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PETER TYRER
Immigration and schizophrenia: the social causation hypothesis revisited*

BRIAN COOPER

Schizophrenia occurs in national populations with an annual prevalence of 1.4 to 4.6 per 1000 and incidence rates of 16–42 per 100 000 (Jablensky, 2000). Although the incidence rates vary between countries by a factor of less than 3, wider ranges of variation are found among population subgroups within single countries. In the UK, for example, incidence rate ratios of 4 or above have been estimated both for the lowest social class in the indigenous White population and for Black immigrant groups. These data provide the most compelling evidence yet to hand for the role of socio-economic factors in aetiology.

SCHIZOPHRENIA AND SOCIAL CLASS

Half a century ago the links between schizophrenia and socio-economic status were highlighted by research in the USA and Britain. By the mid-1960s the relevance of low socio-economic status had been confirmed by a range of studies, some focused on the urban ecology of mental disorders, others on social class differences in prevalence and incidence rates, course and outcome of illness, and patterns of medical treatment and care. A concentration of cases in low-status occupations was confirmed by area surveys and national statistics. Case rates repeatedly displayed class differentials, whether the categories were based solely on occupation, or incorporated other criteria such as education and district of residence.

An analysis for the General Register Office (Brooke, 1959) covered first admissions for schizophrenia in England and Wales in the quinquennium 1949–53. On average there were some 3000 new cases annually among men aged 20 years or over, corresponding to a national rate of 21 per 100 000. For single men (the great majority), the rate in social class V was 4.1 times as high as in social class I, and for the ever-married 3.5 times as high.

Prevalence studies over the same period showed that this relative excess was compounded by a worse clinical prognosis and a greater accumulation of chronic illness among the poor. Lower-class patients with schizophrenia were more likely to be brought to treatment by the police or social agencies, to be compulsorily admitted, to receive physical treatment or custodial care only and to become ‘long-stay cases’ (Cooper, 1961).

The observed social class gradient in schizophrenia generated a good deal of controversy. Initially it was thought to be causal in nature (the environmental ‘breeder’ hypothesis), especially as some researchers reported similarly skewed distributions in the families of origin. Soon, however, contrary evidence began to emerge. Goldberg & Morrison (1963), making use of birth register data, compared the occupations of men aged 25–34 years with a first admission for schizophrenia with those of their fathers at about the same age. They found a large excess of class V cases among the patients, but for the fathers the socio-economic status distribution was similar to that of the general population. Examination of the patient group revealed a pattern of poor scholastic and work achievement, and a career decline beginning typically in adolescence. Therefore, it appeared that the affected men had not been socially disadvantaged from birth, but suffered from functional impairments that had handicapped them at school and in early working life. This study, although not definitive, led many psychiatrists to conclude that premorbid social drift by itself (the ‘selective social drift’ hypothesis) provided a sufficient explanation of the epidemiological findings. Partly in consequence, progress in identifying environmental risk factors drew almost to a halt.

In the intervening years, low socio-economic status has shown no decline in importance as a public-health risk factor in the UK. As social inequality has increased in British society, so class differentials in mortality and morbidity have grown more pronounced (Whitehead et al, 1992). Whether class-specific rates for psychotic illness have also diverged nationally is unclear, although certainly local area rates continue to differ widely according to socio-economic level.

Although the importance of selective social drift stands confirmed, some more recent findings have drawn attention back to the environmental ‘breeder’ hypothesis. First, the broad association is now thought to be characteristic of modern urban society, and much weaker in rural communities, suggesting that features of big-city life may be causally implicated (Eaton et al, 2000). A number of studies support the notion that clustering of schizophrenia in decaying inner-city areas is not simply a consequence of geographic drift or segregation, but that being born or brought up in such areas is in itself a risk factor for the condition (Harrison et al, 2001). Second, data from an ongoing national cohort study in Sweden (Hjern et al, 2004) show convincingly that social adversity in childhood is associated with an increased risk of developing schizophrenia (S. Wicks, personal communication, 2004). Third, interest in environmental causes has been reawakened by evidence from a different quarter: the high rates of psychotic illness found among African–Caribbean and other Black immigrants in the UK.

SCHIZOPHRENIA AND IMMIGRANT STATUS

Evidence of a high frequency of schizophrenia in the Black immigrant population in the UK was first noted in the 1960s, and has been confirmed in reports from different parts of Britain. Case-control studies making use of population denominators from the 1991 or 2001 UK census to estimate standardised incidence rates for schizophrenia in different ethnic groups have underpinned the earlier findings (for review, see Jarvis, 1998; Sharpley et al, 2001). Standardised rate ratios have varied widely, partly because of widely differing estimates for the comparison groups, and

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*This editorial is based on a presentation at the 10th Congress of the International Federation of Psychiatric Epidemiology, 10–13 September 2004, Bristol, UK.
methodological differences between the studies are too great to permit pooling of the data. Nevertheless, in overview they suggest an approximately fourfold increase of risk in the target population. Preliminary findings of a multicentre British collaboration, the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study, provide a rate ratio of 6.8 (95% CI 5.6–8.3) for psychosis in African–Caribbean people compared with White (Fearon et al, 2004).

This phenomenon has aroused wide interest in possible underlying causes. Balanced reviews of the field have tended to favour a primarily social rather than a genetic explanation, on a number of grounds (Jarvis, 1998; Sharpley, 2001):

(a) The excess risk is not specific for African–Caribbean immigrants (themselves ethnically diverse); it is also present among African-born Black immigrants to the UK, and to a lesser extent among immigrants from Asian countries.

(b) Incidence rates of schizophrenia in Caribbean countries are similar to those found in the indigenous UK population, and much lower than reported rates among immigrants from that region. Morbid risk for schizophrenia in parents and siblings is about the same in those two populations. Yet the rate for schizophrenia in second-generation African–Caribbean people born in the UK appears to be higher than in the first generation, as is also the risk among patients’ siblings. This pattern is strongly suggestive of an environmental rather than a genetic effect.

(c) There is no evidence for selective immigration from the Caribbean as part of a pre-psychotic segregation or drift process. Indeed, given economic conditions in the 1950s and 1960s, it seems more likely that migration from the West Indies would have been selective for upwardly striving individuals.

(d) African–Caribbean patients with schizophrenia manifest more social handicaps than their counterparts in the indigenous White population. They are more likely to be unemployed, to have a record of convictions, to be resident in decaying inner-city areas, to be living alone, and to have experienced prolonged separation from both parents in early life.

Moreover, the base population from which these patients are drawn is disadvantaged in terms of socio-economic status, educational attainment, employment and housing standards, as well as being subject to racial discrimination. A study of 10-year-old children, conducted in the 1970s, suggested that a high proportion of second-generation Black immigrant children, raised in Britain, were growing up in overcrowded, multiple-occupancy houses; had mothers in full-time unskilled work; were being looked after by unregulated childminders, and had lived apart from one or both parents for more than 1 month (Rutter et al, 1975). Such children were also at increased risk of being taken into residential or foster care. Since the study was conducted in one inner-city borough of the kind in which Black immigrants are mainly concentrated, the comparative data probably underestimated the true extent of national differences.

(f) Characteristic of the immigrants’ pathways to psychiatric care are long delays in seeking professional help, a lower probability of medical referral, frequent involvement of the police and emergency services and high proportions of compulsory and secure-unit admissions. The long-term outcome tends to be correspondingly unfavourable for African–Caribbean patients (Takei et al, 1998).

**REAPPRAISING THE LINKS BETWEEN SOCIAL CLASS, IMMIGRANT STATUS AND SCHIZOPHRENIA**

There are thus striking parallels, with regard both to schizophrenia rates and to social characteristics, between the lower-class immigrant groups highlighted in earlier psychiatric surveys and the African–Caribbean population of Britain’s inner cities today. Reliable partialling out of the variance in incidence rates between social class and ethnic differences in schizophrenia is only now becoming possible. In one Swedish cohort study, risk ratios for all ethnic minorities were diminished – and among non-Europeans virtually eliminated – by adjusting for socio-economic differences (Hjern et al, 2004). Although comparable data for the UK are not yet available, the parallels outlined above already call for a reappraisal of environmental factors in schizophrenia.

Social drift theory alone does not explain the high rates found among Black immigrants, which must be due – wholly or in part – to environmental exposures. This conclusion lends support to the hypothesis that low socio-economic status is a risk factor for schizophrenia, and argues the need for a perspective that incorporates both social class and immigrant status.

Since the disorder may strike in families at any level of society, and is relatively uncommon at all levels, social disadvantage can be neither a sufficient nor a necessary cause, but must simply increase the probability of pathogenic exposures. What kinds of pathogenic might be implicated? To date most attention has been focused on adversity in adult life, including unemployment and poverty, social isolation, and residence in inner-city areas characterised by poor housing, overcrowding, lack of defensible space, and high levels of crime and illicit drug use. Here, however, two problems arise. To begin with, the population groups most subject to such conditions – namely, White people in the lowest socio-economic groups and Black immigrants to the UK – appear not to have comparatively large increases in risk for the common, non-psychotic forms of mental disorder. Second, the underlying vulnerability in schizophrenia seems to be determined in the earliest stages of life, pointing to the critical importance of harmful exposures at that time. A major challenge for psychiatric epidemiology will be, with the help of matched control and cohort studies, to ascertain the relative frequency of different developmental hazards among children born into the least privileged groups of society and to test their significance for schizophrenia and related psychoses.

**DECLARATION OF INTEREST**

None.

**REFERENCES**


The beginning of the end for the Kraepelinian dichotomy

NICK CRADDOCK and MICHAEL J. OWEN

For the past hundred years most clinical work and research in psychiatry has proceeded under the assumption that schizophrenia and bipolar affective disorder (or the corresponding earlier terms, such as dementia praecox and manic–depressive illness) are distinct entities with separate underlying disease processes and treatments. This so-called ‘Kraepelinian dichotomy’ has pervaded Western psychiatry since Emil Kraepelin (1919) ‘crystallised dementia praecox and manic–depressive illness from an amorphous mass of madness’ (Brockington & Leff, 1979), and remains enshrined in current classifications. However, many individuals with severe psychiatric illness have both prominent mood and psychotic symptoms – raising the possibility, indeed the likelihood, that there is not a neat biological distinction between schizophrenia and bipolar affective disorder. Genetic epidemiology has always been influential in shaping and validating psychiatric nosology (Robins & Guze, 1970). Now molecular genetic studies are beginning to challenge and will soon, we predict, overturn the traditional dichotomous view.

WHY HAS THE KRAEPELINIAN DICHOTOMY SURVIVED SO LONG?

In the absence of ‘laboratory’ tests based on a solid understanding of pathogenesis, the criteria available to psychiatry for validating nosological categories have been restricted to clinical features, outcome and family history (Robins & Guze, 1970). These were the tools used by Kraepelin in formulating his ideas and have been applied to research data in shaping the modern operational classifications. One of the key scientific observations supporting the Kraepelinian dichotomy was that the prototypical disorders tend to ‘breed true’. Thus, a consistent finding has been a substantially increased risk of schizophrenia but not bipolar disorder in the relatives of probands with schizophrenia, and vice versa in corresponding studies of bipolar disorder. It is also true that groups of individuals classified as having typical schizophrenia can be discriminated from sets of individuals classified as having typical bipolar disorder on the basis of clinical features and outcome.

As well as having apparent empirical support, the Kraepelinian view holds attractions for clinicians; it is conceptually simple and allows psychiatrists to demonstrate diagnostic expertise by exercising judgement over an often complex clinical picture and to reach a clear diagnosis. However, most psychiatrists, although willing to make use of the advantages of the dichotomy, are fully aware of its limitations, and this is mirrored in the failure of nosologists to identify any ‘point of rarity’ between the two disorders (Kendell, 1987). Cogent arguments for abandoning a categorical approach in favour of a dimensional or continuous formulation have been advanced (e.g. Crow, 1990). However, these failed to gain widespread support, in part because of a lack of robust scientific data, and possibly also because of the practical complexity of applying dimensional classifications in clinical practice and research settings.

WHY IS THIS DICHOTOMY NOW BEING CHALLENGED?

Evidence from genetic epidemiology has been gradually accumulating over the past two decades that is inconsistent with the dichotomous view, and recent molecular genetic findings seem set finally to overturn it. Key pieces of evidence include the following.

(a) Family studies point to the existence of a non-trivial degree of familial co-aggregation between schizophrenia and bipolar illness and between schizoaffective disorders and both bipolar disorder and schizophrenia (reviewed by Craddock et al, 2005).

(b) A recent twin study – the only one that has used an analysis unconstrained by the diagnostic hierarchy inherent in current classification systems – demonstrated an overlap in the genetic susceptibility to mania and schizophrenia (Cardno et al, 2002) and provided evidence that there are genes that confer susceptibility across the Kraepelinian divide, to schizoaffective disorder and to some cases of schizophrenia and bipolar disorder. This study also confirmed the traditional notion that there are genes specific to the two prototypical disorders.

(c) Systematic, whole-genome linkage studies of schizophrenia and bipolar disorder have implicated some chromosomal regions in common; this is consistent with the presence of shared susceptibility genes (Berrettini, 2003; Craddock et al, 2005).

(d) Most recently, and most convincingly, genes have been identified in which variation appears to confer risk to both schizophrenia and bipolar disorder. One example is the gene encoding D-amino acid oxidase activator (formerly known as the G72/G30 locus) on chromosome 13q, one of the regions implicated in genome scans of both disorders (Craddock et al, 2005). This locus was originally reported as showing association in schizophrenia in two independent samples. Subsequently association has been reported in bipolar disorder in three independent samples. Another example is the gene Disrupted in Schizophrenia 1 (DISCI). The gene, as the name implies, is disrupted in a family in which both schizophrenia and bipolar disorder co-segregate with a chromosomal translocation. Recent findings suggest that schizophrenia, schizoaffective disorder and bipolar disorder might be associated with polymorphisms in this gene (Craddock et al, 2005).

WHAT ARE THE IMPLICATIONS FOR PSYCHIATRIC RESEARCH?

