in the disorganisation class are almost three times less likely to have children than those in the depression class and more than four times less likely to have harmed themselves. Members of the disorganisation class are about five times more likely to have been socially isolated prior to illness onset.

Comparison of DSM-III-R Diagnoses and the empirically derived dimensions and classes

Comparison of the principal components and DSM-III-R diagnoses

The mean values for the principal component scores for each DSM-III-R diagnosis are compared by using one way analyses of variance followed by the Scheffé test. The overall F values are significant at the 0.001 level or better. The comparisons are detailed in table R19 and illustrated in figure R9.

Table R19: Mean principal components scores for the DSM-III-R diagnoses* (short form) (continued on next page)

Dependent Variable	DSM-III-R	DSM-III-R	Mean Difference	Significance.	95% Confidence Interval	
					Lower Bound	Upper Bound
Mania	Depression	Bipolar	-1.999	**<0.001**	-2.352	-1.647
		Sz'aff	-0.838	**<0.001**	-1.266	-0.410
		Sz	-0.141	0.753	-0.457	0.175
		Atypical	-0.143	0.861	-0.531	0.245
	Bipolar	Depression	1.999	**<0.001**	1.647	2.352
		Sz'aff	1.161	**<0.001**	0.766	1.557
		Sz	1.858	**<0.001**	1.587	2.129
		Atypical	1.856	**<0.001**	1.504	2.208
	Sz'aff	Depression	0.838	**<0.001**	0.410	1.266
		Bipolar	-1.161	**<0.001**	-1.557	-0.766
		Sz	0.697	**<0.001**	0.333	1.061
		Atypical	0.695	**<0.001**	0.267	1.123
	Sz	Depression	0.141	0.753	-0.175	0.457
		Bipola	-1.858	**<0.001**	-2.129	-1.587
		Sz'aff	-0.697	**<0.001**	-1.061	-0.333
		Atypical	-0.002	1.000	-0.318	0.314
	Atypical	Depression	0.143	0.861	-0.245	0.531
		Bipolar	-1.856	**<0.001**	-2.208	-1.504
		Sz'aff	-0.695	**<0.001**	-1.123	-0.267
		Sz	0.002	1.000	-0.314	0.318
Reality distortion	Depression	Bipolar	0.059	0.998	-0.423	0.541
		Sz'aff	-1.281	**<0.001**	-1.867	-0.695
		Sz	-0.904	**<0.001**	-1.336	-0.471
		Atypical	-0.399	0.252	-0.930	0.133
	Bipolar	Depression	-0.059	0.998	-0.541	0.423
		Sz'aff	-1.340	**<0.001**	-1.882	-0.798
		Sz	-0.962	**<0.001**	-1.333	-0.592
		Atypical	-0.457	0.074	-0.939	0.025
	Sz'aff	Depression	1.281	**<0.001**	0.695	1.867
		Bipolar	1.340	**<0.001**	0.798	1.882
		Sz	0.378	0.242	-0.121	0.876
		Atypical	0.883	**<0.001**	0.297	1.469
	Sz	Depression	0.904	**<0.001**	0.471	1.336
		Bipolar	0.962	**<0.001**	0.592	1.333
		Sz'aff	-0.378	0.242	-0.876	0.121
		Atypical	0.505	**0.012**	0.072	0.938
	Atypical	Depression	0.399	0.252	-0.133	0.930
		Bipolar	0.457	0.074	-0.025	0.939
		Sz'aff	-0.883	**<0.001**	-1.469	-0.297
		Sz	-0.505	**0.012**	-0.938	-0.072

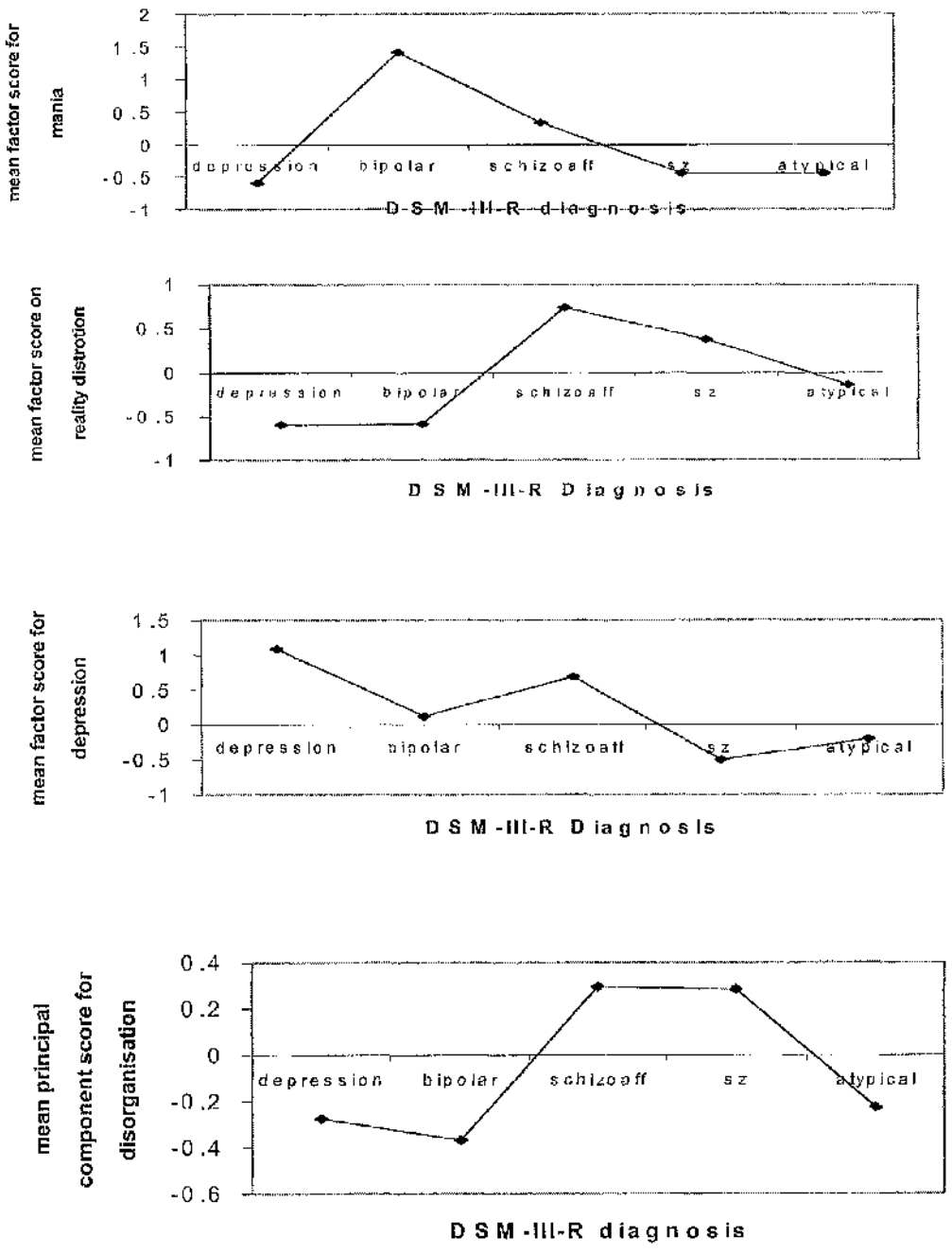
Mean differences significant at the 0.05 level are shown in bold.
*the DSM-II-R classes are shown in table R3

Table R19: Mean principal components scores for DSM-III-R diagnoses* (short form) (continued from previous page)

	DSM-III-R *	DSM-III-R*	Mean Difference	Significance	95% Confidence Interval	
Dependent Variable					Lower Bound	Upper Bound
depression	Depression	Bipolar	1.119	**<0.001**	0.682	1.556
		Sz'aff	0.580	0.024	0.049	1.111
		Sz	1.730	**<0.001**	1.338	2.123
		Atypical	1.490	**<0.001**	1.009	1.972
	Bipolar	Depression	-1.119	**<0.001**	-1.556	-0.682
		Sz'aff	-0.539	**0.022**	-1.030	-0.048
		Sz	0.611	**<0.001**	0.275	0.947
		Atypical	0.371	0.143	-0.066	0.808
	Sz'aff	Depression	-0.580	**0.024**	-1.111	-0.049
		Bipolar	0.539	**0.022**	0.048	1.030
		Sz	1.150	**<0.001**	0.699	1.602
		Atypical	0.910	**<0.001**	0.379	1.441
	Sz	Depression	-1.730	**<0.001**	-2.123	-1.338
		Bipola	-0.611	**<0.001**	-0.947	-0.275
		Sz'aff	-1.150	**<0.001**	-1.602	-0.699
		Atypical	-0.240	0.466	-0.632	0.152
	Atypical	Depression	-1.490	**<0.001**	-1.972	-1.009
		Bipolar	-0.371	0.143	-0.808	0.066
		Sz'aff	-0.910	**<0.001**	-1.441	-0.379
		Sz	0.240	0.466	-0.152	0.632
disorganisation	depression	Bipolar	0.056	0.999	-0.470	0.582
		Sz'aff	-0.607	0.073	-1.246	0.032
		Sz	-0.540	**0.015**	-1.013	-0.068
		Atypical	-0.064	0.998	-0.643	0.516
	Bipolar	Depression	-0.056	0.999	-0.582	0.470
		Sz'aff	-0.663	**0.018**	-1.254	-0.072
		Sz	-0.596	**<0.001**	-1.001	-0.192
		Atypical	-0.119	0.974	-0.645	0.407
	Sz'aff	Depression	0.607	0.073	-0.032	1.246
		Bipolar	0.663	**0.018**	0.072	1.254
		Sz	0.066	0.998	-0.477	0.610
		Atypical	0.543	0.143	-0.096	1.183
	Sz	Depression	0.540	**0.015**	0.068	1.013
		Bipolar	0.596	**<0.001**	0.192	1.001
		Sz'aff	-0.066	0.998	-0.610	0.477
		Atypical	0.477	**0.046**	0.005	0.949
	atypical	Depression	0.064	0.998	-0.516	0.643
		Bipolar	0.119	0.974	-0.407	0.645
		Sz'aff	-0.543	0.143	-1.183	0.096
		Sz	-0.477	**0.046**	-0.949	-0.005

Mean differences significant at the 0.05 level are shown in bold.
*the DSM-III-R classes are shown in table R3

Figure R9: The correspondence between the mean values of the principal components scores and DSM-III-R diagnoses



Description of comparison of principal components scores for DSM-III-R diagnoses

On the mania dimension, a diagnosis of bipolar disorder or schizoaffective disorder are different to all the rest. On the reality distortion dimension, schizoaffective disorder and schizophrenia are different to a diagnosis of depression, bipolar disorder or atypical

psychosis. For the dimension of depression, there is a more complex picture with a diagnosis of depression different to bipolar, schizophrenia and atypical. On this dimension bipolar is different to all except atypical psychosis. Schizoaffective disorder is different to all and schizophrenia is different to depression, bipolar and schizoaffective disorder. Atypical psychosis is different to depression and schizoaffective disorder. On the disorganisation dimension schizophrenia is different to all except schizoaffective disorder.

Comparison of latent classes and DSM-III-R Diagnoses

The distribution of the long form of DSM-III-R diagnoses on the latent classes is shown in Table R20, with the most common latent class for each DSM-III-R diagnosis shown in bold.

Table R20 The latent classes, demographic data and DSM III R diagnoses*

	A Depression N=73	B Disorganisation N=108	C Bipolar N=87	D Depression/Reality distortion N=119	Total N=387	P
Age at time of data collection (mean, sd)	49.5 (11.4)	43.9 (12.4)	51.3 (13.0)	48.8 (13.5)	48.1 (13.0)	<.001
Bipolar disorder (N, % of total with the diagnosis)	**7 63.6%**	-	4 36.4%	-	11	
Depression with psychosis	**42 79.2%**	-	-	11 20.8%	53	
Delusional disorder	**5 55.6%**	4 44.4%	-	-	9	
Schizophreniform disorder	1 11.1%	**5 55.6%**	-	3 33.3%	9	
Schizophrenia	9 6.3%	**83 57.6%**	2 1.4%	50 34.7%	144	
Mania	-	-	**8 100.0%**	-	8	
Mania with psychosis	-	-	**33 97.1%**	1 2.9%	34	
Bipolar with psychosis	-	-	**28 96.6%**	1 3.4%	29	
Schizoaffective Manic	-	1 11.1%	**6 66.7%**	2 22.2%	9	
Schizoaffective depression	-	-	-	**23 100.0%**	23	
Schizoaffective Bipolar	-	-	2 40.0%	**3 60.0%**	5	
Atypical psychosis	9 17.0%	15 28.3%	4 7.5%	**25 47.2%**	53	
Total	73 18.9%	108 27.9%	87 22.5%	119 30.7%	387	

*these are original DSM-III-R diagnoses, ie not condensed.

Distribution of First Rank Symptoms

The distribution of first rank symptoms was examined with respect to gender, latent classes and DSM-III-R diagnoses.

Distribution of first rank symptoms by gender

For the entire study population, first rank symptoms were more common in men (table R21)

Table R21 First rank symptoms by gender

	Men	Women	Statistical test
No first rank symptoms	87 (44.8%)	116 (60.1)%	$\chi^2(1)= 9.0$
At least one first rank symptom	107 (58.2%)	77 (39.9%)	P=0.003

Distribution of first rank symptoms by latent class and DSM-III-R diagnoses

The occurrence of any first rank symptom as defined in OPCRIT was noted for both latent classes and the condensed DSM-III-R diagnoses as shown in table R22

Table R22: First rank symptoms by latent class and DSM-III-R Diagnoses

Latent class	Schneider positive n(%)	Statistical test
Depression	14 (19.2%)	
Disorganisation	56 (51.9%)	
Bipolar	19 (21.8%)	
Reality distortion/depression	95 (79.8%)	$\chi^2(3)=97.2$, $p<0.001$
DSM-III-R Diagnosis*		
Unipolar depression	16 (30.2%)	
Bipolar disorder	16 (19.5%)	
Schizoaffective	27 (73%)	
Schizophrenia	101 (62.3%)	
Atypical psychosis	24 (45.3%)	$\chi^2(4)=56.17$, $p<0.001$

*The DSM-III-R Diagnoses have been condensed as follows: "unipolar depression" includes mjor depression and depression with psychosis; "bipolar disorder" includes hypomania, mania, bipolar disorder, mania with psychosis and bipolar with psychosis; "schizoaffective" includes schizoaffective manic, schizoaffective depressed and schizoaffective bipolar; "schizophrenia includes schizophrenia, delusional disorder and schizophreniform disorder; "atypical psychosis" is DSM-III-R atypical psychosis only.

Thus for both latent classes and DSM-III-R diagnoses first rank symptoms are found in every diagnostic category with an uneven distribution and are most common in reality distortion/ depression and schizoaffective disorder.

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Discussion

Overview

The Hamilton study of psychosis attempted to identify a treated prevalence adult population and describe the characteristics of those identified with respect to psychosocial variables and gender effects. The main goal was to use psychopathological symptoms to define dimensions and classes of psychosis and determine if these identified entities had clinical validity. The underlying principle of the study was to use an atheoretical, data-driven approach to classifying psychosis in a representative sample. Data were used as raw as possible, without grouping items of psychopathology together and the statistical techniques used were model free. The need for the study was justified on the grounds that the current nosological status of the psychoses may be impeding research on the aetiological and pathophysiological substrates underlying these disorders, with advances in identifying susceptibility genes being of particular relevance.

A description of the study population, and the relationship to the variables of interest will be followed by a summary of the empirically defined classes and dimensions. These will be discussed in the context of the literature. The findings of the study will be examined with respect to the following questions. First, are the empirically defined classes and dimensions valid and how do they compare with DSM-III-R diagnoses? Second, what are the limitations of the study, and how might these be overcome? What future work might arise from the study and how might the study inform the future direction of this field of research? Third, does the study provide evidence to support the Kraepelinian dichotomy? What can be concluded from this empirical population based approach?

Description of psychosis in a population based sample and an examination of gender differences

Demographics

In total, 387 people were identified, with an equal gender ratio, and subjects had been ill on average for almost 15 years prior to assessment, with men being assessed at a significantly younger age than women (41.1years vs 44.6 years). The population was shown to be stable with the majority being born in Scotland (approximately 70% born locally) and almost exclusively Caucasian.

Substance misuse

Almost 20% were probably using alcohol or street drugs to the detriment of their health. The lifetime prevalence of substance misuse in schizophrenia in Western samples is about 40–60% (Cantor-Graae *et al.* 2001). The Australian low prevalence study, a population based study examining the same range of psychotic disorders as in the Hamilton study, found a lifetime diagnosis of substance abuse or dependence in 39.8% of the sample (Kavanagh *et al.* 2004). The reported number of people misusing substances in the Hamilton study is likely to be a substantial underestimate. No attempt was made to verify presence or absence of this by interview. A previous attempt to do so in a random 1 in 3 sample of the 1993 cohort however did not produce results that were much higher (unpublished data). Either the people in the Hamilton district have very much lower rates of substance misuse than other populations, or (as seems more likely) approaches by psychiatric researchers who are clearly identified with services is an unproductive means of eliciting accurate data on substance misuse. Since the rate of substance misuse is likely to be unreliable, any further conclusions regarding associations involving this measurement must be suspect.

Learning disability

The inclusion of people with mild learning disability could be justifiably criticised, as there is no clear point of delineation between those included in the study and those excluded by dint of being cared for exclusively by learning disability services. Most other population

based studies exclude learning disability. However the proportion of people with mild learning disability included in the study is small, at 5.9%, and it may be of interest to examine the characteristics of this group, even although the sampling is flawed. Thus, for people suffering from psychosis with and without learning disability there was no significant difference for DSM-III-R diagnoses ($\chi^2(4)=9.7$, p=0.09, Fisher's exact test), or course of disorder ($\chi^2(3)=0.238$, p=0.985). Women were over-represented ($\chi^2(1)=3.79$, p=0.056), but this did not quite reach statistical significance.

Diagnoses

The diagnoses are illustrated in figure R1. Using DSM-III-R criteria the most frequent diagnosis was schizophrenia, which was twice as common in men. Taking the various types of manic syndromes together with schizophrenia accounted for 58.4% of the sample, leaving a substantial minority outwith the Kraepelinian dichotomy.

The sexes differed significantly on the mean age of onset: 26.8 years and 30.1 years for men and women respectively, a difference of 3.3 years. Hafner describes how, if only single men and women are considered, the difference in age at onset in schizophrenia disappears (Hafner 2003), and marital status has been shown to confound the age at onset difference across different cultures (Jablensky & Cole 1997). In the Hamilton study, the mean age at onset is 22.8 vs 26.6 years for single men and women respectively with schizophrenia, a difference of 3.8 years (n=84, Z=-1.61, p=0.109). Although the numbers are relatively small this assertion that the differing age of onset is restricted to married people is not supported by the data. The age at onset curves were different for men and women, with women displaying a second peak in the onset curve around the time of menopause. This is discussed further later in this chapter.

The most similar study for comparison is the Australian National Survey of Psychotic Disorders (Jablensky *et al.* 2000). Here all adults aged 18 – 64 were identified in a four centre urban population by first screening all people in contact with health services (including GPs) in the selected areas then interviewing a stratified random sample. The instrument used was The Diagnostic Interview Schedule which subsumed OPCRIT, in addition to a structured clinical interview. Their interviewed sample represented 902 out of 2002 eligible and those not interviewed were mostly due to refusal, and the authors considered the less severely affected to be under-represented. Their mean age was slightly younger than the Hamilton study at 39.4 years but the range of psychotic disorders used was identical, and OPCRIT was part of the battery of assessment instruments. Of their

sample, 586 (59.8%) were male, compared to 50% in the Hamilton study, and the mean duration of illness was the same, at 14.9 years.

The DSM-III-R diagnoses are very similar to the Hamilton study (table D1).

Table D1: DSM-III-R diagnoses in Hamilton population compared with Australian population

DSM-III-R Diagnosis	Hamilton (%)	Australia (%)
Schizophrenia, delusional disorder and schizophreniform disorder	41.8	50.6
Schizoaffective disorders	9.5	9.2
Bipolar disorder, mania	21.2	18.8
Depressive psychosis	13.7	10.8
Other psychosis	13.7	8.9
Did not meet criteria for psychosis*	1.5	1.7

*In the Australian study cases which did not meet OPCRIT criteria for psychosis were excluded. In the Hamilton study clinical consensus overrode OPCRIT in a few cases and such cases were recategorised, hence the Hamilton figures exceed a total of 100% because such recategorised cases are included in the figures for the DSM-III-R diagnoses. Figures are shown here for comparison, demonstrating that of those case notes which suggested psychotic illness, a very similar percentage in both studies were deemed to be not psychotic by OPCRIT.

Since the Australian study has an over-representation of severe cases, it can be argued that this inflates their figure for schizophrenia, as defined by DSM-III-R diagnostic criteria.

Conclusion

Thus it can be concluded that, when considered as a whole, in treated prevalence samples, at least half of adults suffering from psychosis do not have schizophrenia, despite comparable impact on functioning. This supports the view that when trying to identify aetiological factors, or psychopathological substrates, it makes little sense to lose half of the available information by including only those with schizophrenia.

First Rank Symptoms

Initially thought to be pathognomonic for schizophrenia, it is now well established that these occur in other psychotic disorders. Thus a consecutive case series of 660 in-patients found first rank symptoms occurred commonly in all of the functional psychoses save

delusional disorder (Peralta & Cuesta 1999). Schneider considered them as being grouped under the concept of permeability between the individual and his environment. It has been argued that first rank symptoms are related to temporal lobe pathology in the dominant hemisphere (Trimble 1990) and they remain an integral part of current diagnostic systems. They have been shown to be heritable (Cardno *et al.* 2002) although do not predict the risk of psychosis in relatives (Cardno *et al.* 1997)

First rank symptoms are rated as present in OPCRIT if thought echo, third-person auditory hallucinations, running commentary voices, delusions of passivity, primary delusional perception and thought insertion, withdrawal or broadcast are coded as present. In the Hamilton population the highest incidence of first rank symptoms was found in the reality distortion/depression class at nearly four fifths. They were found in only one fifth of subjects in each of the depression and bipolar classes, and half of the subjects in the disorganisation class. These symptoms were more common in men for the population as a whole (table R21). While the DSM-III-R diagnoses had a similar range of values for first rank symptoms these were more evenly spread throughout the diagnostic range, compared to the latent class distribution of these (table R22).

Since the first rank symptoms comprised part of the input data for the factor analysis and latent class analysis, it is perhaps unreasonable to test their association with the latent classes. This is akin to the inclusion of first rank symptoms in the diagnostic criteria for DSM-III-R schizophrenia, which results in a high incidence within schizophrenia so defined. However, it is the association with the other classes which is important, revealing that in empirically defined classes of psychosis, first rank symptoms are found throughout these classes and apparently do not comprise a single underlying disease entity. The higher incidence of first rank symptoms in the reality distortion/depression class compared with the disorganisation class suggests that the latent classes have divided first rank symptoms more clearly than the DSM-III-R diagnoses.

Season of Birth

The numbers of the study are too modest to allow detection of the expected winter birth effect in schizophrenia which is small, in the order of an odds ratio of 1.1(Davies *et al.* 2003). Considering the distribution curves for men and women (figure R4), it appears that in this population, men are more evenly distributed with respect to birth month than women showing a slight increase March to July and a sharp decrease from September to November. It has been reported that deficit schizophrenia is more common in those born

in the summer months (Kirkpatrick *et al.* 2002). These authors used a proxy for the deficit syndrome comprising restricted affect and lack of dysphoria. In the Hamilton study population, no difference was found using this measure (at n=39, numbers of people with schizophrenia and the deficit syndrome were small). However considering only schizophrenia, coded for presence or absence of restricted affect as a proxy for the deficit syndrome, shows a significant increase for deficit syndrome schizophrenia in the summer months (March to September) (table R1). The latent classes show no significant association between restricted affect and season of birth. However there is a trend apparent in the disorganisation class, with 30 (62.5%) of those born within summer having a restricted affect compared with 18 (37.5%) of those born in winter ($\chi^2(1)=2.98$, p=0.12).