The Kraepelinian dichotomy has served academic psychiatry well. Indeed,
Kraepelinian diagnoses formed the basis of recent successes in genetics, probably because their net effect is to simplify the genetic architecture of the groups defined, albeit at the expense of excluding many cases. The dichotomy also formed the basis of the operational diagnostic criteria that brought a degree of rigour and reproducibility to psychiatric research. However, there is a danger that it will now impede rather than aid progress. The recent findings are compatible with a model of functional psychosis in which susceptibility to a spectrum of clinical phenotypes is under the influence of overlapping sets of genes which, together with environmental factors, determine an individual’s expression of illness (Fig. 1). Such a model, although a better approximation than the dichotomous view, is itself only crude. A more accurate model would probably be based in multidimensional space because, in addition to the interface between bipolar disorder and schizophrenia, there is genetic overlap between the functional psychoses and major depressive disorder – and, indeed, other disorders – with extension into subclinical (or normal) variation. It seems likely that sets of overlapping genes will be identified that confer risks along different domains of psychopathology, corresponding to the disruption of different brain systems. Unravelling the biology underlying these overlaps will shed light on the bewildering degree of ‘comorbidity’ observed across disorders and the widespread non-specificity of treatments.

This research agenda will best be served by adopting broader inclusion criteria for the functional psychoses and by a combination of inductive and hypothesis-driven approaches aimed at relating biological processes to symptoms and syndromes defined at both clinical and endophenotypic levels. This will require more detailed clinical analysis and the integration of data across multiple domains such as genetics, environmental measures, brain imaging and cognitive neurosciences. In order to achieve this, academic psychiatry will need to scale up its ambitions and plan detailed multidisciplinary, multicentre studies of large numbers of individuals with psychosis. The creation of the Mental Health Research Network under the auspices of the UK Clinical Research Collaboration offers a possible route towards such studies in the UK.

Genetics will have an increasingly important role in all research aimed at understanding the aetiology and pathogenesis of psychosis. As risk genes are identified, so it will become possible to determine how genetic variation relates to clinical variation across and outwith current diagnostic categories, and to explore the relationship between variation in specific susceptibility genes and the disruption of functional systems using techniques such as imaging, psychological testing and neuropathological studies. Thus it will become increasingly possible to seek correlations between psychopathology and biological dysfunction. For example, genetic risk for prototypical schizophrenia might in part be mediated by neurodevelopmental abnormalities with associated structural brain changes and cognitive impairments (Murray et al, 2004). Risk of developing positive psychotic symptoms might be conferred by genetically influenced abnormalities in dopamine and glutamate neurotransmission, with abnormalities of synaptic function leading to abnormal connectivity (Owen et al, 2005). These suggestions are illustrative, to indicate the directions that research is likely to take in the coming decade and the power of genetics to shape this agenda. Epidemiology, too, will benefit from integration of the analysis of genetic and environmental risk factors and exploration of the interplay between these two classes of aetiological agent.

**WHAT ARE THE IMPLICATIONS FOR CLINICAL PRACTICE?**

In the coming years psychiatrists are likely to have at their disposal simple and inexpensive tests to help identify the pathways involved in an individual’s illness and thereby inform treatment decisions. Such tests will not replace the clinical skills now used in diagnosis and management but will be tools to aid these processes, much as lipid levels and blood enzyme measurements aid cardiologists in management of cardiovascular disease.

Changes in classification will accompany the improvements in understanding of pathogenesis. These will require clinicians to embrace classifications that are both more complex (more categories or, perhaps, dimensions) and also simpler (because they map on to the biology of the illness more closely). These developments have much to offer patients and the professional standing of psychiatry. Most patients want to be given an unambiguous and accurate diagnosis, but psychiatrists are understandably reluctant to be too dogmatic in the early stages of psychotic illness, recognising that the cross-sectional picture may change longitudinally – often frustrating patients, leading to diagnostic revisions between categories and creating an impression that psychiatrists are indecisive or incompetent. Moving to a spectrum concept (be it with categories or dimensions) with recognition of overlapping pathogenetic factors and varying expression (dependent upon both genetic risk and environmental

**Fig. 1** Possible relationship between susceptibility genes and the clinical picture for disorders in the psychosis–bipolar spectrum. Recent genetic studies suggest that there are genes specific to schizophrenia (S), genes specific to bipolar disorder (B) and genes that confer risk to schizoaffective disorder, schizophrenia and bipolar disorder (M). The combination of susceptibility genes inherited by an individual, together with the environmental exposures, determine the key clinical features of the illness, positioned on a spectrum from prototypical schizophrenia at one end to prototypical bipolar disorder at the other. Most cases lie somewhere in the central part of the spectrum.
exposure) would allow a confident and clear diagnosis to be offered (perhaps ‘psychosis-spectrum illness’ or ‘mood–reality disorder’), with a clear explanation that some specific tests and a period of observation will help to clarify the likely course of illness and response to treatment. This would be greatly preferable to the current situation and the inevitable consequences of damage to the therapeutic alliance caused by diagnostic revisions.

The Kraepelinian dichotomy has been useful for a hundred years. Now it is time to move on.

**DECLARATION OF INTEREST**

The authors are consultants to GlaxoSmithKline and have received honoraria for academic talks from Eli Lilly, AstraZeneca and GlaxoSmithKline.

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From ‘obstetric complications’ to a maternal–foetal origin hypothesis of mood disorder

VERONICA O’KEANE and JAN SCOTT

The original findings of apparently higher rates of maternal obstetric complications among people with schizophrenia, compared with control populations, suggested that non-genetic intra-uterine events might influence the development of schizophrenia in adulthood. This concept evolved into the neurodevelopmental hypothesis of schizophrenia and led to several new lines of investigation, including developmental epidemiological studies examining childhood risk factors for adult schizophrenia. The obstetric complications literature appears to have expanded conceptually in parallel with the evolving story of the neurodevelopmental hypothesis. A large number of studies examining the importance of antenatal and birth-related insults, with a wide range of designs from retrospective case–control studies to ecological studies, are encompassed in this broad category (Cannon et al, 2002). This investigative work has gradually become divorced from the core meaning of the term, i.e. medical complications of pregnancy and labour.

A parallel approach has occurred in the mood disorder literature, where investigations of antenatal risk factors in the aetiology of mood disorders are performed largely using atheoretical models, which may explain why the findings are ostensibly negative. In contrast, there is much evidence from other sources that antenatal events can have profound influences on the subsequent development of mood disorders. This evidence is presented below, together with a hypothesised pathophysiological process.

OBSTETRIC COMPLICATIONS: WHAT ARE WE MEASURING?

Pasaminick et al (1956) first introduced the concept of the ‘continuum of reproductive casualty’ as a possible relevant mechanism in the aetiology of behavioural disorders. Research into mood disorders, as in schizophrenia, has mainly focused on quantifying pregnancy complications (e.g. diabetes, pre-eclampsia or bleeding) or delivery complications (e.g. emergency Caesarean section) in case–control study designs. Although some studies identify an excess of specific events in cases, there is no consistent pattern in their gestational timing or nature. A recent meta-analytic review has found no significant association between ‘broadly defined’ obstetric complications and later affective disorder (Scott, 2004). The majority of these studies, however, have applied measures of obstetric complications that encompass a wide range of unrelated events and exposures, and have generally viewed such complications as a unitary phenomenon. Clustering of the phenomena into a homogeneous group is difficult to justify intellectually and may also camouflage group differences in more discrete areas. A hypothesis-based approach, based upon a consideration of the physiological processes leading to the obstetric complication, would be more informative.

MATERNAL PSYCHOLOGICAL STRESS AND BIRTH OUTCOME

If one moves from a position of measuring a cluster of obstetric events to one of assessing more global measures of obstetric health and gestational outcome, a different picture emerges. Birth weight is the gold standard measure of pregnancy outcome. Barker’s seminal ‘Hertfordshire cohort’ studies demonstrated a relationship between decreasing birth weight and increasing risk of depression in old age in men (Thompson et al, 2001). Furthermore, a study of offspring of parents with bipolar disorder demonstrated that low birth weight was associated with subsequent development of mood disorders, irrespective of genetic loading (Wals et al, 2003).

There is an emerging consensus from the obstetric literature that psychosocial stress during pregnancy is associated with low birth weight and preterm delivery (Dole et al, 2003). Although depression represents the best-studied model of a chronic stress response, there is no report on the effects of operationally defined depression during pregnancy on baby outcome. However, self-reported depression and probable ‘caseness’ measured using the Edinburgh Postnatal Depression Scale have been found to predict preterm delivery and small-for-gestational-age babies (Steer et al, 1992; Dyan et al, 2002).

The association of gestational stress with poor pregnancy outcome is made more pertinent by the relatively new finding that pregnancy-related mood disorder may be both more common and symptomatically more severe than postnatal depression in community populations (Evans et al, 2001). A 4-year follow-up of the offspring from the Avon Longitudinal Study of Parents and Children found increased emotional and behavioural problems in the male offspring of women with high anxiety scores during pregnancy (O’Connor et al, 2002). This is the first prospective human study linking maternal psychopathology in the antepartum period with that in the offspring. These prospective findings confirm earlier retrospective reports of an association between antenatal maternal stress (e.g. following loss of a spouse, or following exposure to famine or earthquake) and subsequent development of psychopathological disorder in the offspring (see Cannon et al, 2002).

MATERNAL–FOETAL ORIGINS HYPOTHESIS

An association between low birth weight and the development of adult medical and metabolic diseases has been repeatedly demonstrated. The foetal origins hypothesis, derived from this association, suggests that exposure of the foetus to an adverse environment in utero leads to permanent programming of tissue function and subsequent increased risk of developing adult cardiovascular and metabolic diseases (Barker, 1998). One system implicated in the putative altered programming in utero is the hypothalamic–pituitary–adrenal (HPA) axis.

A neurobiological model of prenatal stress is now emerging which proposes that
maternal stress exerts a negative influence on foetal developmental outcome that is mediated by the HPA system (Wadhwa et al., 2002). Central to an understanding of how overdrive of the maternal HPA axis may alter foetal development is the knowledge that maternal–foetal communication during gestation is endocrine rather than neural, and cortisol levels in the foetus correlate with those in the maternal circulation. This has important implications, since high levels of cortisol inhibit intra-uterine growth, may accelerate the onset of parturition indirectly and may alter the regulation of glucocorticoid receptors in the brain of the developing foetus. Hypercortisolaemia has been consistently found in association with major depressive disorder, and is widely attributed to oversecretion of the hypothalamic peptide corticotrophin-releasing hormone (CRH), which in turn has been attributed to reduced negative feedback by glucocorticoids on CRH secretion in the brain (Pariante & Miller, 2001). Intra-uterine exposure to high levels of cortisol could permanently increase the ‘set point’ for HPA axis deactivation in relevant brain areas, resulting in stress responses and behavioural alterations consistent with depressive illness (Thompson et al., 2001).

Support for the prenatal stress hypothesis is derived from animal models. The offspring of pregnant rhesus monkeys, exposed to either large amounts of synthetic glucocorticoids or psychological stress, have increased HPA axis stress responses, reduced suppressibility of the HPA axis, increased levels of emotional reactivity, altered immune responses, and reduced hippocampal volume and neurogenesis in the dante gyrus (Coe et al., 2003). These findings are all consistent with those in depression in humans.

There is no empirical evidence at present that the foetal HPA axis is modified by maternal stress, resulting in long-term alterations to the stress response of the offspring. However, some indirect evidence exists that gestational stress results in maternal HPA activation and is associated with poorer baby outcome. Measures of psychosocial stress during pregnancy are correlated with adrenocorticotropic hormone and cortisol levels (Wadhwa et al., 1998), and high CRH levels have been found to predict shorter gestational length (Moawad et al., 2002).

In summary, it is increasingly evident that the health status of an infant at birth is both determined by multiple medical, obstetric and psychological events during pregnancy, and is prospectively a determinant of long-term health and quality of life. The literature on obstetric complications in psychiatry has traditionally examined the impact of adverse events during the antepartum period and birth on the subsequent development of schizophrenia. Transposing this methodology in an unmodified way to mood disorders results in largely negative findings, i.e. a lack of a causal association between obstetric complications and adult mood disorders (Scott, 2004). From the perspective of prenatal stress, however, there is a wealth of evidence to support such an aetiological link. Psychological stress in pregnancy is associated with poor birth outcome; population follow-up studies demonstrate that poor birth outcome is associated with mood disorders in adulthood; and there is compelling animal evidence that gestational stress leads to animal analogues of depression in the offspring. The growing evidence that psychological trauma during childhood permanently alters HPA axis responses (Wadhwa et al., 1998, 2002) demonstrates the prolonged plasticity and vulnerability of these stress systems in humans and underlies the potential impact that maternal stress may have on foetal brain development. Psychiatry must reissue the notion of obstetric complications and the genesis of mood disorders in the light of these findings. An obvious starting point is maternal mental health during pregnancy – an issue that has been overlooked by clinicians and researchers for too long.

DECLARATION OF INTEREST

None.

REFERENCES


Regional volume deviations of brain structure in schizophrenia and psychotic bipolar disorder

Computational morphometry study

COLM MCDONALD, ED BULLMORE, PAK SHAM, XAVIER CHITNIS, JOHN SUCKLING, JAMES MacCABE, MURIEL WALSH and ROBIN M. MURRAY

Background It is unclear whether schizophrenia and psychotic bipolar disorder are associated with similar deviations of brain morphometry.

Aims To assess volumetric abnormalities of grey and white matter throughout the entire brain in individuals with schizophrenia or with bipolar disorder compared with the same control group.

Method Brain scans were obtained by magnetic resonance imaging from 25 people with schizophrenia, 37 with bipolar disorder who had experienced psychotic symptoms and 52 healthy volunteers. Regional deviation in grey and white matter volume was assessed using computational morphometry.

Results Individuals with schizophrenia had distributed grey matter deficit predominantly involving the frontal-temporal neocortex, medial temporal lobe, insula, thalamus and cerebellum, whereas those with bipolar disorder had no significant regions of grey matter abnormality. Both groups had anatomically overlapping white matter deficits in regions normally occupied by major longitudinal and interhemispheric tracts.