Conclusion

The data confirm a summer excess of births in schizophrenia characterised by restricted affect as a proxy for the deficit syndrome. There is a trend towards the same effect in one of the latent classes (disorganisation).

Fertility and fecundity

The possibility of reduced fertility in psychosis is of some importance, from both a theoretical and practical viewpoint. Taking an evolutionary perspective for a particular set of environmental conditions, certain phenotypes are more successful in reproducing. Since the offspring of these successful phenotypes resemble the parents more than the general population, there is selection of the genes responsible for this phenotypic variation. The reduced biological fitness displayed by people (especially men) with schizophrenia suggests that there may be some hitherto unrecognised advantage in carrying susceptibility genes for schizophrenia. There have been many diverse proposals to account for this, (Crow 1995) and consideration of the Hamilton population suggested a theory which is testable (Murray 2000). From a practical viewpoint reduced fertility which is more severe in one sex will impact on morbid recurrence risks in genetic counselling. Morbidity risks usually assume no sex differences and normal fitness in siblings. However, due to differential fitness effects, women with schizophrenia spectrum conditions will have an increased risk of transmitting schizophrenia compared with men. This may explain the high rates of maternal transmission (Bassett *et al.* 1996). Thus women with schizophrenia will have a higher recurrence risk than is suggested if the sexes are considered together, due to the lower recurrence rate in men.

It is of interest to consider if the reduction in fertility is confined to schizophrenia, or present in psychosis as a whole. Unfortunately, this study is limited to making comparisons between groups within psychosis – no data is presented on the fertility or fecundity of the general population of the Hamilton District over the time-scale of the study. Therefore it is not possible to establish whether psychosis itself reduces fertility in our population. However, reduced fertility is of such importance that variability between the classes and dimensions described would suggest that an important biological difference is reflected within the new phenotypes.

Fertility and gender ratio

Most studies on fertility in psychosis have been in schizophrenia, where a reduction especially for men has been noted (Srinivasan & Padmavati 1997) although there has been contradictory evidence (Nimgaonkar 1998). Thus a national cohort study from Finland confirmed the lower than average fertility in both men and women with schizophrenia which was not counterbalanced by an increase in the fertility of siblings (Haukka *et al.* 2003). The reduction in fertility of men with schizophrenia has been described as one of the most robust findings in the epidemiology of schizophrenia. Fitness in men with schizophrenia is lower than the reduced fitness in women (Haukka *et al.* 2003; Odegard 1980)

Fertility and psychosis

Studies of fertility in psychoses are rare. Howard *et al.* (2002) used the UK General Practice Database to determine the general fertility rate (births in one year×1000/number of women aged 15-44 at midyear). Fertility was found to be significantly lower in those aged over 25 years, especially for non-affective psychoses. The rate ratio of patients to comparison subjects was 0.66 for affective psychoses and 0.46 for non-affective psychoses.

Probably the study most comparable to the Hamilton study is the community study by McGrath (McGrath *et al.* 1999). Case ascertainment was different, with no GP cases being included, but DSM-III-R diagnoses were generated by OPCRIT. They identified 819 people with psychotic disorders of whom 342 were studied in a community sample in Australia. This attrition rate has implications for direct comparisons with the Hamilton study. For example their gender ratio was very different, with 68% men compared with

50% men in our study. As could be expected from this gender ratio, the affective psychoses were under-represented compared with our study, with affective psychoses accounting for 21% of their cases compared with 44% in the Hamilton study. Thus women with affective psychoses were under-represented in McGrath et al's study. Nevertheless trends in their findings were similar. They found that 36.3% of their cases were parents, compared with 48.3% of our subjects. In our study 35% of men and 62% of women had children, compared to 25% and 59% respectively in McGrath et al's study. Likewise the Australian low prevalence (psychosis) study found that 21.3% of men had children and 50.5% of women had children (Jablensky *et al.* 2004)

Fecundity and psychosis

Comparing fecundity, McGrath et al found mean number of offspring for males to be 0.5 in contrast to our 1.75 for all psychoses. For women their mean was 1.59 children per women, compared to 2.23 children in the Hamilton study. Thus for both sexes the rates were higher in our study. In addition, women in the Hamilton study had significantly more children compared with men, in contrast to the Australian study, which found no significant difference. However this difference disappeared if only fertile men and women were considered.

Conclusion

In summary, the Hamilton study shows that 35% of men and 61% of women with psychosis are parents, which has implications for delivery of mental health services. (Indeed this proportion is likely to increase since many in the sample were still early in their reproductive life). In recent years there has been an interest in helping the children of a parent with psychosis. Likewise, some limited genetic counselling is now available for people with psychosis who wish to know the risk to their offspring. The fertility and fecundity in this population of people with psychosis do not appear to be very different to those of McGrath *et al* and Jablensky *et al*, when the altered sex ratio is taken into account. The difference in fertility between the sexes is confirmed, with fertility in men reduced relative to women. However, limitations to the methods should be noted. The account of fertility will be inexact. No attempt was made to corroborate self report. In addition, men may have fathered children and been unaware of this. Likewise, some men will be mistaken in their belief of paternity (around 10% of cases referred to a regional genetics clinic for example will have paternity refuted by DNA analysis (D.Wilcox, personal communication). Also no distinction was made between fertility occurring before or after

the onset of psychosis. Nevertheless the data support a reduction in fertility within psychosis. Further consideration of this will be given with respect to the defined classes and dimensions.

Age at onset and gender

When considered as a group, there are differences between the sexes with respect to age at onset. Firstly, men have an earlier age at onset. Examination of the plot of age of onset (figure R2b) reveals the most frequent age at onset for men occurs in the 16-20 age group, while for women it is in 21-25 age group. Half of the subjects have become ill by age 25 years for men and 27 years for women. That psychosis is an illness with its major impact in young adults is often obscured in clinical practice due to the relatively low incidence but often chronic nature of the disorder. It must, of course, be acknowledged that had the upper age limit included those over 65, these figures would require upward revision.

The shape of the curve of age of onset is also different, with a distinct (though smaller) second peak of onset for women at 40 –45 years. This was also found in the Camberwell first episode psychosis study which examined a consecutive population of people presenting with the first episode of non-affective psychosis (Castle *et al.* 1998). There was no upper age limit for the Camberwell study and the later life increased incidence in women compared to men continued to beyond the seventh decade. In addition there was a second but less pronounced peak of onset for men. In the Hamilton study it can be seen that at the time of the second peak in women, the sharp decline in numbers of men with this age of onset flattens slightly before once again sharply declining. Thus while there is no second peak for men, there is a certain attenuation of the decline in incidence in the 36-45 age group. In the ABC Schizophrenia study Hafner and colleagues (Hafner *et al.* 1993) using first ever sign of mental disorder as onset point found a similar late peak for women at 45 years, but no attenuation in the male decline at this age group.

Conclusion

When considered as a group, the psychoses are predominantly disorders of young adults. The increased incidence in mid-life females is confirmed.

Age of onset and family history

For schizophrenia, the difference in age at onset may apply to sporadic, but not familial schizophrenia (Albus & Maier 1996). For example, in a national total population of Finnish multiplex families the age at onset of schizophrenia was 22.2 years (SD 5.5) for men and 22.9 years (SD 6.5) for women. Also, in an isolated subpopulation with an increased incidence of schizophrenia, the age at onset was reduced in women at 20.9 years (SD 5.0) compared to 23.4 years (SD 6.0) in men (Arajarvi *et al.* 2004).

Table R0 confirms this association of earlier age of onset in men with schizophrenia being restricted to those with a negative family history. It is interesting that this effect is not confined to schizophrenia, but seen in the whole population of people with psychosis. When this is considered at the level of the latent classes, it is clear the disorganisation class accounts for the family history effect on the earlier age at onset in men. This is of some significance and will be referred to later in the chapter.

Conclusion

In this population, a family history of any psychiatric disorder negates the earlier onset for men with psychosis. This effect is apparent in only one of the latent classes (disorganisation).

Outcome for women with late onset psychosis

The protective effect of oestrogen has been proposed as an explanation of the delayed onset in women with a resurgence of onset around the menopause. Hafner proposes that the protective effect of oestrogen accounts for the early and severe forms of schizophrenia in men, and a milder form in women until the premenopause. Thereafter he suggests that women should show higher incidence rates and more severe forms of the disorder (Hafner 2003). In terms of outcome this is not supported by the Hamilton data. Thus for those women with an onset at over 40 years who had been ill for at least five years (in order to reduce bias due to recent onset cases) 5/39 (12.8%) had a chronic course compared with 14/58 (24.1%) of those with an earlier onset (table D2).

Table D2: Course of illness for women by early and late onset, aged over 45 years

Course	Onset up to 39 years n (%)	Onset over 40 n (%)	Statistical tests*
Single episode (good recovery)	1 (1.7%)	6 (15.4%)	$\chi^2(3)=7.68$
Multiple episodes (good recovery in between)	26(44.8%)	18(46.2%)	P=0.059
Multiple episodes (partial recovery in between)	17(29.3%)	10 (25.6%)	
Continuous chronic illness	14 (24.1%)	5(12.8%)	

* Fishers exact test

Conclusion

The data provide no evidence for a more severe outcome in women with late onset schizophrenia.

Other illness characteristics

Men and women were significantly different on all premorbid characteristics measured, in addition to forensic history and employment (tables R2a-f). In interpreting these differences it is important to remember that such differences may not be specific to psychosis but more a reflection of differences between men and women in the general population. Thus differences in premorbid social adjustment may reflect the overall better social communication of women relative to men (Baron-Cohen 2002). Considering illness course, men are more likely to have an insidious onset and a worse outcome, and more likely to be detained. Contrary to clinical experience which suggested an excess of deliberate self harm in women, there is no difference with regard to deliberate self harm, although men are over-represented in the small group involved in violent self harm. Likewise, men are much more likely to have a positive forensic history which again reflects the general population. This effect of general sex differences may also be of relevance to the different age at onset. Spauwen *et al.* (2003) found that isolated psychotic symptoms occurring in a general population were found 1.1 years earlier in men compared with women. In contrast to these marked differences between the sexes on many variables, there was no difference between men and women with respect to a family history of psychiatric disorder.

Conclusion

Men and women differ in a wide range of variables which may reflect differences in the general population. There is no gender difference for family history of psychiatric disorder.

Family History

A family history of schizophrenia was relatively rare at around 5%, but approximately one third had a first or second degree relative with some other psychiatric disorder. Around one third of probands had no known family history of any psychiatric disorder, with around a quarter having only one affected relative.

Conclusion

The method of data collection, and lack of controls limits the value of the family history data. Overall it confirms that most people with psychosis lack similarly affected relatives. Subjects are much more likely to have a relative with another psychiatric disorder.

Principal components analysis: the dimensions of psychosis

Principal components analysis was undertaken on 62 symptoms items as defined in OPCRIT. The scree test indicated that only four components accounting for 28.9 % of the variance should be extracted. Use of the other common criterion for extraction, i.e. eigenvalues greater than one, would have yielded 20 components and 64 % of the variance. Independent dimensions were chosen thereby avoiding the problems of oblique rotation of factors (ie deciding which factors might be related and to what extent).

Naming dimensions carries the inherent danger of misleading the reader. Names similar to those of diagnostic labels irresistibly imply constructs which are then undistinguishable from such diagnostic labels. Nevertheless, the principal components and latent classes have been named to facilitate comparison between the two, and clarify subsequent analyses. However, it must be remembered that these dimensions are different both in conceptual structure and content to usual diagnostic categories. Four principal components were extracted which have been named: mania, reality distortion, depression and disorganisation. These accounted for 28.9% of the variance. These dimensions will be considered in turn before considering the literature (table R8d).

The four dimensions

Mania (11.1% of variance)

Mania loads on items which are all unequivocally associated with a manic upswing: excessive activity, pressured speech, elevated mood, thoughts racing, reduced need for sleep, increased self-esteem, recklessness, increased sociability, distractibility, grandiose delusions and irritable mood. There is also a significant loading on degree of affectivity.

Reality distortion (8.1% of variance)

This dimension consists of 14 items: persecutory or jealous hallucinations, hallucinations lasting one week, widespread delusions, abusive, accusatory or persecutory voices, persecutory delusions, delusions of passivity, delusions of influence, bizarre delusions, non-affective hallucination in any modality, third person auditory hallucinations, thought

insertion, broadcast and withdrawal. Running commentary voices load on this factor but just short of significance at 0.265 (significance being set at 0.3). Due to the prevalence of hallucinations and delusions as well as disorders of thought possession, the dimension was named reality distortion.

Depression (5.8% of variance)

The third principal component loads exclusively on 15 items seen in depressive illness: dysphoria, loss of pleasure, poor appetite, suicidal ideation, initial insomnia, loss of energy, poor concentration, excessive self reproach, degree of affectivity, slowed activity, middle insomnia, early morning wakening, diurnal variation, and weight loss. Delusions of guilt just missed significance at 0.271. This dimension is therefore named depression.

Disorganisation (3.9% of variance)

The final principal component loads on nine items relating to disorders of affect and thought disorder, namely, positive thought disorder, restricted, inappropriate and blunted affect, speech difficult to understand, negative formal thought disorder, catatonia, bizarre behaviour and incoherence. This component also has the highest (but not quite significant) loadings for lack of insight (0.288) and other (non-affective) auditory hallucinations (0.288).

Comment on the four dimensions

The factors are complex, with each loading a minimum of 10 items. In addition, items do not load highly on more than one factor, a reflection of varimax rotation in aiming for simple structure (Kline 1994). However the factor analysis accounts for less than one third of the variance. This is lower than many factor analyses of psychoses in the literature which tend to range from around 40% - 60% (McGorry *et al.* 1998; Rosenman *et al.* 2000; Serretti *et al.* 1996). It is not possible to make any comment on the variance unaccounted for by the principal components. In a principal components analysis all the variance is initially explained in the initial correlation matrix (including the error variance). After extraction of the chosen number of factors, error and specific variance are not separated out. The analysis could be criticised on the grounds that so little of the variance is accounted for. This is a reflection of the complex nature of psychiatric symptoms and the imprecise way these are measured. Thus much of the variability within the population cannot be accounted for by the principal components. However this does not explain why

other studies account for more of the variance. It may be that the populations studied were more homogeneous with respect to variables of small effect, or perhaps the methodology of the factor analysis accounted for this. A common feature of several studies which have used OPCRIT is to condense the number of items entered into the factor analysis, which may have affected the amount of variance accounted for.

The second criticism is that the analysis may be invalid because of violation of the underlying assumptions in that there would not be normal distributions on all the 62 items used. However, in the literature, factor analysis is frequently used in these situations and appears to be robust to violations of these assumptions (Tabachnick & Fidell 1996; Hair *et al.* 1998). Here a fairly clear result was obtained, which had strong face validity. But the dimensions identified must be further tested, both by association with external validators and by comparison with the latent class analysis on the same dataset. In addition, the results must be compared with the literature.

Consensus on the dimensions of psychosis?

In considering how these principal components compare with the body of evidence in the literature it is important to identify studies which cover the same range of psychotic disorders, are drawn from general populations and are methodologically sound. For example the input data should be drawn from a source which lacks an inherent factorial structure, and there should be an acceptable number of subjects to number of items factored.

Considering factor analytic studies, those involving people with a broad range of psychosis are much less frequent than those on people with schizophrenia. Studies of people with a broad range of psychoses which are performed in population based samples are rarer still. The study by Rosenman *et al.* (2000) was performed using OPCRIT on 980 Australian community and hospital subjects with a wide range of psychotic illness. They obtained five factors covering 58.9% of the variance. However, unlike our study, substance abuse was included in their item domain. One of their factors is loaded highly by the substance abuse items. The other four are all closely similar to ours ('dysphoria' to depression, 'positive symptoms' to reality distortion, 'mania' to mania and 'negative symptoms/incoherence' to disorganisation). Of the other studies available for comparison, none was as similar in terms of population studied and methodology.

Similar results were found by Serretti *et al.* (1996). Here 38 OPCRIT items on over 1000 patients consecutively hospitalised for schizophrenia or depressive disorder were factor analysed on half the subjects and the factor structure confirmed on the other half. Four factors were obtained accounting for 56.4% of the variance namely "excitement", "depression" "disorganisation" and "delusion". Their excitement factor loaded significantly on dysphoria and not on depression, which is curious. Other than this, these factors are very similar to those of the Hamilton Psychosis study. Serretti *et al's* study is rare in that a confirmatory factor analysis on an independent sample was performed and confirmed the original exploratory analysis.

It could be argued that the similarities in the results are a product of the underlying structure of OPCRIT. In this respect it is noteworthy that a study involving a first episode community sample but using an entirely different assessment tool found similar factors to the Hamilton Psychosis study (McGorry *et al.* 1998). Here the Royal Park Multidiagnostic Instrument for Psychosis (McGorry *et al.* 1990a; McGorry *et al.* 1990b) which constructs a data set of over 350 items from a series of interviews with the patient and an informant provided 92 input items for 509 patients. This population was younger compared with the Hamilton study and predominantly male, with 35% having an affective psychosis. Four factors were found: mania, depression, positive (Schneiderian) and negative/disorganised (Bleulerian) factor. These factors are similar to the Hamilton study, despite the differences in the populations.

Four similar factors were also found in a discharged in-patient sample of 204 patients with functional psychosis which used OPCRIT (McIntosh *et al.* 2001). Examination of the first four admissions found that the factors were stable over time and related to structural brain differences. Kitamura *et al* (1995) found five factors, four of which were very similar to the Hamilton study, the other factor being catatonia, loading on items which are not included in OPCRIT, in a Japanese population of consecutive in-patient admissions.

In a sample of 706 people with chronic psychosis, van Os and colleagues (1999) used both OPCRIT and the Comprehensive Pathological Rating Scale (CPRS) to construct four principal components which were very similar to the Hamilton study. The CPRS items were used to construct cross-sectional psychopathological dimensions, accounting for 24% of the variance. Their "depression" and "mania" factors were directly comparable, with their "positive" and "negative" factors akin to the reality distortion and disorganisation factors. This was not a population based study but 57% of the sample was male, and the subjects had been ill for a mean of 10 years. For lifetime psychopathology OPCRIT was

used to identify five principal components of "manic", "depressive", "negative", positive" and disorganisation syndromes, accounting for 41% of the variance. The first two components were very similar to the Hamilton factors of the same name, as was the "positive" component. However the Hamilton disorganisation dimension appears to be split into two in the study, with the "negative" component loading negative formal thought disorder, restricted affect, blunted affect, initial insomnia and middle insomnia, and their disorganisation component loading on positive formal thought disorder, speech difficult to understand, incoherence, lack of insight and difficult rapport.

In an earlier study Van Os and colleagues, examined 337 consecutive admissions with functional psychosis of recent onset using OPCRIT, but in contrast to the Hamilton study included age and type of onset in the items defining the factors. OPCRIT items were also condensed, with mania and depression items entered as a sum of the ratings on the individual items for mania and depression. A seven factor model accounted for 68% of the variance. To "avoid overinterpreting though terminology" the names given were inappropriate-catatonia, insidious-blunting, delusion-hallucination, mania, depression, paranoid delusion and lack of insight. The authors question the validity of the latter two factors, on the grounds that they may represent a subgroup of patients rather than factors. They also concluded that on the basis of validating the factors, the two separate affective and two separate positive symptom syndromes may be invalid, and a parsimonious approach could be more appropriate. There is some concordance with the Hamilton study, with mania and depression similar, disorganisation akin to their inappropriate-catatonia item (loading bizarre behaviour, catatonia, inappropriate affect and difficult rapport), and reality distortion similar to delusions-hallucinations (delusions of passivity, bizarre delusions, thought interference and hallucinations). However their factor insidious-blunting (insidious onset, blunting of affect and age of onset) is not represented in the Hamilton study because two of the items are not included in the principal components analysis. Likewise this result is very different to the later study by van Os and colleagues previously described, reflecting the effect of different populations (recent onset vs chronic), different input variables for the factor analysis, and different statistical techniques.

Conclusion

On balance the dimensions found in the Hamilton Psychosis study seem to be supported by, and add to, a body of evidence for at least four dimensions acting across functional psychoses.

Validation of the dimensions

While the four dimensions described appear to have face validity and to be supported by the literature, it is crucial that these are validated, otherwise they are interesting but of little relevance.

Univariate analysis

Each principal component will be discussed with respect to association with external validators prior to discussing multivariate analysis (table R15 onwards)

Mania is associated with being female, fertile, being detained under the Mental Health Act and negatively associated with an insidious onset, being single or having a poor social adjustment.

Reality Distortion is associated with having a poor outcome and being detained, and negatively associated with being female, having a long duration of illness, or having forensic involvement.

Depression is associated with being female, fertile, having a family history of psychiatric illness other than schizophrenia, having ECT, deliberately self harming, having a long duration of illness, and forensic involvement. It is negatively associated with being single, having a past history of poor social adjustment, having a family history of learning disability, or being detained.

Disorganisation correlates with being male, single, early age of onset, insidious onset, poor social adjustment, poor outcome, and long duration of illness. Disorganisation is negatively associated with fertility, having a family history of neurosis or learning disability, or having forensic involvement.

Multivariate analysis

Age of onset

Since the age of onset is known to differ between males and females, gender was included as a possible predictor in the multiple regression model along with the factor scores.

Gender ($p=0.038$) and the disorganisation factor ($p<0.001$) were found to be significant in predicting the age of onset with the average age of onset of illness for males being 26.7 years and 30.1 years for females. For every one unit increase in the disorganisation factor scores, there was a decrease in age at onset of 2.7 years.

Fertility

The logistic regression model for fertility included gender and age of onset as possible predictors in addition to the factor scores. Gender, age at onset and factors mania, depression and disorganisation were significantly associated with fertility. Females are more likely to have had children and the odds of having had children increase slightly with age. The mania and depression factors are associated with increasing fertility and the disorganisation factor is associated with decreasing fertility.

Deliberate Self Harm (DSH)

The relationship between deliberate self-harm and factor scores was investigated using logistic regression with gender and duration since illness onset included in the model. The depression factor was the only significant variable where the odds of DSH increased by 1.82 as the factor score increased by one unit.

Principal components analysis conclusion

The dimensions are shown to have differential patterns of association with external validators. These associations would tend to support the dimensions as clinically relevant, and reflecting an underlying psychopathological entity.

Latent Class Analysis

Latent classes identified

Latent class analysis also yielded four classes as the best model and there was a reasonably close correspondence between the four classes obtained and the four principal components. Latent class one is composed of people who have symptoms of depression and psychosis and account for 19% of the sample ('depression'). The 28% found in class two are mainly characterised by bizarre behaviour, disorders of affect and thought and lack of insight, but little depressive symptomatology although positive symptoms are present ('disorganisation'). Class three members (23%) have symptoms of mania and depression ('bipolar'), while the 30% in class four score the highest on positive symptoms but also score highly on depression ('reality distortion/depression').

Latent classes in other studies

The most comparable latent class study to the Hamilton study is that of Kendler *et al* (1998). Their population was somewhat different consisting of 343 individuals from a defined geographical area who had suffered from broadly defined schizophrenia or from affective illness (of whom only a proportion were psychotic). They used 19 items based on the OPCRIT checklist, seven of these being composites of more than one item, with two items added to assess course and outcome. From this they obtained six classes, the smallest of which ('hebephrenia') contained only 3.0% of the sample. Their 'major depression' class was virtually confined to affective illness and is similar to the Hamilton depression class. Of their four remaining classes, the 'bipolar-schizomania' and 'schizodepression' are reasonably close to the Hamilton bipolar and reality distortion/depression classes respectively. However, their 'classic schizophrenia' while incorporating many of the features of our disorganisation class also includes positive symptoms to a greater extent. Lastly, their 'schizophreniform disorder' has no correlate in the Hamilton study. It is not clear if such divergent outcomes may be attributable to differences in the study populations. Also, the choice of items included in the latent class analysis is different, and this is likely to have had a major effect. The Hamilton study includes purely symptoms within the latent class analysis, in keeping with the most elementary approach. Kendler *et al's* study included two items for illness course and

outcome. Nonetheless given the differences in populations and procedures there is clear correspondence with the latent classes found in the Hamilton study.