Conclusions Schizophrenia and psychotic bipolar disorder are associated with distinct grey matter deficits but anatomically coincident white matter abnormalities.

Declaration of interest None. Funding detailed in Acknowledgement.

The Kraepelinian dichotomy of schizophrenia and bipolar disorder has been controversial since it was introduced over a century ago (Kraepelin, 1899). There are no pathognomonic symptoms by which clinicians can reliably differentiate the two illnesses and there is increasing evidence that those with the two diagnoses may share some of the same genetic and environmental risk factors and neurological abnormalities (Walker et al, 2002). Schizophrenia is associated with a range of subtle abnormalities of brain volume identified using both hypothesis-driven region-of-interest and exploratory computational morphometry techniques. These include enlarged lateral and third ventricles and reduced prefrontal, temporal, thalamic and insular volumes (Wright et al, 2000; Hulshoff Pol et al, 2001; Sigmundsson et al, 2001). Brain structural abnormalities associated with bipolar disorder have been less extensively investigated, but may include lateral ventricular enlargement, an excess of white matter hyperintensities and volume reduction in some prefrontal regions (Bearden et al, 2001). Studies comparing brain volumetric deficits in individuals with schizophrenia and bipolar disorder against each other or the same control group are infrequent, inconclusive and confined to region-of-interest methodologies. In the present study we used computational morphometry to identify grey and white matter volume abnormalities throughout the entire brain in individuals with schizophrenia and those with bipolar I disorder who had experienced psychotic symptoms during exacerbation of illness. We hypothesised that both groups would demonstrate brain structural abnormalities compared with the same group of healthy volunteers. The similarities and differences in the pattern of abnormality were further clarified by a direct comparison between the two patient groups.

METHOD

Sample
Brain scans were successfully obtained by magnetic resonance imaging (MRI) from 114 individuals, comprising 25 with schizophrenia, 37 with bipolar I disorder and 52 healthy volunteers. Those with bipolar I disorder had experienced psychotic symptoms at some stage during exacerbation of illness. These participants were part of a larger study of families with more than one member with schizophrenia or bipolar disorder that included their unaffected first-degree relatives (McDonald et al, 2004). No unaffected relatives were included in the present study. We recruited patients through voluntary support groups or by direct referral from their mental health services; all had at least one other family member among their first- and/or second-degree relatives with the same or a related disorder. All patients were out-patients at the time of assessment. Healthy volunteers were recruited from the community via newspaper advertisements and from local staff, and were group matched to the patients and their unaffected relatives on the basis of age, gender and parental social class. None of the healthy volunteers had a personal history of any psychotic, bipolar or schizophrenia-spectrum disorder or a known family history of any functional psychosis. Participants were not included if they had a history of organic brain disease, head trauma resulting in loss of consciousness for more than 5 min or met DSM–IV criteria (American Psychiatric Association, 1994) for substance or alcohol dependence in the 12 months prior to assessment. The study protocol was approved by the ethics (research) committee of the South London and Maudsley NHS Trust. After a complete description of the study and its aims, informed consent was obtained in writing from all participants.

Patients and healthy volunteers were assessed using the same clinical scales. Structured diagnostic interviews were performed using the Schedule for Affective Disorders and Schizophrenia–Lifetime Version (SADS–L) (Spitzer & Endicott, 1978) and additional information regarding the timing and nature of psychopathology was collected to enable DSM–IV diagnoses to be made. Socio-economic status based on details of parental
Acquisition and pre-processing of magnetic resonance imaging data

For each participant a set of 1.5 mm thick contiguous coronal $T_1$-weighted magnetic resonance images encompassing the whole brain was acquired using a three-dimensional spoiled gradient echo sequence running on a GE N/Vi Signa System scanner (General Electric, Milwaukee, Wisconsin, USA) operating at 1.5T with the following parameters: time to repetition $= 13.1$ ms, inversion time $= 430$ ms, echo time $= 5.8$ ms, number of excitations $= 1$, flip angle $= 20^\circ$ and acquisition matrix $= 256 \times 256 \times 128$.

Optimised voxel-based morphometry (Good et al, 2001) was used to segment MRI data and to record probabilistic maps of grey matter and white matter volume density for each participant in a standard anatomical space. These pre-processing steps were implemented in Matlab version 6.0 (MathWorks, Natick, Massachusetts, USA) using SPM99 statistical parametric mapping software (Wellcome Department of Imaging Neuroscience, 2003). Each MRI scan was segmented into grey, white and cerebrospinal fluid (CSF) tissue classes in native space, and global tissue volumes were estimated. This and each other segmentation step used a modified mixture model cluster analysis technique with correction for non-uniformity of image intensity, combined with prior probabilistic knowledge of the spatial distribution of tissues, and included an automated procedure to remove non-brain tissue such as skull, scalp and venous sinuses (Good et al, 2001). Customised study-specific grey, white and CSF template images in standard stereotactic space were then created from the control group, in order to minimise any scanner-specific bias and provide a template matched to the sample. The tissue maps of controls were smoothed using an 8 mm full-width at half-maximum (FWHM) isotropic Gaussian kernel and then spatially normalised using parameters derived from applying a 12-parameter affine transformation of each unsmoothed grey matter map to the standard SPM $T_1$ grey matter template and applying these to the smoothed segmented images. The images were then averaged to create customised grey, white and CSF tissue templates in standard stereotactic space. The original brain scan of each participant was then normalised to the customised grey matter template, thus removing any contribution of non-brain tissue or other tissue types to this spatial normalisation step. The spatial normalisation used residual sum of squared differences to match images and both an affine transformation and linear combination of smooth cosine basis functions to model global non-linear shape differences. These normalisation parameters were applied back onto the original brain image to produce an image ‘optimally’ normalised for grey matter segmentation and the images were resliced at a final voxel size of $1.5$ mm$^3$. All images were checked visually to confirm that they were well matched to the template. The images were then resegmented, using the customised tissue templates as probability maps, and the grey matter maps retained. These grey matter maps were thus in standard stereotactic (Talairach) space. This procedure was repeated using parameters derived from normalising each white matter map to the white matter template and re-applying to the original image, in order to derive white matter tissue maps for each participant. The grey and white matter images were then modulated through multiplying voxel values by the Jacobian determinants from the spatial normalisation to correct for volume changes introduced at this step (Ashburner & Friston, 2000; Good et al, 2001). Finally, all normalised, segmented, modulated grey and white matter tissue maps were smoothed at 4 mm using a FWHM isotropic Gaussian kernel.

Statistical analysis of MRI data

Differences in grey matter and white matter volume between each patient group and the healthy volunteer group, and differences between the two patient groups, were estimated by fitting an analysis of covariance (ANCOVA) model at each intracerebral voxel in standard space, with age, gender and global tissue volume as covariates. We tested the null hypothesis by permutation at the level of spatially contiguous voxel clusters, as described in detail elsewhere (Bullmore et al, 1999). Briefly, a map of the standardised ANCOVA model coefficient of interest ($\beta$) at each voxel was thresholded such that if $\beta > 1.96$ (approximately, null probability of $\beta < 0.05$) the voxel value was set to $\beta = 1.96$, otherwise the voxel value was set to 0. This procedure generated a set of suprathreshold voxel clusters in three dimensions, each described by its ‘mass’ or the sum of suprathreshold voxel statistics it comprised. The mass of each cluster was tested against a null distribution ascertained by repeatedly re-estimating and thresholding the $\beta$ coefficient of the ANCOVA model at each voxel after repeated random permutations of group membership; the results of ten permutations at each voxel were pooled over all intracerebral voxels to sample the permutation distribution of three-dimensional cluster mass under the null hypothesis of no differences in brain structure between the two groups. A critical value for statistical significance of cluster mass was derived from this permutation distribution. For each between-group comparison, we used probability thresholds for cluster level testing such that the expected number of false-positive tests for each map was less than one; typically one-tailed cluster-wise $P < 0.01$. Significant clusters were anatomically labelled using the standard atlas of Talairach and Tournoux (Talairach & Tournoux, 1988). The principal advantages of cluster-level testing are that it confers greater sensitivity by incorporating information from more than one voxel in the test statistic, and it also substantially reduces the search volume or number of tests required for a whole brain analysis, thereby mitigating the multiple comparisons problem. Parametric tests for spatial extent statistics in brain mapping may be over-conservative; hence our preferred use of a relatively assumption-free non-parametric permutation test based on data resampling (Bullmore et al, 1999; Hayasaka & Nichols, 2003).

The mass of each cluster for each individual was transferred to a spreadsheet and, where multiple clusters were present, principal components analysis without rotation was used to explore the extent of correlation between discrete clusters and to reduce the dimensionality of the data prior to further analyses. Multiple linear regression with principal components scores as the dependent variable, and age, gender and global tissue volume as covariates, was used to test for a pathophysiological effect of gender on case-control differences in brain structure. The two-tailed probability threshold for significance was set at $P = 0.05$. 

MCDONALD ET AL
RESULTS

Sample characteristics

The socio-demographic profile of the participants is summarised in Table 1. There were no significant differences between the groups in age, years of education, proportion of subjects with higher parental social class or left-handedness. There was a significant gender difference between the groups because of a larger proportion of males in the schizophrenia group. The mean age at onset of first psychotic symptoms was 20.0 years (s.d.=5.0) for those with schizophrenia and the mean age at onset of first episode of affective disorder was 22.9 years (s.d.=5.5) for those with bipolar disorder. The mean duration of illness was 17.4 years (s.d.=10.4) for schizophrenia and 17.8 years (s.d.=11.3) for bipolar disorder. Of those with schizophrenia, 18 were taking atypical antipsychotic drugs at the time of scanning and the remaining seven were taking typical antipsychotics. Of those with bipolar disorder, 31 were taking mood stabilisers at the time of scanning (lithium carbonate in 22 cases), 1 was taking olanzapine alone and 5 were on no medication; 8 of those on mood stabilisers were also taking antipsychotic medication.

Grey matter differences between those with schizophrenia and healthy volunteers

Compared with healthy volunteers, those with schizophrenia had spatially distributed regions of grey matter volume deficit in 12 three-dimensional voxel clusters (Fig. 1, Table 2). These deficits were predominantly bilateral and included the hemispheres and vermis of the cerebellum, orbitofrontal cortex and temporal pole (more prominently on the right) extending to the lateral temporal cortex, anterior cingulate gyrus, basal ganglia, thalamus, medial temporal lobe, insula, dorsolateral prefrontal cortex (more prominently on the left), right postcentral gyrus and inferior parietal lobule, and the precuneus. Principal components analysis showed that deficits were highly correlated between regions. All clusters of grey matter volume deficit loaded positively on the first principal component, which explained 74% of the total variance. Schizophrenia was strongly associated with reduced scores on this first component (B=-1.07, P<0.001, 95% CI –1.49 to –0.66) and there was no significant interaction between diagnostic group and gender (B=0.27, P=0.55, 95% CI –0.61 to 1.14), indicating that this pattern of grey matter deficit was not differentially expressed by males and females with schizophrenia. There were no significant regions of relative grey matter excess in those with schizophrenia compared with healthy volunteers.

Grey matter differences between those with bipolar disorder and healthy volunteers

Compared with healthy volunteers, those with bipolar disorder demonstrated no significant abnormalities (neither deficits nor excesses) of grey matter structure.

Grey matter differences between those with bipolar disorder and schizophrenia

Participants with schizophrenia also demonstrated a distributed pattern of grey matter deficit when compared with those with bipolar disorder rather than with healthy volunteers (Fig. 2, Table 3). These deficits were located in several of the regions identified as abnormal in the case-control comparison for schizophrenia, including bilateral superior temporal neocortex, basal ganglia, insula, prefrontal cortex and precuneus, and right medial temporal lobe and thalamus. There were no regions of significant grey matter excess in those with schizophrenia compared with those with bipolar disorder.

White matter differences between those with schizophrenia and healthy volunteers

Compared with healthy volunteers, those with schizophrenia had deficits of white matter volume in two spatially extensive three-dimensional voxel clusters (Fig. 3, Table 4). These included parts of prefrontal, temporal and parietal lobes normally occupied by the long white matter tracts of the superior longitudinal fasciculus and occipito-frontal fasciculus bilaterally and the left inferior longitudinal fasciculus, as well as anterior and posterior parts of the corpus callosum. White matter volumes were highly correlated between clusters (r=0.90, P<0.001); mean cluster volume was therefore used to examine gender interactions. Those with schizophrenia had significantly reduced mean white matter volumes compared with controls (B=-1.59, P<0.001, 95% CI –2.46 to –0.72) and there was no significant interaction between diagnostic group and gender (B=0.64, P=0.49, 95% CI –1.18 to 2.46).

White matter differences between those with bipolar disorder and healthy volunteers

Compared with healthy volunteers, those with bipolar disorder had distributed regional deficits of white matter in four voxel clusters (Fig. 3, Table 5). These included parts of the brain-stem, prefrontal, temporal and parietal lobes normally occupied by the long white matter tracts of the superior longitudinal fasciculus and occipito-frontal fasciculus bilaterally, as well as anterior and posterior parts of the corpus callosum. All regions of white matter volume deficit loaded positively on the first principal component, which explained 72.4% of the total variance. Bipolar disorder was strongly associated with reduced scores on the first component (B=-0.79, P<0.001, 95% CI –1.19 to –0.39) and there was no significant interaction between diagnostic group and gender (B=-0.37, P=0.37, 95% CI –1.18 to 0.44).
White matter differences between those with bipolar disorder and schizophrenia

Notably, in both patient groups compared with healthy volunteers, there were extensive areas of white matter abnormality in anatomically coincident regions of bilateral frontal and temporo-parietal cortex (Fig. 3). Hence, the anatomical profile of white matter deficit was much more consistent between types of psychosis than the profile of grey matter deficit, which was highly specific to schizophrenia. We found no evidence for a significant difference in white matter structure between those with schizophrenia and those with bipolar disorder.