The Camberwell First Episode Study (Sham *et al* 1996, Castle *et al*. 1998) considered only non- affective psychoses in an epidemiological sample of people presenting with their first episode of psychosis. OPCRIT items were again used in a sample of 447, but premorbid items such as family history and social adjustment as well as sex and age of onset were included in the latent class analysis. Three types of illness were found: 'neurodevelopmental', 'paranoid' and 'schizoaffective'. The 'neurodevelopmental' subtype is akin to the Hamilton study's disorganisation class, with restricted and inappropriate affect, negative features, thought disorder and catatonia. The Hamilton reality distortion/depression class is comparable to their 'schizoaffective' subtype but their 'paranoid' subtype is not represented in the Hamilton study. Likewise, the Hamilton bipolar and depression classes have no correlate, since affective psychoses were excluded from the Camberwell study. Overall the results are comparable despite major methodological differences.

Conclusion

The broad consensus between the Hamilton study and those above suggests that within the domains of symptoms in psychotic patients there are four latent classes which describe the underlying syndromes.

Validation of the Latent Classes

The external validators of the four-class model will be considered in turn.

Age at onset

The main finding was in the disorganisation class where men had a significantly earlier age at onset (23.8 years) than women (31 years). This is entirely in keeping with the well established but unexplained finding that age at onset of schizophrenia is earlier in men than women (Hafner et al 1989). Earlier age at onset in men distinguishes the disorganisation class from the reality distortion/depression class where members also have more affective symptoms. The difference in ages between the sexes is greater than that previously reported, suggesting that the disorganisation latent class identified here delineates more clearly an underlying biological construct.

When the age at onset curves are compared for the latent classes (figure R3a) it is seen that the curves for depression and disorganisation both have a second onset peak in middle age. Over younger ages the depression curve is much flatter. The gender differences in the latent classes may be relevant here. Depression is predominantly female and disorganisation predominately male. This raises the intriguing possibility that depression and disorganisation latent classes represent perhaps the same disease entity modified by sex. Thus being female converts otherwise disorganisation cases into depression, with later mean age of onset and better outcome. This would also account for the (initially surprising) frequency of restricted affect and rapport difficulties within the depression class. The second peak in middle age for women suggests that the same developmental or environmental process triggers the expression of psychosis in both the depression and disorganisation classes.

Gender

The classes were distinguished by varying sex ratios. The depression and bipolar classes had significantly more women than men whereas the disorganisation and reality distortion classes had a higher proportion of men. These findings are generally in agreement with other reports of increased prevalence of affective disorders in females. This is well established in depression (Angold and Worthwan 1993; Wilhelm *et al.* 1997) but equal sex ratios are usually reported in bipolar disorder and schizophrenia. The National Comorbidity Survey of the life-time and twelve month prevalence of psychiatric disorders reported higher prevalence of affective disorders in women than men except for mania for which there was no sex difference (Kessler *et al.* 1994). Here the latent classes appear to have a clearer division along gender lines compared with categorically based diagnoses.

The age at onset distribution curve is of interest (figure R2b). When considered as a group, the curves for men and women are different in shape, with women displaying an additional increase in incidence at 40 –45 years old. A middle age increase in onset for women was also found in the Camberwell first episode study.

Fertility

The main result is reduced fertility in the disorganisation class. Reduced fertility in schizophrenia compared to the general population is a persistent finding (Nimgaonkar 1998; Odegard 1980) although there has been some contradictory evidence (Bhatia *et al.* 2004; Lane *et al.* 1995). In considering community patients with psychoses, McGrath *et*

al (1999) noted that the reduction in fertility is most marked in those with non-affective psychosis, which is confirmed here.

Deliberate self harm

Both the depression and reality distortion/depression classes have a higher risk of deliberate self harm, with members of the disorganisation class least likely to do so. This clear difference between the DSH incidence in the disorganisation class and reality distortion/depression class highlights the utility of the latent classes in sorting individuals into groups which have better clinical significance than categorical diagnoses. This difference in risk of self harm between the latent classes may be of practical import in clinical risk assessment, since previous suicide attempts have been associated with completed suicide (Potkin *et al.* 2003; Krupinski *et al.* 1998). Support for our findings is suggested by de Hert *et al.* (2001) who found that early onset of a defect state was a protective factor in a case control study of completed suicide in young people with schizophrenia. Also, in a Finnish study of all people with schizophrenia who completed suicide Heila *et al* (1997) found that the paranoid and undifferentiated subtypes were most common, and two thirds of those completing suicide had a depressive syndrome during the course of their illness.

Latent Class Analysis conclusion

These results suggest differences between membership of the latent classes and add validity to the four class model of psychosis which has been devised empirically from symptom patterns in a population based cohort of people. Certain classes identified are familiar clinically and have been observed in other studies. It would appear that the neurodevelopmental/praecox subtype of schizophrenia is most closely identified with the disorganisation class with premorbid social difficulties, early and insidious onset, poor outcome, low fertility and predominately male. This is similar to the neurodevelopmental class found in a study of non-affective psychoses (Castle *et al.* 1994). In contrast the bipolar class is of abrupt onset, with a relatively benign outcome, few premorbid problems, high rates of fertility and predominately female. The usefulness of the latent class approach is demonstrated however not by these clear prototypes but in the classification of cases between these extremes. Thus the reality distortion/depression class is distinguished from the depression class by a more even sex ratio, and greater incidence of premorbid social isolation and higher rates of detention. Surprisingly, these classes are very similar in rapport difficulties and mode of onset. It is interesting that both these classes have very

high rates of deliberate self harm suggesting that members of the reality distortion/depression class are as high a risk to themselves as those in the depression class.

Comparison between dimensions and classes

Correlation between component loadings and conditional probabilities

The latent class analysis and principal components analysis were compared in two ways. Firstly correlations were run between the component loadings and the conditional probabilities (table R13). Thus latent class one (depression) is significantly correlated with the depression dimension. Class two (disorganisation) has positive correlations for reality distortion and disorganisation and a negative correlation for depression. Class three (bipolar) is significantly correlated with mania. Class four (reality distortion/depression) has significant correlations with both reality distortion and depression.

Comparison of the mean factor scores for the latent classes

Secondly, the mean values of the principal component scores for the latent classes were compared as illustrated in figure R8. Thus latent class one (depression) scores highest on the depression dimension. Latent class two (disorganisation) scores highest on the disorganisation dimension. Latent class three (bipolar) scores highest on the mania dimension, and latent class four (reality distortion/depression) has the highest score on the reality distortion component, and also scores highly on the depression dimension.

Conclusion

It is coincidental that principal component analysis and latent class analysis find four dimensions and classes, but it is interesting that the dimensions operate selectively across the latent classes. The fact that the symptom data from men and women, when considered separately, produces the same four factors (tables R11a&b) suggests that these dimensions are not sex specific, and the gender differences in the latent classes reflects different amounts of these dimensions acting differentially with regard to gender.

Latent class analysis and principal components analysis are useful for different reasons. Factor analysis is concerned with dimensions along which individuals may be classified. If these dimensions are kept independent then a subject who is high on one dimension may or may not be high on any other. Latent class analysis is, in principle, more similar to cluster analysis (McCutcheon, 1987). It seeks out groups of cases (e.g. there might have been a particular latent class which was simultaneously high on two of our dimensions). In the Hamilton study the latent class analysis makes a distinction between disorganisation (characterised by bizarre behaviours and the negative symptoms of schizophrenia) and a reality distortion class which includes people with delusions and hallucinations. The other two types of patient, those in the depression class or bipolar class, are clearly distinct from these. This allows estimation of the proportions of each type of patient to be found among those suffering psychotic disorder, and direct comparison with traditional diagnostic categories. On the other hand, the dimensional principal components analysis does not force people into these particular categories thereby allowing, for instance, a person to be both disorganised and manic. Thus at an individual level the dimensional approach makes best use of the data and describes the pattern of symptoms much more accurately. The difference between the categorical and dimensional approach might be best illustrated by considering how individuals could be graphically represented under the two procedures. Latent class analysis would be illustrated simply as a Venn diagram where the universal set was represented by all people with psychosis, with each and every individual occupying only one of four discrete subsets. In contrast, illustrating the position in space of each individual on the four factors would require a four dimensional graph, with each individual in an exploratory factor analysis occupying a unique point in space. Thus, while the categorical approach is more intuitive and familiar, being the basis of our diagnostic systems, the dimensional approach offers more efficient use of the available data.

Comparison of latent classes and DSM-III-R diagnoses

For genetic studies, four latent classes which are well demarcated are a useful alternative to the classical diagnostic systems. This is of particular relevance when population samples of people with psychosis are studied because a substantial minority of these do not fall neatly into bipolar disorder or schizophrenia and the categorisation of schizoaffective disorders, atypical psychosis and paranoid states are recognised as being particularly unreliable. However these four classes are of little advantage if the DSM-III-R diagnoses show stronger and more consistent associations with the external variables. In comparing the main outcome tables for the latent classes and the DSM-III-R diagnoses the following can be noted (table D3).

Table D3: comparison of outcomes for latent classes and DSM-III-R diagnoses

External validator	Statistical significance of association with latent class		Statistical significance of association with DSM-III-R diagnoses	
		Group with least positive outcome		Group with least positive outcome
Gender	P<0.0001	male	P<0.0001	male
Evidence of poor premorbid social adjustment	p=0.037	disorganisation	P<0.0001	schizophrenia
Age at onset (males)	P=0.009	Males earlier	ns	
Age at onset (females)	ns		ns	
Deliberate self harm	P<0.0001	Reality distortion/depression	P=0.021	unipolar
Onset mode	P<0.0001	disorganisation	P=0.004	schizophrenia
Difficult Rapport	ns	disorganisation	P=0.021	schizophrenia
Deterioration	P=0.001	disorganisation	P<0.0001	schizophrenia
Course	P<0.0001	disorganisation	P<0.0001	schizophrenia
ECT ever received	P=0.013	bipolar	P<0.0001	schizoaffective
Fertility	P<0.0001	disorganisation	P<0.0001	schizophrenia
Married or lived as married	P<0.0001	disorganisation	P<0.0001	schizophrenia
Family history other psychiatric disorder	P=0.02	bipolar	P=0.012	schizoaffective
Ever detained	P=0.013	disorganisation and bipolar		schizophrenia
Street drugs exposure	ns		P=0.003	schizophrenia
Alcohol use	P=0.032	Reality distortion/depression	ns	
Forensic involvement	P=0.005	disorganisation	P=0.001	schizophrenia

In general, for external validators showing significant associations, these occur for both the DSM-III-R diagnoses and for the latent classes. The exceptions are that the latent classes identify an earlier age of onset in males, which is specific to the disorganisation class. Also, difficult rapport is significantly associated with the diagnostic categories (with schizophrenia being the highest scorer), but not with the latent classes.

Where the associations are significant, the most severely affected classes or diagnostic categories appear to be correlated. Thus when the disorganisation class is the most

severely affected, it is almost always schizophrenia which is likewise worst affected. Also, when the worst affected class is bipolar, it is the schizoaffective class which is the most severely affected diagnostic group.

Conclusion

It may be tentatively concluded that formation of the latent classes does not appear to result in any decreased association with external validators compared with DSM-III-R diagnoses. A correlation between disorganisation class and schizophrenia on the one hand and bipolar class and schizoaffective disorder on the other is suggested by the data.

Why these apparent correlations occur is clarified by examination of the distribution of the latent classes on the DSM-III-R diagnoses (table R20). When considering how the reality distortion/depression and depression classes are spread over the original DSM-III-R diagnoses, it can be seen that while the depression class draws heavily on depression with psychosis, and delusional disorder, the reality distortion/depression class is drawn from almost all of the diagnostic categories. In particular it identifies a substantial subgroup within schizophrenia, and incorporates almost all of the schizoaffective cases. This implies identification of this class has sorted cases in a novel way which reveals similarities obscured by traditional diagnostic practice. Validation of this, and the other classes, suggests that perhaps the term non-affective psychosis should be reserved for only those within the disorganisation class. Each of the other classes has a substantive affective component. While the affective influence in schizophrenia has always been acknowledged, its importance may be obscured by the mixing of the heterogeneous cases within the term schizophrenia.