DISCUSSION

Grey matter differences

This study provides evidence that schizophrenia and bipolar disorder are characterised by quite distinctive abnormalities of brain structure in cortical and subcortical grey matter, and thus appear relatively discrete from this neurobiological perspective. Schizophrenia was associated with extensively distributed grey matter deficits involving the fronto-temporal neocortex, medial temporal lobe, insula and medial thalamic regions, all of which have been consistently reported to display volume deficits in prior region of interest and computational morphometric neuroimaging studies of schizophrenia (Wright et al., 2000; Hulshoff Pol et al., 2001; Sigmundsson et al., 2001). Other areas of volume deficit identified in the present study have also been described previously, including parts of the cerebellum (Nopoulos et al., 1999), right inferior parietal lobule (Kubicki et al., 2002) and precuneus (Hulshoff Pol et al., 2001).

The presence of grey matter deficit in prefrontal regions, thalamus and cerebellum provided the basis for the concept of ‘cognitive dysmetria’ in schizophrenia (Andreasen et al., 1998), i.e. the hypothesis that distributed pathology throughout key information processing nodes underlies the deficits in integrating and coordinating information associated with schizophrenia. We also found volume deficit of the basal ganglia in those with schizophrenia compared with healthy volunteers; this is at variance with several other studies which have reported increased basal ganglia volume. The basal ganglia is rich in dopaminergic input, and increased volume in patients with schizophrenia has usually been attributed to conventional or typical antipsychotic drugs, which potently block dopamine D2 receptors; thus, basal ganglia volume increase has not been found in patients who have had minimal exposure to typical antipsychotics or purely atypical antipsychotic drug treatment (Lang et al., 2001). In this context, we note that the majority of those with schizophrenia in our sample (18 out of 25) were taking atypical antipsychotic drugs; this may have disclosed disease-related reductions in basal ganglia volume that could be obscured by the volume-increasing effects of typical antipsychotics.

In sharp contrast to those with schizophrenia, grey matter volume was relatively well preserved (statistically indistinguishable from normal) in those with bipolar disorder, despite the fact that they were chosen to be closely akin to those with schizophrenia in terms of severity of illness and experience of positive psychotic symptoms. Brain structural changes in bipolar disorder are arguably under-researched, although some groups have reported volumetric abnormality within grey matter structures, such as enlargement of the amygdala (Altshuler et al., 2000) and reduction of the subgenual cingulate gyrus (Drevets et al., 1997); these were not found in the present study. Variable sample size and heterogeneity may account for some of these discrepancies. Structural neuroimaging studies of bipolar disorder have often been conducted using broad diagnostic categories such as ‘affective disorder’ or ‘affective psychosis’ which encompass a heterogeneous sample of patients. Since brain structural abnormalities in unipolar depression may differ from those in bipolar disorder (e.g. hippocampal volume is reportedly reduced in unipolar depression (Frodell et al., 2002) but preserved in bipolar disorder (Altshuler et al., 2000)), it is
arguable that adoption of broad diagnostic categories may have obscured brain structural differences specifically related to bipolar disorder. The possibility that medication could reverse or prevent grey matter volume deficit in bipolar disorder also cannot be excluded. Most of our patients were taking lithium, which is neurotrophic and has been reported to increase grey matter volume in vivo (Moore et al., 2000).

To the best of our knowledge, no prior neuroimaging study has specifically compared individuals with familial bipolar I disorder and a history of psychotic symptoms with those with schizophrenia. When compared directly in this way, individuals with schizophrenia demonstrated distributed regions of grey matter volume deficit which involved most of the regions identified in the comparison of those with schizophrenia and healthy volunteers, namely bilateral fronto-temporal cortex, insula, basal ganglia, precuneus and right medial temporal lobe and thalamus. These findings further emphasise the specificity to schizophrenia of regional grey matter volume deficits in these areas. Previous studies that compared individuals with schizophrenia and bipolar disorder (or ‘affective psychosis’) either with each other or with the same control group have reported conflicting findings. Some found that grey matter or medial temporal lobe volume deficit was specific to schizophrenia (Harvey et al., 1994; Pearlson et al., 1997; Zipursky et al., 1997; Altschuler et al., 2000; Hirayasu et al., 2001), whereas others found evidence for deficit in both disorders (Friedman et al., 1999; Lim et al., 1999; Velakoulis et al., 1999). A recent study reports that insular cortex reduction is specific to schizophrenia, whereas both schizophrenia and affective psychosis share volume reduction of the left temporal pole (Kasai et al., 2003). However, there are multiple methodological differences between these studies conducted over the course of a decade, including changes in scanner technology and data analysis as well as variation in sample size and diagnostic inclusion criteria. In a previous voxel-based morphometry study of individuals with a first episode of psychosis, Kubicki et al. (2002) found distributed regional grey matter deficit in schizophrenia but not in affective psychosis, which is consistent with the present study (although a subsequent analysis confined to limited areas revealed mild volume reduction in the insula among patients with affective psychosis).

Our study has provided clear evidence for greater salience of grey matter abnormalities in those with schizophrenia compared with matched individuals with bipolar disorder, suggesting that schizophrenia may generally be associated with more severe and extensive disorganisation of cortical and subcortical grey matter. Our ‘negative’ finding, that there is no significant grey matter abnormality in those with bipolar disorder, should probably be evaluated more cautiously in the light of the moderate sample size and the necessarily conservative nature of multiple hypothesis testing entailed by whole brain morphometry.

### White matter differences

There was evidence for white matter abnormalities in both patient groups; moreover, there was a striking degree of anatomical coincidence in the distribution of white matter deficits in schizophrenia and bipolar disorder. In both groups of individuals with psychotic disorder, white matter volume was significantly reduced in the frontal and temporo-parietal territory.
of major longitudinal tracts and in the corpus callosum.

Reduction of regional white matter volume has been less comprehensively studied than grey matter in schizophrenia, partly because methods for morphometric subdivision of white matter have only recently been developed. Earlier studies focused on area or shape measurements of the corpus callosum and most found reduced callosal area of distorted shape (Woodruff et al., 1995).

There have also been neuroradiological reports of qualitatively diagnosed white matter hyperintensities in schizophrenia, especially among elderly subjects with late onset of psychotic symptoms (Davis et al., 2003). More recently studies using computational morphometry have identified regional white matter volume deficit in schizophrenia within fronto-temporal and parietal regions and anterior corpus callosum (Sigmundsson et al., 2001; Spalletta et al., 2003). This evidence is in accordance with that from magnetic transfer imaging and diffusion transfer imaging, which have identified white matter abnormalities in those with schizophrenia compared with controls, predominantly involving fronto-temporal regions; this is also in accordance with evidence from neurocytochemistry, neuropathology and gene expression studies implicating white matter dysfunction in schizophrenia (Davis et al., 2003).

In bipolar disorder, increased rates of hyperintense white matter lesions in subcortical and periventricular regions are among the most consistently reported anatomical abnormalities (Bearden et al., 2001) but regional morphometry of white matter has rarely been studied. A recent twin study reported reduced white matter volume in frontal regions bilaterally in those with bipolar disorder, which is consistent with the present study (Kieseppa et al., 2003); another study found no white matter volume change in prefrontal subregions (Lopez-Larson et al., 2002).

Our finding that schizophrenia and bipolar disorder are both characterised by white matter volume deficit in frontal and parietal regions is in accordance with the

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<tr>
<th>Area</th>
<th>Brodmann area</th>
<th>Talairach coordinate of centroid voxel</th>
<th>Number of voxels in cluster</th>
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<tbody>
<tr>
<td>Right superior, middle, temporal gyr, amygdala, hippocampus, parahippocampal gyrus, right putamen</td>
<td>–21/27/28/34/38</td>
<td>31 1 19</td>
<td>439</td>
</tr>
<tr>
<td>Left middle, superior temporal gyr</td>
<td>21/22</td>
<td>–58 –17 –6</td>
<td>280</td>
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<tr>
<td>Left lenticular nucleus, bilateral caudate nucleus, right thalamus</td>
<td>–27</td>
<td>7 3 3</td>
<td>577</td>
</tr>
<tr>
<td>Right middle, superior temporal gyr</td>
<td>21/22/42</td>
<td>56 –14 4</td>
<td>299</td>
</tr>
<tr>
<td>Left inferior, middle frontal gyr, insula, precentral gyr</td>
<td>4/6/9/44/45/46</td>
<td>–50 12 25</td>
<td>955</td>
</tr>
<tr>
<td>Right inferior frontal gyr, insula, precentral gyr, postcentral gyr</td>
<td>6/22/43/44</td>
<td>35 6 16</td>
<td>415</td>
</tr>
<tr>
<td>Right inferior, middle frontal gyr</td>
<td>9/44/45/46</td>
<td>56 7 20</td>
<td>201</td>
</tr>
<tr>
<td>Bilateral precuneus</td>
<td>7/31</td>
<td>1 –42 47</td>
<td>938</td>
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hypothesis that both major types of psychosis represent a disorder of anatomical connectivity between components of large-scale neurocognitive networks (Bullmore et al., 1997; Wright et al., 1999). It is also in accordance with recent evidence from gene expression profiling studies of frontal cortical tissue, which have identified specific downregulation of genes related to myelination and oligodendrocyte function in both schizophrenia and bipolar disorder (Hakak et al., 2001; Tkachev et al., 2003). Ultrastructural abnormalities and reduced density of oligodendroglial cells in the prefrontal cortex have also been reported in both disorders (Uranova et al., 2001, 2004).

**Methodological issues**

Strengths of this study include the moderately large numbers of carefully characterised participants who were selected to optimise the clinical homogeneity of the groups with psychotic disorder and to ensure that the comparison between groups was reasonably well controlled for illness duration and severity. The same group of healthy volunteers was used for both case-control comparisons and was well matched for key socio-demographic variables to both patient groups. We used contemporary computational tools for fully automated whole-brain morphometric analysis and non-parametric hypothesis testing, sourcing and combining relevant software from different laboratories to construct a customised image-processing ‘pipeline’.

The study also had a number of limitations besides the general issue of type 2 error already discussed. In common with many previous studies, the bipolar and schizophrenia groups were not well matched for gender, owing to an excess of males within the schizophrenia group. However, gender was included as a covariate in all case-control and case–case comparisons, and there was no evidence for a significant interaction between gender and diagnostic group, implying that there was no major modulatory effect of gender on volumetric deficits due to disorder. Both groups of patients were recruited on the

<table>
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<tr>
<th>Area</th>
<th>Talairach coordinate of centroid voxel</th>
<th>Number of voxels in cluster</th>
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<tbody>
<tr>
<td>Bilateral frontal lobe between medial frontal gyrus, anterior cingulate gyrus medially and inferior and middle frontal gyri laterally, extending on the left to the superior frontal gyrus, insula and precentral gyrus; genu of the corpus callosum, right anterior limb of the internal capsule; right temporoparietal lobe between the superior and middle temporal gyri, postcentral gyrus, inferior parietal lobule, supramarginal gyrus and angular gyrus laterally and the hippocampus, lateral ventricle, cuneus, posterior cingulate gyrus and precuneus medially; left splenium</td>
<td>-18 -2 23</td>
<td>5471</td>
</tr>
<tr>
<td>Right temporoparietal area between the lateral ventricle, posterior cingulate gyrus and precuneus medially and the superior temporal gyrus, insula, postcentral gyrus, precentral gyrus and inferior parietal lobule laterally; right splenium</td>
<td>27 -29 35</td>
<td>2523</td>
</tr>
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basis of having other family members with a similar illness. It is therefore possible that the results of this study may not be generally applicable to those with non-familial forms of psychosis. Both groups of patients had chronic illnesses with many years of exposure to psychotropic medication, and thus it is theoretically possible that the common white matter morphometric deficit resulted from such exposure. However, medication exposure differed between the two groups, with most individuals with bipolar disorder only exposed to antipsychotic medication during exacerbation of illness. Although the morphometric analysis of white matter volume deficit suggested involvement of certain longitudinal and interhemispheric tracts, the anatomical labelling of tracts on the basis of Talairach coordinates should be regarded as heuristic. A more compelling demonstration that specific tracts are involved in both psychotic disorders, and that anatomical connectivity between frontal and tempo-parietal cortex is compromised as a result, could be provided by future studies incorporating diffusion tensor imaging and tractography techniques.

The Kraepelinian dichotomy

Our findings neither wholly support nor wholly negate the Kraepelinian dichotomy of psychosis. Support for the Kraepelinian position comes from the fact that schizophrenia was characterised by a distinctive pattern of distributed grey matter deficit in fronto-temporal, subcortical and cerebellar regions, whereas psychotic bipolar disorder was not associated with significant grey matter abnormality. However, the classic dichotomy is partially subverted by our demonstration of common white matter abnormalities in the two disorders, suggesting that anatomical disconnection between frontal and tempo-parietal cortex may be important for emergence of psychotic syndromes in general.

ACKNOWLEDGEMENT

C.McD. and E.B. were supported by the Wellcome Trust.

REFERENCES


**CLINICAL IMPLICATIONS**

- The Kraepelinian dichotomy of psychosis is partially upheld since distributed grey matter deficit in fronto-temporal, subcortical and cerebellar regions was found only in schizophrenia and not in bipolar disorder.

- White matter volume deficit in frontal and temporo-parietal regions is a morphometric characteristic of both major psychiatric disorders.

- Anatomical disconnectivity between frontal and temporo-parietal cortices may be important for the emergence of psychotic syndromes in general.

**LIMITATIONS**

- All patients were from families with other affected members and results may not be applicable to epidemiological samples.

- The patient groups were not well matched for gender.

- The impact on brain structure of the differing medications used to treat these patient groups could not be assessed in the present study.

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(First received 4 March 2004, final revision 5 November 2004, accepted 16 November 2004)

**BRAIN STRUCTURE IN SCHIZOPHRENIA AND BIPOLAR DISORDER**

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Neuropsychological impairments in people with schizophrenia or bipolar disorder and their unaffected relatives

ANDREW M. MCINTOSH, LESLEY K. HARRISON, KAREN FORRESTER, STEPHEN M. LAWRIE and EVE C. JOHNSTONE

Background Neuropsychological abnormalities in schizophrenia are well replicated and are present in unaffected relatives. Cognitive findings in bipolar disorder are less clearly established.