Gradient of severity: latent classes

The continuum theory holds that the psychoses represent a continuum of severity of a single underlying disorder. It is therefore of interest to consider whether the data suggest a consistent gradient with respect to outcome variables. These will be considered for the variables where a significant difference exists between the classes or diagnoses.

Table D4: ordering of latent classes on external variables

External validator	Latent class			
	Highest scoring class			**Lowest scoring class**
Male gender	Disorganisation	Reality distortion/depression	Depression	Bipolar
Worst premorbid social adjustment	Disorganisation	Depression	Reality distortion/depression	Bipolar
Youngest age at onset (males)	Disorganisation	Bipolar= Reality distortion/depression		Depression
Low deliberate self harm	Disorganisation	Bipolar	Depression	Reality distortion/depression
Most insidious onset	Disorganisation	Depression	Reality distortion/depression	Bipolar
Most difficult rapport*	Disorganisation	Depression	Reality distortion/depression	Bipolar
Most deterioration	Disorganisation	Reality distortion/depression	Depression	Bipolar
Most severe course	Disorganisation	Reality distortion/depression	Depression	Bipolar
Least fertility	Disorganisation	Reality distortion/depression	Depression	Bipolar
Least married	Disorganisation	Reality distortion/depression	Depression	Bipolar
Least family history other psychiatric disorder	Disorganisation	Reality distortion/depression	Depression	Bipolar
Most detained	Disorganisation= Bipolar		Reality distortion/depression	Depression
Street drugs exposure*	Disorganisation	Reality distortion/depression	Bipolar	Depression
Most alcohol use	Reality distortion/depression	Disorganisation	Depression	Bipolar
Most forensic involvement	Disorganisation	Reality distortion/depression	Bipolar	Depression

* denotes a non-significant difference between the groups.

This table (D4) suggests a gradient which runs from the disorganisation class at the most severely affected pole to bipolar at the least severely affected pole. Considering the course and outcome of the illness, the suggested gradient would be disorganisation, reality distortion/depression, depression and bipolar, but the ordering of the classes in the centre

of the continuum is less consistent. It is interesting that the one family history item which had a significant association with the latent classes (other psychiatric disorder which mostly represents affective disorders) suggests a gradient of affectivity liability running in the opposite direction from severity.

Gradient of severity: DSM-III-R categories

A similar gradient is produced when the DSM-III-R diagnoses are considered, with schizophrenia clearly at the most severe pole and bipolar and unipolar at the opposite pole (table D5). Between these poles, atypical appears closest to schizophrenia and schizoaffective closest to the bipolar end. In comparing this table with the previous one (D4) there is a suggestion that the latent classes produce a more consistent gradient. It must be remembered however that there are four latent classes and five condensed DSM-III-R diagnoses which predisposes to this outcome in any case.

Table D5: ordering of DSM categories on external validators

External validator	Highest scoring diagnosis				Lowest scoring diagnosis
Male gender	Schizophrenia	Atypical	Sz affective	Bipolar	Unipolar
Worst premorbid social adjustment	Schizophrenia	Atypical	Unipolar	Sz affective	Bipolar
Youngest age at onset (males)	Schizophrenia	Sz affective	Atypical	Unipolar	Bipolar
Low deliberate self harm	Bipolar= Schizophrenia= Atypical			Sz affective	Unipolar
Most insidious onset	Schizophrenia	Atypical= Sz affective		Unipolar	Bipolar
Most difficult rapport*	Schizophrenia	Sz affective	Atypical	Unipolar	Bipolar
Most deterioration	Schizophrenia	Sz affective	Atypical	Unipolar	Bipolar
Most severe course	Schizophrenia	Sz affective= Atypical		Unipolar	Bipolar
Least fertility	Schizophrenia	Atypical	Sz affective	Bipolar	Unipolar
Least married	Schizophrenia	Atypical	Sz affective	Bipolar= Unipolar	
Least family history other psychiatric disorder	Schizophrenia= Atypical		Bipolar	Sz affective= Unipolar	
Most detained					
Street drugs exposure	Schizophrenia	Atypical	Sz affective= Bipolar		Unipolar
Most alcohol use*	Atypical	Schizophrenia	Sz affective	Bipolar= Unipolar	
Most forensic involvement	Schizophrenia	Atypical	Bipolar	Sz affective	Unipolar

*denotes a non-significant difference between the diagnoses

Conclusion

In summary, both the latent classes and the condensed diagnoses are validated by several external variables. The reduced number of latent classes does not appear to produce a less valid division of the underlying disease entity, and in terms of age of onset appears to delineate those affected more clearly. It can be concluded that the latent classes are at least as useful as the traditional diagnostic categories in this population with respect to association with external validators.. However, the latent classes are not superior to DSM-III-R diagnoses in identifying homotypic disorders in affected relatives (table R6).

Usefulness of the classes and dimensions

Genetic studies

For genetic studies, four latent classes which are well demarcated are a useful alternative to the classical diagnostic systems. This is of particular relevance when population samples of people with psychosis are studied because a substantial minority of these do not fall neatly into bipolar disorder or schizophrenia and the categorisation of schizoaffective disorders, atypical psychosis and paranoid states are recognised as being particularly unreliable (Roy *et al.* 1997). However, a decision still has to be made regarding whether all the classes should be considered as a group for association and linkage studies, or if there should be three classes, since in terms of outcome and other variables, bipolar class and disorganisation class are very different. The reality distortion/depression class and the depression classes, while able to be separated on some variables, are less clearly defined in terms of external validators. The data in this study are as yet untested in terms of association studies of putative susceptibility genes. While further empirical studies may support these latent classes, ultimately their validity can only be proven unequivocally by the identification of these or other biological markers.

A similar caveat applies to the dimensions of psychosis which have been identified. These should prove useful in quantitative trait loci (QTL) approaches in genetic studies. Although the factors identified appear valid, this apparent validity will ultimately depend upon the identification of biological markers which are differentially distributed among these dimensions.

Other studies

It would be of great interest to determine if the four latent classes were different with respect to traits which have been previously identified in people with schizophrenia and their relatives e.g. P50, Continuous Performance Test, or eye tracking difficulties. The regression factor scores on the various dimensions are particularly useful for tests which have continuous scores.

Clinical work

It is not suggested that the four latent classes described should replace the current diagnostic criteria, but they may nevertheless inform the future evolution of these criteria. If four classes adequately represent functional psychosis can a case be made for the current plethora of diagnostic categories? More empirical work is required using population based samples.

Factor analysis may be of more immediate clinical value. Once the factors are derived a simple scale can be constructed for each dimension, and a person's longitudinal course plotted with respect to each dimension. This would have the added benefit of continuing to apply even if the diagnostic category changed due to a fluctuating clinical picture. Thus the use of factor analysis need not be confined to research settings. However this would require integration into current training methods in psychiatry before being used to augment traditional diagnoses.

Some limitations of the Hamilton psychosis study

The major limitations in the study methodology are referred to in the methods chapter and at relevant points in the discussion but two are worth mentioning here. The use of a large number of statistical comparisons in establishing the validity of the dimensions and classes may have caused some false positives. However, two tailed tests of significance were used and significance levels were often well below the 5% cut-off. In addition, all of the classes and dimensions were supported by a pattern of associations with a variety of different variables, and did not rely on any one single outcome measure.

The major problem in the study is one common to retrospective case note analyses: how can the impartiality and reliability of the original clinicians be confirmed? Thus while OPCRIT was coded by the author and all attempts were made to impartially interpret the notes an inherent bias on the mindset of the clinician describing the symptoms cannot be accounted for. It can be observed that some clinicians interpret symptoms through a schizophrenia lens. An effort was made to make use of all notes available, and it is hoped that where such biases occur these are averaged out over the lifetime of the case notes. Inherent biases in this author's approach to OPCRIT are unlikely to have confounded the outcome of the two analyses since these were unknown when the notes were coded.

Suggested improvements to the Hamilton psychosis study

Improved case detection

During the time frame of the Hamilton Psychosis study it was clear that some cases which should have been identified in the 1993 cohort were missed, subsequently being identified in the 1996-1999 cohort. No formal analysis of why the cases were overlooked was undertaken. Such an analysis may help improve the pick up rate if systematic failures were identified. Since the end of the Hamilton psychosis study, a needs assessment randomised controlled trial has been undertaken, using the population identified and enhancing this with incident cases and other cases hitherto missed. The latter was augmented by a hand search of all case notes from the Hamilton area. Thus there will soon be an estimate of the error in case ascertainment. Meanwhile an insight into the scale of the difficulty was afforded by a study subject who reported that several siblings had, at one time or another, suffered very similar illnesses without ever seeking medical attention.

Exclusion of learning disabillty cases

A weakness of the study was the indistinct boundary for learning disability. It would be easy to conclude that those whose intelligence quotient places them within the mild learning disability range should simply be excluded from such a study. However, the decrease in intelligence associated with schizophrenia suggests this would be a missed opportunity. Instead any future study should include all those with psychosis, no matter the degree of learning disability. This may cause logistical difficulties in terms of diagnosis but avoids the risk of missing potentially important information.

Inclusion of a wider range of psychopathological parameters

While OPCRIT provided a fairly comprehensive set of information, it lacks a good account of anxiety or obsessional symptoms, both of which are common in psychotic disorders. This would be a minimal baseline. However, the inclusion of some measures of temperament and early developmental milestones may be highly informative. In a recent consideration of the difficulties in measuring symptom dimensions in schizophrenia Peralta & Cuesta (2001) listed 48 studies with sample sizes in excess of 100, and concluded that the measurement instrument had the strongest influence. Other influences included statistical analysis, phase of the illness, level of analysis of the symptoms (ie whether grouped or not) and descriptive bias. In their view there was a need to develop a comprehensive instrument to properly ascertain dimensions.

Different statistical approaches

Latent class analyses forces each subject into one of a set of mutually exclusive classes. It could be argued that this can never model the true underlying psychosis entities, which are unlikely to have such sharply defined boundaries. Since there are a finite number of behavioural or other measurable attributes in psychosis it is likely that the boundaries between these disorders are less clearly defined. Under such circumstances a more appropriate approach in defining the underlying entities would be Grade of Membership analysis (GoM). This multivariate statistical procedure was devised to process categorical data for diagnostic purposes. Here a "fuzzy" clustering approach is adopted. The procedure identifies "pure types" which are intended to correspond to some proptotypical cases and subjects are assigned a score describing their degree of membership to each pure type on the basis of both the number of features of that pure type they exhibit and dissimilarity from the features of the other pure types. Thus each individual can be

assigned partial membership to more than one pure type. This approach has been used successfully in psychiatry (Manton *et al* 1994) and also in linkage analysis where composite neurocognitive and personality trait measurements supplemented clinical diagnosis, allowing identification of subsets of families at high genetic risk, increasing the power of genetic analysis (Hallmayer *et al.* 2003).

An alternative to new studies: recycle data

While more population-based empirical approaches are necessary, a less expensive approach which would be of more short-term benefit would be to re-examine data from previously undertaken empirical studies. It would be of great interest to re-examine Kendler *et al's* data from the Roscommon family study, but using latent classes derived purely from symptoms and observing the familial patterns. While a family study of the Hamilton cohort is unlikely in the near future it would be fascinating to discover how the familial risk for these latent classes is distributed. One might expect the disorganisation group to have an excess of first degree relatives with schizophrenia. An alternative hypothesis is that it is the reality distortion/ depression class which has an excess of relatives with schizophrenia and the disorganisation class is less "genetic" than the others.

There will be in existence several datasets which could be re-analysed using different methodologies and the results compared. The goal would be to make best use of the existing data, and attempting to make valid comparisons across studies which would avoid unnecessary repetition and inform the degree to which empirical studies can ever address the question of the true psychosis phenotype in the absence of biological markers.

Future studies: a caveat

It is important that as different models of psychosis emerge, superficial similarities are not mistaken for truly similar results. There is a particular danger in this if many studies show the existence of four classes or dimensions with similar titles. In each case the methodologies and results need careful scrutiny to avoid spurious apparent replications. Likewise, it is important that the number of classes or dimensions does not become a focus of concern. It has been shown that all of these are very sensitive to the methodologies applied. The focus of effort should rather be delineating the best methodological approach to the problem and applying this in multicentre studies. Debates about numbers and

characteristics of dimensions or classes which are rooted in disparate methods are wasteful and meaningless.

However it must be remembered that rating instruments often provide reliability at the expense of losing some of each of the subjective and intersubjective components of psychosis assessment (Parnas 2000). These should not be ignored because of difficulties in measurement. Perhaps inclusion of such subtle characteristics might substantially enhance our ability to identify the underlying psychopathological entities.

Is the Kraepelinian dichotomy justified?

It may be that the Hamilton study confirms the Kraepelinian model in the same way that Murray and O'Callaghan (1991) describe in their chapter "Kraepelin lost, Kraepelin found". They argue, based on data from the Camberwell first episode psychosis study, that while the empirical approach does not support the current syndrome of schizophrenia, it does support a clear distinction between dementia praecox and bipolar disorder. Certainly the Hamilton results show a very clear distinction between disorganisation and bipolar classes, in terms of symptoms and almost every external validator tested. But following Kendell and Jablensky's assertion, has a zone of rarity been identified by the Hamilton data? There is a clear zone of rarity between disorganisation and bipolar classes, but the intermediate classes are less distinct in terms of outcome.

Arguably the disorganisation class does appear to be of a different substance compared with the other classes. It is intriguing that it is this class alone which accounts for the difference in age at onset. This may confound the observation that it is only this class which shows an association between a gender difference in the age at onset and negative family history. Likewise, it is the disorganisation class alone which shows a strong trend towards an association between summer birth and deficit syndrome. These findings support the view that this class has a lesser (or at least different) genetic influence compared to the other classes. Such a conclusion must be tentative, since the definition of deficit syndrome and family history used in this study are not strict equivalents of those reported in the literature. However, the distinctive pattern of external validation which includes a wide range of different sorts of data from first rank symptoms to fertility strongly suggests that the disorganisation class is a class apart.

Thus the Hamilton data challenges but does not disprove the continuum theory. The problem with suggesting that it lends support to the binary theory is this. There was never

any real supposition that the binary model accounted for all of psychosis, with even Kraepelin agreeing that interforms were common. One suspects that the model was retained in Kraepelin's day because the alternative was chaos, and the binary model at least provided a coherent framework on which to investigate these disorders. The retention of the binary model into the present day has been due to the lack of a readily identifiable alternative. It can be argued that different means of categorising may have different uses, and that the current diagnostic system for the psychoses works as a clinical tool, even if in terms of research it is inherently flawed.

An identifiable alternative would be to take the bold (and almost unthinkable) step of reclassifying the psychoses from first principles, based on a series of larger population based empirical studies than the one described here. The clear danger in retaining the current classification systems is that the binary model pervades all aspects of thinking about psychotic disorders. Yet the concept of having a research nosology distinct from clinical nosology is untenable. How could the clinical diagnostic criteria continue to be supported if research did not refer to these categories? What must be addressed is the reluctance of psychiatry to let go of a concept which has been useful but has served its purpose. The current concept of schizophrenia is not that of Kraepelin, and is probably too heterogeneous. The latent classes identified here point to the utility of dementia praecox (disorganisation class) as an entity which may have a lesser genetic component and very different presentation to the reality distortion/ depression class. Indeed the former class captures that which is quintessentially schizophrenia, and is the only class which can truly be called non-affective. The bipolar class is likewise very different. A new vocabulary may be required to name the other two classes. Perhaps after a hundred years of service, the term schizophrenia needs to be rested, and solid and substantive reasons established before any future re-introduction of the term. Until the terminology is changed, the assumptions inherent to the word will persist and continue to restrict the recognition of the true underlying subtypes in psychosis.

Conclusion

Factor analysis and latent class analysis are useful in attempting to reveal the latent variables in psychosis which might better represent underlying diseases compared to traditional diagnoses. Validation of the four latent class, four orthogonal factor model of psychosis supports the hypothesis that examining a population based cohort with these statistical methods more clearly defines the underlying diseases. The four factors derived from factor analysis are likely to be useful in a quantitative trait loci approach in psychiatric genetics. Likewise the four latent classes should provide clearer phenotypes for linkage and association studies of the psychoses. While it is hoped that the four latent classes may truly be "dividing nature at its joints", this can only be proven if, and when, biological markers are found which are differentially distributed across these four classes.

Appendix 1

Glossary of input items for OPCRIT Version 3.31

1. Source of rating
   1= Hospital case notes (charts).
   2= Structured interview with subject
   3= Prepared abstract
   4= Interview with informant
   5= Combined sources including structured interview
   6= Combined sources not including structured interview

2. Time frame
   1=Present or most recent episode
   2=Worst ever episode
   3=Lifetime ever occurrence of symptoms & signs
   4=Other specified episode or time period

3. Sex Code:
   0 = male, 1 = female.

4. Age of onset: This should be given to the nearest year and is defined as the earliest age at which medical advice was sought for psychiatric reasons or at which symptoms began to cause subjective distress or impair functioning.
   (enter age in years,eg 35)

5. Mode of onset
   1= Abrupt onset definable to within hours or days
   2= Acute onset definable to within 1 week
   3= Moderately acute onset definable within 1 month
   4= Gradual onset over period up to 6 months
   5= Insidious onset over period greater than 6 months
   Rate up if in any doubt

6. Single : The subject has never married or lived as married.
   (0=married,1=single)

7. Unemployed at onset: The subject was not employed at onset as defined above. Women working full time in the home score as if employed. Students attending classes on full time course, score as if employed.
   Employed = 0, Unemployed = 1.

8. Duration of illness in weeks (max=99)
   Total duration of illness includes prodromal and residual disabilities as well as the active phase of illness.In psychotic disorder 'prodromal/residual phase' symptoms count as any 2 of the following before or after an active episode: Social isolation/marked impairment in role/markedly peculiar behaviour/marked impairment in personal hygiene/blunted, flat or inappropriate affect/digressive, vague, over-elaborate speech/odd or bizarre ideation/unusual perceptual experiences.

Appendix 1 Glossary of input items for OPCRIT Version 3.31(continued)

9. Poor work adjustment: Refers to work history before onset of illness. It should be scored if the patient was unable to keep any job for more than 6 months, had a history of frequent changes of job or was only able to sustain a job well below that expected by his educational level or training at time of first psychiatric contact. Also score positively for a persistently very poor standard of housework (housewives) and badly failing to keep up with studies (students). (0,1)

10. Poor premorbid social adjustment: Patient found difficulty entering or maintaining normal social relationships, showed persistent social isolation, withdrawal or maintained solitary interests prior to onset of psychotic symptoms. (0,1)

11. Premorbid personality disorder: Evidence of inadequate/ schizoid/schizotypal/paranoid/cyclothymic/ psychopathic/sociopathic personality disorder present since adolescence and prior to the onset of psychotic symptoms.(0,1)

12. Alcohol/drug abuse within one year of onset of psychotic symptoms.Alcohol abuse where quantity is excessive (rater judgement) where alcohol related complications occur, during the year prior to first psychiatric contact (rated strictly as exclusion criteria for some definitions of schizophrenia)

    Drug abuse where non-prescribed drugs are repeatedly taken or prescribed drugs are used in excessive quantities and without medical supervision in year prior to first psychiatric contact.(0,1)(nb also items 77-82)

13. Family history of schizophrenia. Definite history of schizophrenia in first or second degree relative. (0,1)

14. Family history of other psychiatric disorder First or second degree relative has another psychiatric disorder severe enough to warrant psychiatric referral. (0,1)

15. Coarse brain disease prior to onset. There is evidence from physical examination and/or special investigations of physical illness that could explain all or most mental symptoms. This may include an overt brain lesion (or lesions),marked metabolic disturbance, or drug induced state known to cause psychotic disturbance,confusion or alteration of conscious level. Non specific abnormalities (eg enlarged lateral ventricles on ct brain scan) should not be included.(0,1)

Appendix 1 Glossary of input items for OPCRIT Version 3.31(continued)

16. Definite psychosocial stressor prior to onset.
A severely or moderately severely threatening event has occurred prior to onset of disorder that is unlikely to have resulted from the subjects own behaviour.(ie the event can be seen as independent or uncontrollable). (0,1)

17. Bizarre behaviour Behaviour that is strange and incomprehensible to others. Includes behaviour which could be interpreted as response to auditory hallucinations or Thought interference.(0, 1)

18. Catatonia : Patient exhibits persistent mannerisms, stereotypies, posturing, catalepsy, stupor, command automatism or excitement which is not explicable by affective change.
(0,1)

19. Excessive activity. Patient is markedly over-active. This includes motor, social and sexual activity. Score '1' for hyper-activity lasting at least one week and '2' for duration of at least two weeks.

20. Reckless activity. Patient is excessively involved in activities with high potential for painful consequences which is not recognised, e.g. excessive spending, sexual indiscretions, reckless driving, etc.
Duration of at least one week is scored '1' and of at least two weeks scored '2'.

21. Distractibility. Patient experiences difficulties concentrating on what is going on around because attention is too easily drawn to irrelevant or extraneous factors. Duration of at least one week scores '1' and at least two weeks scores '2'

22. Reduced need for sleep. Patient sleeps less but there is no complaint of insomnia. Extra waking time is usually taken up with excessive activities. Duration of at least one week scores '1' and two weeks scores '2'.

23. Agitated activity. Patient shows excessive repetitive activity, such as fidgety restlessness, wringing of hands, pacing up and down, all usually accompanied by expression of mental anguish. Score '1' if present for at least one week, '2' if present for two weeks and '3' if present for at least one month.

24. Slowed activity. Patient complains that he feels slowed up and unable to move. Others may report subjective feeling of retardation or retardation may be noted by examining clinician. Score '1' if present for at least one week, '2' if present for at least two weeks and '3' if present for at least one month.

Appendix 1 Glossary of input items for OPCRIT Version 3.31(continued)

25. Loss of energy/tiredness. Subjective complaint of being excessively tired with no energy. Score '1' for at least one week duration, '2' for two weeks and '3' for one month.

26. Speech difficult to understand. Speech which makes communication difficult because of lack of logical or understandable organisation. Does not include dysarthria or speech impediment.(0,1)

27. Incoherent Normal grammatical sentence construction has broken down. Includes "word salad" and should only be rated conservatively for extreme forms of formal thought disorder.(0,1)

28. Positive formal thought disorder The patient has fluent speech but tends to communicate poorly due to neologisms, bizarre use of words, derailments, loosening of associations. (0,1)

29. Negative formal thought disorder Includes paucity of thought, frequent thought blocking, poverty of speech or poverty of content of speech.(0,1)

30. Pressured speech. Patient much more talkative than usual or feels under pressure to continue talking. Include manic type of formal thought disorder with clang associations, punning and rhyming etc. Score '1' for duration of at least one week and '2' for a duration of at least two weeks.

31. Thoughts racing. Patient experiences thoughts racing through his head or others observe flights of ideas and find difficulty in following what patient is saying. or in interrupting because of the rapidity and quantity of speech. Score '1' for a duration of at least one week and '2' for a duration of at least two weeks.

32. Restricted affect. Patient's emotional responses are restricted in range and at interview there is an impression of bland indifference or 'lack of contact'. (0,1)

33. Blunted affect. Where the patient's emotional responses are persistently flat and show a complete failure to 'resonate' to external change. (NB. Differences between restricted and blunted affect should be regarded as one of degree, with 'blunted' only being rated in extreme cases).(0,1)

34. Inappropriate affect. Patient's emotional responses are inappropriate to the circumstance, e.g. laughter when discussing painful or sad occurrences, fatuous giggling without apparent reason .(0,1)

Appendix 1 Glossary of input items for OPCRIT Version 3.31(continued)

35. Elevated mood. Patient's predominant mood is one of elation lasting at least one week to score '1', or lasting at least two weeks to score '2'. If elation lasted less than one week but patient was hospitalised for affective disorder score '1'.

36. Irritable mood. Patient's mood is predominantly irritable and lasts at least one week to score '1' or at least two weeks to score '2'. If hospitalised for affective disorder a period of less than one week of irritable mood Score '1'.