Aims To examine the possibility that these abnormalities may provide a means by which the disorders might be separated and to clarify the associations of phenotypic expression and genetic liability.

Method A neuropsychological test battery was administered to 50 control participants, 74 patients and 76 unaffected relatives recruited for the study. Patients included those with schizophrenia from families affected by schizophrenia alone, those with bipolar disorder from families affected by bipolar disorder alone and those with bipolar disorder from families affected by both disorders. Unaffected relatives were also recruited.

Results Current, verbal and premorbid IQ were impaired in people with schizophrenia and in their close relatives. Memory was impaired in all patient and relative groups. Psychomotor performance and performance IQ were impaired in patients, regardless of diagnosis.

Conclusions This study finds evidence that intellectual abnormalities are related to a genetic liability to schizophrenia. Abnormalities of memory appear to be related to an increased liability to psychosis in general. No impairment was specific to bipolar disorder.

Declaration of interest None.

Impairments in neuropsychological function have been demonstrated in people with schizophrenia at first presentation and in their unaffected relatives (Cannon et al., 1994; David et al., 1997; Heinrichs & Zakzanis, 1998; Johnson-Selfridge & Zalewski, 2001). Some impairments are also found in people with bipolar disorder (Quraishi & Frangou, 2002), although deficits in general intellectual function are not generally shown (Robertson & Taylor, 1985). We sought to clarify these issues by examining neuropsychological functioning in families affected by schizophrenia, bipolar disorder or both. Relatives were compared with controls to examine abnormalities contingent upon genetic liability, whereas phenotypic abnormalities were inferred from patient-relative differences.

METHOD

Sample

Patients diagnosed with schizophrenia or bipolar disorder were identified at the Royal Edinburgh Hospital and associated hospitals and their informed consent was sought. Those with a family history of one or both disorders were selected, and DSM-IV operational criteria (American Psychiatric Association, 1994) were applied to the patients and to their affected relatives wherever possible using the Operational Criteria Checklist for Psychotic Illness (OPCRIT; McGuflin & et al, 1991). Healthy relatives from the families were also invited to participate. The intention was to recruit 24 people in each of the following groups.

(a) Patients with schizophrenia from 'schizophrenia' families: this group consisted of people with DSM-IV schizophrenia with at least one first- or second-degree relative with schizophrenia.

(b) Unaffected participants from 'schizophrenia' families: this group consisted of healthy people with at least two first- or second-degree relatives with schizophrenia.

(c) Patients with bipolar disorder from 'bipolar' families: this group consisted of people with DSM-IV bipolar I disorder with at least one first- or second-degree relative with bipolar disorder.

(d) Unaffected participants from 'bipolar' families: this group consisted of unaffected people with at least two first- or second-degree relatives with bipolar disorder.

(e) Patients with bipolar disorder from 'mixed' families: this group consisted of people with DSM-IV bipolar I disorder with at least one first- or second-degree relative with schizophrenia.

(f) Unaffected participants from 'mixed' families: this group consisted of unaffected people with at least one first- or second-degree relative with schizophrenia and one with bipolar disorder.

All people fulfilling study inclusion criteria were interviewed using version 9 of the Present State Examination (PSE; Wing et al., 1974). The PSE was used to supplement the information obtained from case notes, confirm the diagnosis of affected participants and confirm that apparently healthy people were indeed unaffected.

A control group consisting of 50 people with no personal or family history of schizophrenia or affective disorder was also recruited from the social network of the participants. Control status was confirmed using the Schedule for Affective Disorders and Schizophrenia, Lifetime version (SADS-L; Endicott & Spitzer, 1978) and using data about previous medical treatment obtained at interview. Unaffected relatives were similarly interviewed to confirm the lifetime absence of major depressive disorder, bipolar disorder or schizophrenia.

Additional demographic and historical information was collected at interview on all participants using a semi-structured questionnaire. All eligible subsample members and controls were interviewed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), the Hamilton Rating Scale for Depression (HRSD;
Hamilton, 1960) and the Young Mania Rating Scale (YMRS; Young et al, 1978).

All relatives and controls gave informed consent to their participation. The study protocol and consent procedures were approved by the relevant ethics committees. Sample sizes were chosen on the basis of a power calculation for two independent groups at a significance level of 0.05.

**Neuropsychological assessments**

All neuropsychological assessments were administered by two investigators (L.H. and K.F.), masked to diagnosis. The test battery chosen included tests that had previously been shown to distinguish individuals with schizophrenia or bipolar disorder from controls and was organised according to domain of neuropsychological function (see Appendix). Genetic liability to psychosis was estimated using a continuous measure described elsewhere (Lawrie et al., 2001), developed originally by Professor Sham of the Institute of Psychiatry, which assumes a liability threshold model (Pearson & Lee, 1901) of genetic disease. Using the estimated prevalence of the disorder and published heritability estimates, the average genetic liability of someone selected at random from a population can be calculated. Using this information on average genetic liabilities combined with family history data, a revised liability estimate for individuals is given.

**Statistical analysis**

The distribution of each neuropsychological variable was examined for normality using a normal probability plot for each group. Where data were not normally distributed a ladder of transformations was applied, and that resulting in the greatest approximation to normal distribution was chosen. The assumption of multivariate normality was checked further using a Mahalanobis plot. Standardised residuals from the mixed-effects analyses of variance (ANOVAs) conducted were also examined for normality.

Domains of neuropsychological function (IQ, executive function and psychomotor performance) were compared between groups using a multivariate analysis of covariance (MANCOVA). All tests conducted included psychiatric symptoms and, where appropriate, age as covariates. Tests of executive function and psychomotor performance were conducted, adjusting additionally for Wechsler Abbreviated Scale of Intelligence (WASI) Full-Scale IQ (Wechsler, 1999). All multivariate analyses were conducted using the PROC GLM procedure within the statistical package SAS, version 8.2 (SAS Institute, Cary, North Carolina, USA). Memory, having only one measure, the Extended Rivermead Behavioural Memory Test (E–RBMT; de Wall et al., 1994), was compared between groups using mixed-effects ANOVA.

Where the MANOVA showed an overall difference within a domain of neuropsychological function, further tests were conducted to examine first, which specific neuropsychological variable means differed between the groups, and second, specific pairwise effect sizes. Both analyses were conducted using a mixed-model ANOVA, with ‘family’ modelled as a random factor to take account of the correlation within pedigrees. Where differences were found in the overall ANOVA, controlling for WASI Full-Scale IQ (for memory and executive function) and psychiatric symptoms (HRSD, PANSS positive sub-scale and YMRS scores), the pairwise between-group contrasts were estimated, controlling for the comparison-wise error rate. Age was also included as a potential confound where this was not adjusted for in the calculation of individual test scores. All analyses were conducted using the PROC MIXED procedure within SAS.

The influence of medication and alcohol consumption were checked by plotting the unstandardised residuals (unexplained variation) from each analysis against current conventional antipsychotic dosage (in chlorpromazine equivalents), lithium dosage and estimated weekly alcohol consumption.

**RESULTS**

The flow of participants through the study is shown in Fig. 1. Over 300 patients with a diagnosis of either schizophrenia or bipolar disorder were identified. Of the 110 patients with a family history of either schizophrenia or affective disorder who were invited to participate, 102 gave their consent. On the basis of combined information from the PSE and case notes, 80 patients met study inclusion criteria and 74 provided complete clinical data and near-complete neuropsychological data. From the families of eligible patients meeting study inclusion criteria, a further 160 apparently unaffected close family members were identified; 85 of them then underwent a semi-structured interview about previous psychiatric problems using the PSE. On the basis of this information 80 persons met study inclusion criteria, of whom 76 provided complete clinical data and near-complete neuropsychological data. Fifty-four potential control participants were identified. All completed a semi-structured interview using the SADS-L. Three were excluded because of a history of previous psychiatric disorder (one with anorexia nervosa and two with a major depressive episode). Fifty individuals provided near-complete neuropsychological data. Demographic information about the participants is given in Table 1.

The patient groups were closely balanced in terms of duration of illness (estimated from current age minus age at first presentation), but differed in terms of psychiatric symptom measurements and prescribed medication (Table 2). Patients with schizophrenia were prescribed more
antipsychotic medication and had higher levels of (positive) psychotic and depressive symptoms than patients with bipolar disorder from either ‘bipolar’ or ‘mixed’ families. In contrast, patients with bipolar disorder from ‘bipolar’ families had the highest doses of lithium prescribed and patients with bipolar disorder from ‘mixed’ families had the highest numbers of manic symptoms compared with the other groups.

Neuropsychology

The vectors of intellectual function (F_{20,203}=2.02, \ P<0.01) and psychomotor function (F_{15,146}=2.0, \ P=0.02) differed significantly between the groups using MANCOVA. Executive function showed no evidence of variation between the groups overall (F_{20,196.6}=1.29, \ P=0.19). Since the numbers in each group were not sufficiently large to allow the conclusion that the groups were equal in terms of executive function, further mixed-effects ANOVAs were conducted to explore whether any single measure of executive function differed between the groups, despite the absence of a statistically significant difference overall. The means and standard deviations of test performance scores are shown in Table 3; these are raw scores unadjusted for confounders and for the effects of intrafamilial clustering.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of participants/families</th>
<th>Age; years</th>
<th>Male</th>
<th>Education¹</th>
<th>Parental SES²</th>
<th>Married¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>50/50</td>
<td>35.5 (11.2)</td>
<td>23 (46)</td>
<td>39 (78)</td>
<td>32 (64)</td>
<td>22 (44)</td>
</tr>
<tr>
<td>SCZ from SCZ family</td>
<td>27/24</td>
<td>37.6 (14.0)</td>
<td>13 (48)</td>
<td>10 (37)</td>
<td>16 (59)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>UA from SCZ family</td>
<td>25/18</td>
<td>38.8 (12.6)</td>
<td>11 (44)</td>
<td>11 (44)</td>
<td>13 (52)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>BPD from BPD family</td>
<td>27/21</td>
<td>40.3 (11.9)</td>
<td>14 (52)</td>
<td>20 (74)</td>
<td>15 (56)</td>
<td>11 (41)</td>
</tr>
<tr>
<td>UA from BPD family</td>
<td>24/10</td>
<td>33.5 (12.8)</td>
<td>9 (38)</td>
<td>17 (71)</td>
<td>13 (54)</td>
<td>10 (42)</td>
</tr>
<tr>
<td>BPD from ‘mixed’ family</td>
<td>20/18</td>
<td>40.5 (9.6)</td>
<td>7 (35)</td>
<td>12 (60)</td>
<td>10 (50)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>UA from ‘mixed’ family</td>
<td>27/14</td>
<td>34.4 (12.8)</td>
<td>14 (52)</td>
<td>13 (48)</td>
<td>9 (33)</td>
<td>14 (52)</td>
</tr>
</tbody>
</table>

BPD, bipolar disorder; SCZ, schizophrenia; SES, socio-economic status; UA, unaffected.

¹ Number having education past compulsory school-leaving age.
² Parental socio-economic status: number whose father’s occupation was non-manual.
³ Number married.

Table 2 Illness duration, prescribed medication and current symptoms

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Illness duration, years</th>
<th>Antipsychotic dosage¹</th>
<th>Lithium dosage¹</th>
<th>PANSS²</th>
<th>HRSD</th>
<th>YMRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>50</td>
<td>15.8 (11.4)</td>
<td>171.5 (200)</td>
<td>7 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>SCZ from SCZ family</td>
<td>27</td>
<td>16.2 (9.2)</td>
<td>37.0 (0)</td>
<td>8 (5)</td>
<td>5 (9)</td>
<td>2 (8)</td>
<td></td>
</tr>
<tr>
<td>UA from SCZ family</td>
<td>25</td>
<td>15.7 (10.5)</td>
<td>21.9 (0)</td>
<td>8 (5.75)</td>
<td>7 (14.25)</td>
<td>4.5 (6.5)</td>
<td></td>
</tr>
<tr>
<td>BPD from BPD family</td>
<td>24</td>
<td>15.7 (10.5)</td>
<td>173.6 (100)</td>
<td>7 (0)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>UA from ‘mixed’ family</td>
<td>27</td>
<td>15.7 (10.5)</td>
<td>21.9 (0)</td>
<td>8 (5.75)</td>
<td>7 (14.25)</td>
<td>4.5 (6.5)</td>
<td></td>
</tr>
</tbody>
</table>

BPD, bipolar disorder; HRSD, Hamilton Rating Scale for Depression; IQR, interquartile range; PANSS, Positive and Negative Syndrome Scale; SCZ, schizophrenia; UA, unaffected; YMRS, Young Mania Rating Scale.

¹ Chlorpromazine equivalents.
² Lithium carbonate equivalents.
³ Positive sub-scale (items 1–7).


had significantly lower WASI scores than controls, but both bipolar disorder groups and their unaffected relatives did not differ significantly from controls. A greater difference was observed between unaffected relatives from ‘mixed’ families and controls than between unaffected relatives from ‘bipolar’ families and controls. Patients with schizophrenia also had significantly lower WASI Verbal IQ scores than either their own relatives (difference –9.8, 95% CI –17.45 to 1.83) or either group of patients with bipolar disorder. The latter two groups did not differ significantly from their unaffected relatives on this measure.

The pattern of impairment in terms of WASI Performance IQ differed from that of other intellectual measures. Patients with schizophrenia or bipolar disorder (whether from ‘bipolar’ or ‘mixed’ families) had significantly lower Performance IQ scores than controls. The effect size was greatest in those with schizophrenia (difference 25.3, 95% CI 16.68 to 33.92), intermediate in patients with bipolar disorder from ‘mixed’ families (difference 14.50, 95% CI 5.79 to 23.20) and least in patients with bipolar disorder from ‘bipolar’ families (difference 10.43, 95% CI 2.50 to 18.37). Unaffected relatives from ‘schizophrenia’ or ‘mixed’ families were also significantly more impaired in terms of Performance IQ than controls. No trend to significance was found for the unaffected relatives from ‘bipolar’ families. Patients with schizophrenia were also significantly more impaired than their own relatives. Although no significant differences between the unaffected relative groups were found, impairments were greatest in the unaffected relatives from ‘schizophrenia’ families, intermediate in the unaffected relatives from ‘mixed’ families and least in the unaffected relatives from ‘bipolar’ families.