37. Dysphoria. Persistently low or depressed mood, irritable and sad mood or pervasive loss of interest. Present for at least one week score '1', or score '2' if present for two weeks and '3' if present for one month.

38. Diurnal variation (mood worse mornings). Dysphoria/low mood and/or associated depressive symptoms are at their worst soon after awakening with some improvement (even if only slight) as the day goes on.(0,1)

39. Loss of pleasure. Pervasive inability to enjoy any activity. Include marked loss of interest or loss of libido. Score '1' for at least one week duration, '2' for at least two weeks and '3' for at least one month.

40. Diminished libido. Definite and persistent reduction in sexual drive or interest as compared with before onset of disorder. (0,1)

41. Poor concentration. Subjective complaint of being unable to think clearly, make decisions etc. Score '1' for at least one week's duration, '2' for at least two weeks and '3' for at least one month.

42. Excessive self reproach. Extreme feelings of guilt and unworthiness. May be of delusional intensity ('worse person in the whole world'). Score '1' for duration of at least one week, '2' for at least two weeks and '3' for at least one month.

43. Suicidal ideation. Preoccupation with thoughts of death (not necessarily own). Thinking of suicide, wishing to be dead, attempts to kill self. Score '1' for at least one week duration or a suicide attempt, '2' for at least two weeks duration and '3' for at least one month.

44. Initial insomnia. Patient complains that unable to get off to sleep and lies awake for at least one hour. Score '1' for duration of at least one week, '2' for duration of at least two weeks and '3' for duration of at least one month.

Appendix 1 Glossary of Input items for OPCRIT Version 3.31(continued)

45. Middle insomnia (broken sleep)
Most nights sleep disturbed; subject awakes in the middle of sleep and experiences difficulty in getting back to sleep.(0,1)
NB IF YOU ONLY HAVE INFORMATION ON 'INSOMNIA', SCORE ITEM 44 AND 45.

46. Early morning waking. Patient complains that persistently wakes up at least one hour earlier than usual waking time. Duration of at least one week scores '1', two weeks scores '2' and one month scores '3'.

47. Excessive sleep. Patient complains that sleeping too much. Score '1' if present for at least one week, '2' if present for at least two weeks and '3' if present for at least one month.

48. Poor appetite. Subjective complaint that patient has poor appetite. Not necessarily observed to be eating less. Score '1' if present for at least one week, '2' if present for at least two weeks and '3' for at least one month.

49. Weight loss. Score '1' for a loss of 1 lb per week over several weeks. Score '2' for a loss of at least 2 lb's a week over several weeks. Score '3' for a loss of at least 10 lb a over one year. Do not score those who have reduced weight as a result of dieting.

50. Increased appetite. Patient reports increased appetite and/or 'comfort eating'. Duration of at least one week scores '1', for at least two weeks scores '2' and at least one month scores '3'.

51. Weight gain. Score '1' for a gain of 1 lb a week over several weeks. Score '2' for a gain of at least 2 lb's a week over several weeks. Score '3' for a gain of at least 10 lb's over one year.

52*. Relationship between psychotic and affective symptoms.
0=No co-occurrence.
1=Psychotic symptoms dominate the clinical picture although occasional affective disturbance may also occur.
2=Psychotic and affective symptoms are balanced, with neither group of symptoms dominating the overall course of the illness.
3=Affective symptoms predominate although psychotic symptoms may also occur.
4=As in rating '2' (see above) plus delusions or hallucinations for at least 2 weeks but no prominent mood symptoms.

Appendix 1 Glossary of input items for OPCRIT Version 3.31(continued)

53. Increased sociability (0-2)
Score '1' for over-familiarity and score '2' for loss of social inhibitions resulting in behaviour which is inappropriate to the circumstances and out of character.

54. Persecutory delusions. Includes all delusions with Persecutory ideation.(0,1)
NB. WHEN SCORING DELUSIONS PLEASE SCORE EACH SEPARATE DELUSION UNDER ONE AND ONLY ONE CATEGORY DESCRIBING THE SPECIFIC TYPE OF THE DELUSION i.e. AS EITHER; PERSECUTORY, GRANDIOSE, INFLUENCE/REFERENCE, BIZARRE, PASSIVITY, PRIMARY DEL PERCEPTION,OTHER PRIMARY DEL, THOUGHT WITHDRAWAL, THOUGHT BROADCAST, THOUGHT INSERTION, GUILT, POVERTY OR NIHILISTIC.

55. Well organised delusions. Illness is characterised by a series of well organised or well systematised delusions. (0,1)
NB. THIS ITEM SHOULD BE SCORED IN ADDITION TO SCORING THE TYPE OF DELUSION/S DESCRIBED.

56. Increased self esteem. Patient believes that he is an exceptional person with special powers, plans, talents or abilities. Rate positively here if overvalued idea but if delusional in quality also score item 57 (grandiose delusions). Score '1' if duration at least one week and '2' if lasts at least two weeks.

57. Grandiose delusions. Patient has grossly exaggerated sense of own importance, has exceptional abilities or believes that he is rich or famous, titled or related to Royalty. Also included are delusions of identification with God, angels, the Messiah etc. (See also item 56). Any duration score '1', if symptom lasts at least 2 weeks score '2'.

58. Delusions of influence. Events, objects or other people in patient's immediate surroundings have a special significance, often of a persecutory nature. Include ideas of reference from the TV or radio, or newspapers, where patient believes that these are providing instructions or prescribing certain behaviour.(0,1)

59. Bizarre delusions. Strange, absurd or fantastic delusions whose content may have a mystical, magical or 'science fiction' quality.(0,1)

60. Widespread delusions. Delusions which intrude into most aspects of the patient's life and/or preoccupy the patient for most of his time.(0,1)
NB. THIS ITEM SHOULD BE SCORED IN ADDITION TO THE SCORING THE TYPE OF DELUSION/S DESCRIBED.

61. Delusions of passivity. Include all 'made' sensations, emotions or actions. Score '1' for all experiences of influence where patient knows that his own feelings, impulses, volitional acts or somatic sensations are controlled or imposed by an external agency (0,1).

62. Primary delusional perception. Score '1' where the patient perceives something in the outside world which triggers a special, significant relatively non understandable belief of which he is certain and which is in some way loosely linked to the triggering perception (0,1)

63. Other primary delusions. Includes delusional mood and delusional ideas. Delusional mood is a strange mood in which the environment appears changed in a threatening way but the significance of the change cannot be understood by the patient who is usually tense, anxious or bewildered. Can lead to a delusional belief. A delusional idea appears abruptly in the patient's mind fully developed and unheralded by any related thoughts.(0,1)

64. Delusions & hallucinations last for one week. Any type of delusion accompanied by hallucinations of any type lasting one week.(0,1)
NB. THIS ITEM SHOULD BE SCORED IN ADDITION TO SCORING THE TYPE OF DELUSION/S DESCRIBED.

65. Persecutory/jealous delusions & hallucinations .
This is self explanatory.
But note that abnormal beliefs are of delusional intensity and quality and are accompanied by true hallucinations.
(0,1)
NB. THIS ITEM SHOULD BE SCORED IN ADDITION TO SCORING THE TYPE OF DELUSION/S DESCRIBED.

66. Thought insertion. Score '1' when patient recognises that thoughts are being put into his head which are not his own and which have probably or definitely been inserted by some external agency.

67. Thought withdrawal. Score '1' when patient experiences thoughts ceasing in his head which may be interpreted as thoughts being removed (or 'stolen') by some external agency (0,1).

* This is called degree of affectivity in the list of items in the factor and latent class analyses

Appendix 1 Glossary of input items for OPCRIT Version 3.31(continued)

68. Thought broadcast. Score '1' when patient experiences thoughts diffusing out of his head so that they may be shared by others or even heard by others (0,1).

absence of any evidence to support this.(0,1)

70. Delusions of poverty.
Firm belief held by subject that they have lost all or much of their money or property and have become impoverished despite absence of any evidence to support this.(0,1)

71. Nihilistic delusions.
Firmly held belief that some part of patient's body has disappeared or is rotting away or is affected by some devastating or malignant disorder despite a lack of any objective supporting evidence.(0,1)

72. Thought echo. Score '1' if patient experiences thoughts repeated or echoed in his or her head or by a voice outside the head (0,1).

73. Third person auditory hallucinations. Two or more voices discussing the patient in the third person. Score '1' if either 'true' or 'pseudo' hallucinations, i.e. differentiation of the source of the voices is unimportant (0,1).

74. Running commentary voices. Patient hears voice(s) describing his actions, sensations or emotions as they occur. Score '1' whether these are possible 'pseudo' hallucinations or definite ('true') hallucinations (0,1).

75. Abusive/accusatory/persecutory voices. Voices talking to the patient in an accusatory, abusive or persecutory manner.(0,1)

76. Other (non affective) auditory hallucinations. Any other kind of auditory hallucination. Includes pleasant or neutral voices and non verbal hallucinations. (0,1)

77. Non-affective hallucination in any modality .
Hallucinations in which the content has no apparent relationship to elation or depression. Score '1' if present throughout the day for several days or intermittently for at least one week.

Appendix 1 Glossary of input items for OPCRIT Version 3.31(continued)

78. Life time diagnosis of alcohol abuse/dependence
Continued use despite knowledge of having a persistent or recurrent social,occupational,psychological or physical problem that is caused or exacerbated by alcohol; or recurrent use in situations in which it is physically hazardous; or symptoms definitely indicative of dependence.

One of the above must have occurred persistently for at least one month, or repeatedly over a longer period.(0,1)

79. Life time diagnosis of cannabis abuse/dependence
Continued use despite knowledge of having a persistent or recurrent social,occupational,psychological or physical problem that is caused or exacerbated by cannabis; or recurrent use in situations in which it is physically hazardous; or symptoms definitely indicative of dependence.

One of the above must have occurred persistently for at least one month, or repeatedly over a longer period.(0,1)

80. Life time diagnosis of other abuse/dependence
Continued use despite knowledge of having a persistent or recurrent social,occupational,psychological or physical problem that is caused or exacerbated by substance use; or recurrent use in situations in which it is physically hazardous; or symptoms definitely indicative of dependence.

One of the above must have occurred persistently for at least one month, or repeatedly over a longer period.(0,1)

81. Alcohol abuse/dependence with psychopathology
Abuse or dependence as defined under item 78 accompanied by any of the preceding items describing psychopathology.(0,1)

82. Cannabis abuse/dependence with psychopathology
Abuse or dependence as defined under item 79 accompanied by any of the preceding items describing psychopathology.(0,1)

83. Other abuse/dependence with psychopathology
Abuse or dependence as defined under item 80 accompanied by any of the preceding items describing psychopathology.(0,1)

84. Information not credible. Patient gives misleading answers to questions or provides a jumbled, incoherent or inconsistent account.
(0,1)

Appendix 1 Glossary of input items for OPCRIT Version 3.31(continued)

85. Lack of insight. Patient is unable to recognise that his experiences are abnormal or that they are the product of anomalous mental process, or recognises that his experiences are abnormal but gives a delusional explanation.
(1=lack of insight,0=insight present)

86. Rapport difficult. Interviewer finds difficulty in establishing contact with patient who appears remote or cut off. Does not include patients who are difficult to interview because of hostility or irritability.
(0,1)

87. Impairment/incapacity during disorder.
0= No impairment
1= Subjective impairment at work, school, or in social functioning
2= Impairment in major life role with definite reduction in productivity and/or criticism has been received
3= No function at all in major life role for more than 2 days or in patient treatment has been required or active psychotic symptoms such as delusions or hallucinations have occurred

88. Deterioration from premorbid level of functioning. Patient does not regain his premorbid social, occupational or emotional functioning after an acute episode of illness.(0,1)

89. Psychotic symptoms respond to neuroleptics. Rate globally over total period. Score positively if illness appears to respond to any type of neuroleptics, (depot or oral) or if relapse occurs when medication is stopped.(0,1)

90. Course of disorder.
1= Single episode with good recovery
2= Multiple episodes with good recovery between
3= Multiple episodes with partial recovery between
4= Continuous chronic illness
5= Continuous chronic illness with deterioration
(nb score this item in hierarchical fashion, eg if patient's course in past rated '2',but for the time-period now being considered it rates '4', then the correct rating is '4'.)

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