**Executive function**

No difference was found between the groups in terms of performance on the Hayling Sentence Completion Test (HSCT; Burgess & Shallice, 1996), whether controlled for current IQ or not. Total verbal fluency and performance on the Stockings of Cambridge test (Sahakian & Owen, 1992) differed among the groups in the non-IQ-controlled analysis. Patients from all groups performed worse in terms of verbal fluency and the Stockings of Cambridge test than controls. Unaffected relatives from either ‘schizophrenia’ or ‘mixed’ families also performed significantly worse than controls on the Stockings of Cambridge test. Once these analyses were adjusted for current intellectual function, no significant difference remained.

**Psychomotor performance**

The number of correct substitutions on the Digit–Symbol Substitution Test (DSTT; Erber, 1976) differed significantly between...
were significantly impaired compared with controls, although no difference was found between controls and any unaffected relative group. Patients with bipolar disorder from ‘mixed’ families showed significantly worse than those from ‘bipolar’ families (difference $-56.41$, $95\%$ CI $-104.94$ to $-7.89$). Patients with schizophrenia and patients with bipolar disorder from ‘mixed’ families did significantly worse than their unaffected relatives.

Choice reaction time also differed between groups. All patient groups were significantly impaired compared with controls, although no difference was found between the control group and any unaffected relative group. Patients with schizophrenia performed less well than their unaffected relatives (difference $77.93$, $95\%$ CI $30.11$ to $125.76$) and patients with bipolar disorder also did less well than their unaffected relatives (difference $-104.70$, $95\%$ CI $-178.79$ to $-30.61$). However, no significant difference was found between patients with bipolar disorder from ‘mixed’ families and their unaffected relatives. Differences between affected or unaffected groups showed no diagnostic or familial specificity.

### Effects of medication and weekly alcohol consumption

There was no statistically significant association between weekly alcohol consumption, prescribed daily lithium or conventional antipsychotic dosages and any measure of psychomotor performance.

### Relationship of neuropsychology to genetic liability

The relationship of measures of intellectual and mnemonic function (NART IQ and WASI Full-Scale, Verbal and Performance IQ scores) to genetic liability was computed for all six groups where there was a family history of psychiatric disorder. Within the group of patients with schizophrenia, genetic liability to schizophrenia was inversely related to NART IQ ($r = -0.49$, $P = 0.01$), WASI Full-Scale IQ ($r = -0.33$, $P = 0.1$) and WASI Verbal IQ ($r = -0.55$, $P = 0.004$) (Fig. 2) but not WASI Performance IQ ($r = -0.01$, $P = 0.94$). However, within the unaffected relatives from ‘schizophrenia’ families, genetic liability to schizophrenia was positively related to Performance IQ ($r = 0.45$, $P = 0.03$) (Fig. 3) and Full-Scale IQ ($r = 0.36$, $P = 0.08$, trend only). No relationship was found between NART IQ ($r = 0.31$, $P = 0.13$) or WASI Verbal IQ and genetic liability ($r = 0.06$, $P = 0.78$).

Within the group of patients with bipolar disorder from ‘mixed’ families there was no significant relationship between genetic liability to schizophrenia and measures of IQ, and no suggestion of any trend. Within unaffected relatives from ‘mixed’ families, genetic liability was not related to NART IQ or WASI Full-Scale or Performance IQ; however, WASI Verbal IQ showed a trend to a negative association with genetic liability to schizophrenia ($r = -0.39$, $P = 0.05$). There was no evidence of a relationship between genetic liability to schizophrenia and scores on the E–RBMT within any group. There

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**Table 4: Mixed-effects analysis of variance by domain of neuropsychological function**

<table>
<thead>
<tr>
<th>Function</th>
<th>$F$ ratio for group</th>
<th>$P$</th>
<th>Between-group contrasts $^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>General intellectual function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NART</td>
<td>$F_{6,64} = 3.12$</td>
<td>0.01</td>
<td>CTR, BPD, MIX $&gt;$ SCZ, uBPD $&gt;$ BPD and CTR $&gt;$ uSCZ, uMIX</td>
</tr>
<tr>
<td>WASI FSIQ</td>
<td>$F_{6,64} = 6.24$</td>
<td>$&lt; 0.000$</td>
<td>CTR, BPD, MIX, uSCZ $&gt;$ SCZ</td>
</tr>
<tr>
<td>WASI PIQ</td>
<td>$F_{6,64} = 5.93$</td>
<td>$&lt; 0.000$</td>
<td>CTR $&gt;$ uSCZ</td>
</tr>
<tr>
<td>WASI VIQ</td>
<td>$F_{6,64} = 4.04$</td>
<td>0.002</td>
<td>CTR $&gt;$ uSCZ, uBPD, uMIX and uMIX $&gt;$ MIX</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E–RBMT</td>
<td>$F_{6,64} = 8.8$</td>
<td>$&lt; 0.000$</td>
<td>CTR $&gt;$ BPD, MIX $&gt;$ SCZ</td>
</tr>
<tr>
<td>E–RBMT (IQ corrected)</td>
<td>$F_{6,64} = 5.9$</td>
<td>$&lt; 0.000$</td>
<td>CTR $&gt;$ SCZ, MIX, BPD</td>
</tr>
<tr>
<td>Executive function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS total</td>
<td>$F_{6,64} = 2.98$</td>
<td>0.13</td>
<td>CTR $&gt;$ SCZ, MIX, BPD</td>
</tr>
<tr>
<td>FAS total (IQ corrected)</td>
<td>$F_{6,64} = 2.00$</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>SOC total</td>
<td>$F_{6,64} = 3.53$</td>
<td>0.005</td>
<td>SCZ, MIX, BPD, uSCZ, uMIX</td>
</tr>
<tr>
<td>SOC total (IQ corrected)</td>
<td>$F_{6,64} = 1.41$</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>HSCT TSS</td>
<td>$F_{6,64} = 1.25$</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>HSCT TSS (IQ corrected)</td>
<td>$F_{6,64} = 0.55$</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Psychomotor performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSST</td>
<td>$F_{6,64} = 4.81$</td>
<td>0.0004</td>
<td>CTR $&gt;$ SCZ, MIX, BPD</td>
</tr>
<tr>
<td>SRT $^2$</td>
<td>$F_{6,64} = 3.54$</td>
<td>0.005</td>
<td>CTR $&lt;$ SCZ, MIX, BPD</td>
</tr>
<tr>
<td>CRT $^2$</td>
<td>$F_{6,64} = 2.91$</td>
<td>0.015</td>
<td>SCZ $&lt;$ uSCZ and uBPD $&lt;$ BPD</td>
</tr>
</tbody>
</table>

$^1$ Key to groups: CTR, controls; MIX, patients with bipolar disorder from ‘mixed’ families; UBS, patients with schizophrenia; UBP, unaffected relatives from ‘bipolar’ families; uMIX, unaffected relatives from ‘mixed’ families; uSCZ, unaffected relatives from ‘schizophrenia’ families.

$^2$ Checked using Satterthwaite approximation, making adjustment of inhomogeneity of variance.

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*McIntosh ET AL*
was no evidence of a relationship between genetic liability to bipolar disorder and any measure of IQ within the groups of patients with bipolar disorder from ‘bipolar’ families, their unaffected relatives or patients with bipolar disorder from ‘mixed’ families. However, unaffected relatives from ‘mixed’ families showed negative associations between genetic liability to bipolar disorder and WASI Full-Scale ($r = -0.50, P = 0.009$), Verbal IQ ($r = -0.47, P = 0.01$) and Performance IQ ($r = -0.40, P = 0.04$), but not NART IQ. There was no evidence of a relationship between genetic liability to bipolar disorder and scores on the E–RBMT within any group.

**DISCUSSION**

In a study of 200 people – patients with functional psychosis, their healthy relatives and controls – several measures of neuropsychological function were estimated with correction for current psychiatric symptoms, the non-independence of observations within families and, where appropriate, age and current IQ. Current, verbal and premorbid IQ were impaired in people with schizophrenia and in their relatives. People with bipolar disorder and their relatives were not impaired on these measures, unless at least one other family member had schizophrenia. Performance IQ, in contrast, was impaired in all the patient groups, but not in unaffected individuals who had two or more relatives with bipolar disorder only. Memory was impaired across all patient and relative groups compared with controls, although patients with schizophrenia were affected more severely than those with bipolar disorder. This difference was not accounted for by differences in IQ. Psychomotor performance was impaired in patients compared with controls, regardless of diagnosis and regardless of whether the test involved a strong motor (reaction time) or cognitive (DSST) component. However, unaffected individuals with two or more relatives with schizophrenia showed impairments on the DSST test that were not present in the other unaffected relative groups.

This study did not find an overall difference in executive function across the groups. Post hoc testing revealed possible impairments in verbal fluency within all patient groups and reductions in planning ability (Stockings of Cambridge test) in all patients and in unaffected individuals with at least one relative with schizophrenia. However, neither of these findings survived correction for current intellectual function.

These findings suggest that intellectual function, planning ability and psychomotor tests with a high cognitive component are preferentially impaired in the relatives of people with schizophrenia. The fact that, among relatives of people with schizophrenia, Verbal IQ is positively related to a genetic liability to schizophrenia is somewhat counterintuitive. However, it finds precedent in an earlier study showing that ‘obligate carriers’ (unaffected people who appear to transmit a parental diagnosis of schizophrenia to their offspring) of schizophrenia had a higher IQ than controls (Steel et al., 2002). Since our sample included people who will develop schizophrenia or other psychiatric illnesses in later years, it is possible that their inclusion explains the reduced mean IQ in this group overall. Furthermore, the positive association between IQ and genetic liability provides some evidence that genes for schizophrenia may convey an advantage in unaffected individuals.

**Strengths and weaknesses of the study**

All groups were well balanced in terms of age, gender, paternal social class and weekly alcohol consumption. A history of compulsory education only or less was more common both in patients with schizophrenia and in their unaffected relatives than in the other five groups. Although all groups had relatively low scores on the HRSD, YMRS and PANSS, none of the groups was symptom-free and most patients were taking medication. However, allowance for current symptoms was made at the analysis stage and none of the remaining variation in test scores could be accounted for by medication.

**Relationship to other research**

This study confirms others that suggest that intellectual deficits are related to a genetic liability to schizophrenia, but is one of the few to study contemporaneously patients with schizophrenia and bipolar disorder. The positive association between genetic liability to schizophrenia and IQ in unaffected relatives is novel, as far as we know.

Studies of patients with schizophrenia (Aleman et al., 1999) and bipolar disorder (Quraishi & Frangou, 2002) have shown reductions in memory compared with controls which are also evident in direct comparisons (Seidman et al., 2002; McClellan et al., 2004) and are of similar magnitude regardless of diagnosis. However, the propensity of psychotropic medication and symptoms to confound these results has rarely been investigated.

For the HSCCT, no difference was observed between any groups and controls for overall scaled score or error score. This finding is in contrast to several others, including one from the Edinburgh High-Risk Study (Byrne et al., 2003). However, patients in our study were on average 10–20 years older than those in the Edinburgh study. The unaffected sample therefore includes fewer people likely to develop psychosis in future.

Deficits in cognitive tasks with a high attentional component have previously been found in the relatives of patients with...
schizophrenia (Pogue-Geile et al., 1991; Franke et al., 1993). This has suggested to some that attentional deficits may be a mechanism by which schizophrenia might develop. The finding of attentional deficits in unaffected individuals with relatives with schizophrenia supports this view. However, their presence in people with bipolar disorder suggests that once the disease is apparent, attentional deficits show no diagnostic specificity and may possibly act to maintain psychiatric symptoms regardless of the factors leading to their development.

**Future work**

Although our study examined groups of people with ‘functional psychosis’, it is unclear whether the differences observed relate only to diagnosis or whether they relate to psychotic symptoms. Most people included in this study had such symptoms, although the numbers involved do not allow enough statistical power to perform sensitivity analyses. It has also been suggested that dimensions of psychotic symptoms found in affected individuals represent the extremes of a range of variation within the population as a whole. Brain anatomy and physiology may be more closely related to these dimensions than to diagnosis. A future study could usefully re-examine symptom dimensions in a range of people with psychotic illness and relate these findings to neuropsychological test performance, brain structure and perhaps function.

**ACKNOWLEDGEMENTS**

We thank all the participants for agreeing to take part in the study and the UK Medical Research Council for funding the principal investigator (A.M.) through a Clinical Training Fellowship.

**APPENDIX**

**Neuropsychological test battery**

**Current intellectual function**

Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

**Premorbid intellectual function**

National Adult Reading Test (Nelson, 1982).

**Memory**

Extended Rivermead Behavioural Memory Test, version A (de Wall et al, 1994).

**REFERENCES**


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Pathogenesis of schizophrenia: a psychopathological perspective

D. G. CUNNINGHAM OWENS, P. MILLER, S. M. LAWRIE and E. C. JOHNSTONE

Background Despite interest in early treatment of schizophrenia, premorbid and prodromal symptomatology remain poorly delineated.

Aims To compare pre-illness symptomatology in patients at high risk of schizophrenia who progress to illness with that of high-risk subjects who remain well and with normal controls.

Method Using Present State Examination (PSE) data, symptomatic scales were devised from participants of the Northwick Park Study of first-episode schizophrenia and scores were compared on the first and last PSEs of participants of the Edinburgh High Risk Study.

Results At entry, when still well, high-risk individuals who subsequently became ill (mean time to diagnosis 929 days; s.e. = 138 days) scored significantly higher on ‘situational anxiety’, ‘nervous tension’, ‘depression’, ‘changed perception’ and ‘hallucinations’ than those remaining well and normal controls, who did not differ. With illness onset, affective symptomatology remained high but essentially stable.

Conclusions In genetically predisposed individuals, affective and perceptual disorders are prominent before any behavioural or subjective change that usually characterises the shift to schizophrenic prodrome or active illness.

Declaration of interest None. Funding detailed in Acknowledgements.

Although the phenomenology of schizophrenia is well delineated, the symptomatic profile prior to diagnosis and the progression to illness have not been characterised reliably.

Background There are three strands to the literature on pre-illness features associated with schizophrenia. First, it has been well established that in childhood and the years before evidence of schizophrenia emerges, individuals differ from normal controls on a range of measures, including psychological test performance and patterns of behaviour (Baum & Walker, 1995; Jones, 1997). Such findings frequently are regarded as evidence that schizophrenia is a disorder of neurodevelopment that arises early but in some way is compensated until the typical age of clinical onset in young adulthood (Murray & Lewis, 1987; Weinberger, 1987). Second, using retrospective patient and third-party accounts, it has been shown that psychopathology of various kinds can precede the emergence of diagnosable illness by months or years (Chapman, 1966; Hafner et al, 1995). Some authors have concluded that the psychotic shift is driven by affective change, either anxiety or depression (Birchwood & Iqbal, 1998; Garety et al, 2001), whereas others have concluded that affective change itself is consequent upon disturbances in either cognition or perception (Chapman, 1966), something that would be difficult to determine with even detailed retrospective techniques. Third, greater emphasis has been given recently to minor psychotic or psychotic-like phenomena such as referential ideas, perceptual disturbances and magical thinking, in an attempt to determine the point at which early treatment, especially with antipsychotic drugs, would be appropriate (McGlashan & Jønnesen, 1996; McGorry, 1998; McGorry et al, 2002; Woods et al, 2003).

Although the onset of schizophrenia can be very acute, it is often more gradual and the point at which symptomatology could be regarded as predictive or prodromal, rather than representative of the early features of illness itself, is often far from clear (Beiser et al, 1993). Prospective population-based studies utilising the controlled and masked assessment of prepsychotic states would be impractical, but the possibility of such assessment has arisen within the context of the Edinburgh High Risk Study of schizophrenia.

The purpose of the present study is to relate initial symptomatic assessments of the high-risk participants and controls to those characteristic of patients already ill with a first episode of schizophrenia, with a view to considering whether nonpsychotic symptoms are secondary to developing psychosis and to define the characteristics of the pre-illness state in high-risk individuals who eventually progress to an acute schizophrenic illness.

METHOD

The Edinburgh High Risk Study concerns young people at enhanced risk of developing schizophrenia by virtue of having at least two close relatives affected by the illness (Hodges et al, 1999; Johnstone et al, 2000). Participants aged 16–24 years were recruited and were considered to be well at that point. They have been followed up for 9 years, with the prediction at onset that 10–15% would develop schizophrenia. A total of 162 high-risk individuals were recruited, along with two control groups: well young people without a relevant family history (n=36); and patients with a first episode of schizophrenia but no family history of the disorder (n=37). The size of the control samples was determined by the number of high-risk individuals anticipated to develop schizophrenia.

The first-episode controls were seen only once, at the point of their initial assessment, but the high-risk participants and the well controls were seen every 18 months and assessed in psychopathological, neuropsychological and imaging terms (Johnstone et al, 2005).

The instrument chosen for assessing the presence of psychopathological was the 9th edition of the Present State Examination (PSE; Wing et al, 1974), conducted at entry and at each follow-up. This had been chosen because of its reliability in providing a standardised diagnosis that would be
used, along with ICD–10 (World Health Organization, 1993), to classify those high-risk individuals who developed a formal schizophrenic illness and who thereby had reached the end of their participation in the study. The PSE is a very detailed instrument giving a standardised assessment of a wide range of symptomatology and therefore would be helpful in evaluating the extent of any psychopathology shown by the high-risk participants and controls.

When the study was designed, it had been predicted that those destined to develop schizophrenia would show a range of prodromal symptoms, which were likely initially to be non-specific in nature but would be followed by the emergence of referential ideas, magical thinking, etc., as much of the recent literature has suggested. It had been anticipated that those who were not going to develop schizophrenia within the study period would be little different from the normal controls, with both groups showing some non-psychotic symptomatology.

These predictions were not altogether borne out. Clinical symptoms of all kinds occurred in high-risk participants and controls but all were more marked in the high-risk individuals, in whom symptoms increased with the passage of time. Possibly psychotic phenomena such as referential ideation and magical thinking occurred in many more of the high-risk individuals than were ever anticipated to develop schizophrenia and considerable degrees of anxiety and depression were found in the high-risk sample at the outset, long before those individuals had developed psychotic features. The CATEGO diagnostic programme (for the PSE) was not helpful in the assessment of this because it does not give emphasis to non-psychotic symptomatology not scoring as severe.

At the outset, when designing the study, we were conscious of the need to limit the number of assessments in order not to overburden the participants and thereby reduce the likelihood of their persisting in the programme. In retrospect, we regret that no well-established psychopathological rating scale sensitive to change, such as the Positive and Negative Syndrome Scale (PANSS; Kay et al, 1987), was included in the design. In view of the findings that the study has produced, it seems important, however, to attempt to unlock some of the trends that the data suggest. Consequently, we sought to develop a rating scale from the PSE using data from a large alternative sample to which we had access. This comprised the admission PSEs of the 229 individuals assessed for the Northwick Park Study of first episodes of schizophrenia (Crow et al, 1986; Johnstone et al, 1986) who received a diagnosis of schizophrenia. These assessments were conducted within 2 weeks of admission for a first psychotic illness and often were done within the first week, before antipsychotic treatment had been instituted.

From this data-set we derived 12 severity scales rating ‘situational anxiety’, ‘nervous tension’, ‘depression’, ‘mania’, ‘overactivity’, ‘disorganisation’, ‘changed perception’, ‘hallucinations’, ‘disorder of possession of thought’, ‘delusional construction’, ‘outside control’ and ‘negative symptoms’. The derivation and details of these scales are shown in the Appendix. Comparing the scores derived from patients with an already established first episode of schizophrenia (and hence exhibiting those features inherently part of the acute syndrome) with those of the participants of the Edinburgh High Risk Study at entry and over time, we were able to provide an analysis of baseline phenomena and their evolution, with an attempt to identify those that may be harbingers of illness.

**Analysis**

The PSE data on participants entering the Edinburgh High Risk Study were available at entry on 175 individuals, divided into 127 high-risk participants who remained well through follow-up, 21 who developed a first formal schizophrenic illness (i.e. high-risk ill participants) and 27 normal controls. One-way analyses of variance (ANOVs) were run, comparing these three groups and the Northwick Park first-episode patients on all the log-transformed symptom scales. Follow-up planned comparisons, not assuming equal variances, compared the 21 high-risk ill participants with the other Edinburgh High Risk Study groups and also to the Northwick Park patients. Non-parametric Kruskal–Wallis tests also were run and in all cases they confirmed the overall parametric findings. Possible gender effects were examined, using $\chi^2$-tests to assess group composition and two-way ANOVAs to search for interaction effects. A separate comparison was made of the Northwick Park patients with high-risk participants who fell ill and were assessed at the time of illness onset.

A second analysis examined changes in symptoms between the first and last assessments for the Edinburgh High Risk Study participants. This was attempted using repeated-measure ANOVAs, with group (high-risk ill, high-risk well and control) as a between-participants variable.

**RESULTS**

Results are shown in Table 1. The first part of the table shows that, at entry, those individuals who subsequently fell ill had higher scores than the normal controls and those high-risk participants who remained well on ‘situational anxiety’, ‘nervous tension’, ‘depression’, ‘changed perception’ and ‘hallucinations’. Furthermore, their scores on ‘situational anxiety’ were significantly greater than those of the Northwick Park sample. On none of the scales did those destined to become formally ill score significantly less than the controls and those destined to remain well. They did, however, score significantly less than the Northwick Park sample on ‘depression’, ‘overactivity’ ‘disorganisation’, ‘changed perception’, ‘hallucinations’, ‘disorder of possession of thought’, ‘delusional construction’, ‘outside control’ and ‘negative symptoms’. Those who became ill did not differ significantly from the Northwick Park sample on ‘nervous tension’ or ‘mania’.

In the last two columns of Table 1, high-risk participants who fell ill are compared at the time of their illness with the Northwick Park patients. The mean scores of the high-risk group are now similar to those of the Northwick Park patients. Only two significant differences remain: on ‘situational anxiety’ the high-risk participants’ scores are higher and on ‘delusional construction’ they are lower than the Northwick Park patients.

The groups were similar in gender composition (controls, 40.7% female; high-risk well, 53.5%; high-risk fell ill, 42.9%; Northwick Park, 41.4%; $\chi^2=5.1$, NS). No significant interactions between gender and group were discovered on any of the scales.

Scores were calculated for each group from their entry PSE and the last PSE conducted. Because the high-risk sample was drawn from all over Scotland, formal PSEs were available only at illness onset on 19 of those who became unwell. Results are shown in Fig. 1. As would be anticipated, ‘psychotic’ symptomatology covered by ‘disorganisation’, ‘hallucinations’, ‘disorder of possession of thought’, ‘delusional
construction’ and ‘outside control’ increased significantly in those who became formally ill, as did ‘negative features’ (time, group and interaction terms all significant, $P < 0.001$), and significant deterioration also was evident in ‘changed perception’. No significant changes occurred in the other participant groups, who continued to hold to low and stable symptomatic levels. On the other hand, ‘situational anxiety’, ‘nervous tension’ and ‘depression’ remained high in those who fell ill, significantly more so than in the controls and high-risk participants remaining well.

**DISCUSSION**

**Methodology**

The methodology adopted in this study is unusual and the reasons why it was adopted require explanation. At the planning stage, the primary objective of interest lay in establishing ‘caseness’?‘non-caseness’, an aim to which the PSE as traditionally used is eminently suited. It subsequently became clear that symptomatology at entry was more prominent and less group specific than the literature or our own predictions had led us to believe and that it was desirable to make more detailed measurements. In the absence of other measures sensitive to symptom change it was decided to adapt the PSE for this purpose.

The PSE is an extensive instrument comprising 140 elicited and observed mental state phenomena, most of which are recorded as continuous variables along a range of ‘absent’?‘mild’?‘severe’, and it proved a relatively straightforward matter to construct the 12 scales with high $\alpha$ coefficients (see below and Appendix). In many ways they are similar to other measures of mental state and would be expected to be reliable, valid, sensitive to change and inclusive. The PANSS now has been incorporated into the study and the new PSE scales will be compared with these ratings at completion.

The 12 scales were derived from one of the largest samples of patients with first-episode schizophrenia to which the PSE was applied on admission (i.e. the Northwick Park sample). These patients were early in the course of their florid illness and for the most part only briefly exposed or not exposed at all to psychotropic medications. Because the PSE applies to the previous 4 weeks, it is unlikely that medication or other factors relating to admission significantly altered the ratings in this sample, which may be taken as generally representative of the illness in its acute state. This

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**Table 1 Mean symptom scores in participants from the Edinburgh High Risk Study and Northwick Park patients with first-episode schizophrenia**

<table>
<thead>
<tr>
<th>Scale</th>
<th>Control (n=27)</th>
<th>High-risk well (n=127)</th>
<th>High-risk ill assessed at entry (n=21)</th>
<th>Northwick Park patients (n=229)</th>
<th>Overall F</th>
<th>High-risk ill v. high-risk well +controls (t)</th>
<th>High-risk ill v. Northwick Park patients (t)</th>
<th>High-risk ill assessed at illness (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Situational anxiety (range 0–12)</td>
<td>0.30</td>
<td>0.60</td>
<td>1.48</td>
<td>0.32</td>
<td>9.26***</td>
<td>2.61*</td>
<td>3.22**</td>
<td>1.32</td>
</tr>
<tr>
<td>Nervous tension (range 0–18)</td>
<td>1.15</td>
<td>1.75</td>
<td>3.52</td>
<td>4.08</td>
<td>20.41***</td>
<td>2.25*</td>
<td>1.05 NS</td>
<td>3.84</td>
</tr>
<tr>
<td>Depression (range 0–41)</td>
<td>0.85</td>
<td>1.13</td>
<td>3.81</td>
<td>6.59</td>
<td>75.16***</td>
<td>2.93**</td>
<td>2.82**</td>
<td>5.95</td>
</tr>
<tr>
<td>Mania (range 0–6)</td>
<td>0.26</td>
<td>0.16</td>
<td>0.33</td>
<td>0.35</td>
<td>1.06 NS</td>
<td>–</td>
<td>–</td>
<td>0.32</td>
</tr>
<tr>
<td>Overactivity (range 0–12)</td>
<td>0.00</td>
<td>0.08</td>
<td>0.14</td>
<td>0.67</td>
<td>17.21***</td>
<td>1.08 NS</td>
<td>3.65***</td>
<td>0.53</td>
</tr>
<tr>
<td>Disorganisation (range 0–16)</td>
<td>0.00</td>
<td>0.02</td>
<td>0.19</td>
<td>1.11</td>
<td>41.44***</td>
<td>1.31 NS</td>
<td>5.32***</td>
<td>1.26</td>
</tr>
<tr>
<td>Changed perception (range 0–14)</td>
<td>0.26</td>
<td>0.20</td>
<td>0.71</td>
<td>1.64</td>
<td>25.50***</td>
<td>2.27*</td>
<td>2.23*</td>
<td>1.74</td>
</tr>
<tr>
<td>Hallucinations (range 0–19)</td>
<td>0.04</td>
<td>0.14</td>
<td>0.52</td>
<td>4.51</td>
<td>97.97***</td>
<td>2.47*</td>
<td>8.84***</td>
<td>2.74</td>
</tr>
<tr>
<td>Disorder of possession of thought (range 0–14)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.24</td>
<td>1.67</td>
<td>48.44***</td>
<td>1.71 NS</td>
<td>6.17***</td>
<td>1.63</td>
</tr>
<tr>
<td>Delusional construction (range 0–22)</td>
<td>0.00</td>
<td>0.04</td>
<td>0.67</td>
<td>12.34</td>
<td>539.32***</td>
<td>1.71 NS</td>
<td>15.07***</td>
<td>7.89</td>
</tr>
<tr>
<td>Outside control (range 0–16)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.19</td>
<td>4.14</td>
<td>131.71***</td>
<td>1.77 NS</td>
<td>13.71***</td>
<td>2.89</td>
</tr>
<tr>
<td>Negative symptoms (range 0–14)</td>
<td>0.00</td>
<td>0.01</td>
<td>0.24</td>
<td>1.01</td>
<td>37.53***</td>
<td>1.30 NS</td>
<td>4.32***</td>
<td>0.58</td>
</tr>
</tbody>
</table>

1. Present State Examination scores at illness onset were unavailable for two participants.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. 

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OWENS ET AL
The concept of schizophrenia has not changed radically in the 20 years separating the two studies, and the PSE remains a valid instrument. However, different raters were involved in the two studies, raising the question of reliability. Both E.C.J. and D.G.C.O. conducted PSEs in both studies.

Sample was preferable to the first-episode patients participating in the Edinburgh High Risk Study, in view of its much larger size and the fact that the Edinburgh patients mainly had been exposed to significant antipsychotic drug treatment, sometimes for months, by the time their PSEs were conducted.

The concept of schizophrenia has not changed radically in the 20 years separating

![Fig. 1 Changes in symptom scores between the first and last assessments. HR, high-risk.](image-url)
and did the great majority in the second phase of the Edinburgh High Risk Study. In addition, for many years they ran a PSE training course, the first such course to be approved outside the Institute of Psychiatry. Research colleagues all received their clinical training in the same institutions as those in which the principal authors worked—a factor known to improve reliability (Kendell, 1975)—and in addition underwent similar PSE training.

Thus, notwithstanding its limitations, we believe that the material presented here is reliable and valid.

**Pre-illness symptomatology**

This study shows that high levels of non-specific, affective symptoms are evident in patients with first-episode schizophrenia substantially before the onset of psychosis and that these separate those high-risk individuals destined to develop schizophrenia from the other high-risk individuals who remain well. These non-specific abnormalities remain essentially stable over time (and in most instances by ‘time’ we mean more than 2 years), both in those who progress to illness and in those remaining well, despite a non-significant tendency for ‘situational anxiety’ to diminish and ‘depression’ to exacerbate in those who progress to illness. These results suggest that such non-specific affective symptomatology is not merely secondary to emerging psychosis but is more fundamental to the illness process that it antedates. Furthermore, entry scores comprising ‘situational anxiety’ were significantly higher in those destined to progress to psychosis than in the sample who had been diagnosed with a first episode of schizophrenia (the Northwick Park sample), supporting the view that anxiety-type phenomena may partially remit as psychotic features escalate. Although this study cannot address the question of whether a greater risk accrues from anxiety (Garety et al, 2001; Turnbull and Bebbington, 2001) or depression (Birchwood & Iqbal, 1998), a key role for anxiety is in keeping with other results from the Edinburgh High Risk Study, in which the best predictors of illness from mothers’ accounts recorded on the Childhood Behaviour Checklist (Achenbach et al, 1991) were withdrawn and deviant behaviour, which includes anxiety and depression (Miller et al, 2002). Using different measures, participants in the Israeli high-risk study who subsequently progressed to a schizophrenic-spectrum diagnosis were found to have had higher pre-illness levels of anxiety assessed at age 16 years (Kugelmann et al, 1995). Thus, anxiety phenome- na may be an inherent part of the pathophysiological process mediating the schizophrenic syndrome.

The more specific symptomatology associated with pre-illness states relates to perceptual abnormalities and comprises both distortions and deceptions. Although ‘changed perception’ and ‘hallucinations’ were found in normal controls and high-risk participants who remained well, hallucinations in particular were infrequent but were more relevant at entry in those who progressed to illness. Abnormalities of thought form and content did not differ significantly between the groups at entry. Group scores were very low and these features were found only in those destined to become ill. Together they comprised the major changes associated with formal illness development.

**Premorbid or prodromal?**

In the high-risk population, the mean time to illness onset was 929 days (s.e.=138). Because it has been reported that prodromal symptomatology can be present for many years prior to formal diagnosis (Hafner et al, 1999), this raises the question of what type of phenomenology the high-risk participants who fell ill were exhibiting at entry—premorbid or prodromal.

Interest in the pre-diagnostic phenomena associated with schizophrenia is long-standing but has increased markedly in recent years. Based on the wish to introduce earlier treatment that may have a favourable impact on outcome, attempts have increased to delineate the prodromal phase of illness from both its premorbid characteristics and the features of the florid first psychotic episode. There is a wealth of evidence that schizophrenia is associated with a wide range of premorbid deviations evident in a series of behavioural, neuro-psychological and even brain structural domains—observations confirmed in the Edinburgh High Risk Study sample (Lawrie et al, 1999; Cosway et al, 2000). These are essentially stable characteristics that do not necessarily result in disadvantage and are certainly not viewed as ‘clinical’ phenomena. What is less clear is how the illness prodrome (representing the first shift from the premorbid state towards illness) should be conceived: what features it comprises, how it evolves and where its ‘break’ points lie between normality and illness. This is an increasingly important question because present conceptualisations of prodrome, essentially derived from retrospective methodologies, have led to the advocacy of early treatment interventions with antipsychotic drugs, often in very young individuals. A significant impact on progression to psychosis has yet to be reported extensively (e.g. McGorry et al, 2002) and it remains unclear that very early interventions do result in better long-term outcomes.

A major problem is the definition of ‘prodrome’ in the context of schizophrenia, which of necessity is a retrospective concept (Yung & McGorry, 1996; Cornblatt et al, 2001), whose constructs have arisen largely on the basis of interviews with patients already diagnosed and, in more recent work, with their families, supplemented with reference to medical records. Although this methodology may produce systems of assessment that are reliable (Hafner et al, 1999), the sources of bias continue to challenge their validity. Using these methods, current views of the contents of the prodrome do include a prominent place for non-specific symptomatology, including affective features, as reported here.

Chapman, on the basis of patient interviews conducted within 3 years of a first episode, found ‘intense anxiety’ to be ‘almost invariable’ and also that perceptual disorders were common, something he placed in a key role in his theory on the origins of florid symptomatology (Chapman, 1966). This also would be compatible with our finding that, on entry, those who eventually became unwell demonstrated higher levels of perceptual abnormalities than the other two Edinburgh High Risk Study groups.

Thus, on this evidence, our high-risk sample destined for illness may indeed have been ‘prodromal’ at entry. However, no matter how the schizophrenic prodrome is conceptualised, some element of change from a previous state (essentially behavio- rial, but also subjective) is inherent to the concept (Keith & Matthews, 1991; Hafner et al, 1992; Loebel et al, 1992; Beiser et al, 1993; Yung & McGorry, 1996; Cornblatt et al, 2001). This key criterion did not apply to the participants of the Edinburgh High Risk Study, who were selected specifically on the basis of being well at entry, in both their own and their families’ eyes. Because these individuals came from families in which at least two
members were already affected with schizophrenia, we take this information, especially that from family sources, as sound.

This might suggest that change need not be an inherent part of the schizophrenic prodrome, which if true would make the concept more arbitrary and difficult to pin down clinically than is currently believed. An alternative proposal might be that high levels of affectivity and perceptual aberration can, in a stable behavioural context, represent part of the premorbid state, perhaps the result of a gradual process of adaptation to underlying cognitive deficits.

ACKNOWLEDGEMENTS

This study was carried out with the approval of the Ethics Committees of the relevant areas. It was supported financially by two Programme Grants from the Medical Research Council. The sustained cooperation of the families involved is acknowledged with gratitude. Our thanks to Norma Brearley for careful preparation of the manuscript.

APPENDIX

Derivation of PSE scales

The PSE data from the Northwick Park Study of first episodes of schizophrenia were reduced to those who received CATEGO diagnoses of S+/S\(\), P+/P\(\) or O+/O\(\), corresponding to schizophrenic psychoses, paranoid psychoses or 'other' psychoses (Wing et al., 1974). The protocols from the resulting 229 patients were used in the derivation of 12 scales.

The PSE is set out in 20 sections: 17 sections comprising symptomatology elicited by formal questioning; and 3 sections for recording mental state features observed during interview. Within these sections most of the items are rated on one of three anchor points, from absent to severe.

The scales were constructed in four stages.

Stage I

The starting point lay in six broader groupings of the original 20 sections, corresponding to 'anxiety', 'depression', 'mania', 'psychotic disorder', 'delusions' and 'negative symptoms', as follows:

Group 1: Anxiety — health; worrying; tension; autonomic anxiety; items 105, 106 ('insight'); item 120 ('behaviour, affect and speech').

Group 2: Depression — thinking, concentration, etc.; depressed mood; self and others; item 121 ('behaviour, affect and speech').

Group 3: Manic Reaction — expansive mood and ideation; items 111–116, 122, 124, 126, 127, 129 and 135 ('behaviour, affect and speech').

Group 4: Perceptual Disorder — derealisation and depersonalisation; other perceptual disorders;

<table>
<thead>
<tr>
<th>Scale</th>
<th>Items included</th>
<th>Derivation (\alpha)</th>
<th>Confirmatory (\alpha)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Situational anxiety</td>
<td>14. Panic attacks</td>
<td>0.73</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>15. Situational autonomic anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>16. Autonomic anxiety on meeting people</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>17. Specific phobias</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18. Avoidance of anxiety-provoking situations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous tension</td>
<td>4. Worrying</td>
<td>0.75</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>5. Tension pains</td>
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<tr>
<td></td>
<td>6. Tiredness</td>
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<td></td>
<td>7. Muscular tension</td>
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<td></td>
<td>8. Restlessness</td>
<td></td>
<td></td>
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<td></td>
<td>10. Feeling of nervous tension</td>
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<td></td>
<td>11. Free-floating autonomic anxiety</td>
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<td></td>
<td>12. Anxious foreboding with autonomic accompaniments</td>
<td></td>
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<td></td>
<td>120. Observed anxiety</td>
<td></td>
<td></td>
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<tr>
<td>Depression</td>
<td>19. Inefficient thinking</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>20. Poor concentration</td>
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<td></td>
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<tr>
<td></td>
<td>21. Neglect due to brooding</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>22. Loss of interest</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>23. Depressed mood</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>24. Hopelessness</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>25. Suicidal plans or acts</td>
<td></td>
<td></td>
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<td></td>
<td>27. Morning depression</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>29. Self-depreciation</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>32. Guilty ideas of reference</td>
<td></td>
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<tr>
<td></td>
<td>33. Pathological guilt</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34. Loss of weight due to poor appetite</td>
<td>0.80</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>35. Delayed sleep</td>
<td></td>
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<tr>
<td></td>
<td>36. Subjective retardiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>37. Early waking</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>121. Observed depression</td>
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<td></td>
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<tr>
<td>Mania</td>
<td>41. Expansive mood</td>
<td>0.88</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>42. Ideomotor pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>43. Grandiose ideas</td>
<td></td>
<td></td>
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<tr>
<td>Over-</td>
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<td>perception</td>
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(continued overleaf)
Table A1 (continued)

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<th>Confirmatory x</th>
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<td>Voices speaking to the patient</td>
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<td>56.</td>
<td>Thought broadcast</td>
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<td>Thought block</td>
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<td>59.</td>
<td>Thoughts being read</td>
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<td>72. Delusions of reference</td>
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<td>80.</td>
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<td>96.</td>
<td>Acting out delusions</td>
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<td>Outside control</td>
<td>71. Delusions of control</td>
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<td>75.</td>
<td>Delusions of assistance</td>
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<td>76.</td>
<td>Delusions of grandiose abilities</td>
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<td>Religious delusions</td>
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<td>Primary delusions</td>
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<td>92.</td>
<td>Delusions of catastrophe</td>
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<td>Negative symptoms</td>
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<td>110.</td>
<td>Slowness</td>
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<td>119.</td>
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<td>Muteness</td>
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<td>134.</td>
<td>Restricted quantity of speech</td>
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<tr>
<td>Items not included</td>
<td>1, 2, 3, 9, 13, 26, 28, 30, 31, 38, 39, 40, 44—46, 49, 54, 61, 67,</td>
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<td></td>
<td>69, 77, 83—91, 97—107, 109, 117, 118, 124, 125, 137—140</td>
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</tr>
</tbody>
</table>

1. Cronbach’s α in the derivation sample.
2. Cronbach’s α in the confirmatory sample.

Anxiety was divided into situational anxiety and nervous tension.

Depression remained undivided.

Manic Reaction was divided into mania, overactivity and disorganisation.

Perceptual Disorder was divided into changed perception, hallucinations and disorder of possession of thought.

Delusion was divided into delusional construction and outside control.

Negative Schizophrenia remained undivided.

**Stage 3**

Cronbach’s α coefficients were calculated for each of the 12 scales and adjustments were made to improve these, where possible, by deleting some items, moving others and including a few that had not been included previously.

**Stage 4**

Cronbach’s α coefficients for each of the 12 scales were reassessed in a mixed sample of patients comprising 26 with first-episode schizophrenia in hospitals local to Edinburgh in 1994, 19 high-risk patients who fell ill (assessed at the time of their illness) and 98 patients from Northwick Park with psychoses not classified as schizophrenia.

The details of the final scales derived are set out in Table A1.

**REFERENCES**


The Danish National Schizophrenia Project: prospective, comparative longitudinal treatment study of first-episode psychosis

BENT ROSENBAUM, KRISTIAN VALBAK, SUSANNE HARDER, PER KNUDSEN, ANNE KØSTER, MATILDE LAJER, ANNE LINDHARDT, GERDA WINTHER, LONE PETERSEN, PER JØRGENSEN, MÆRÆTE NORDENTOFT and ANNE HELMS ANDREASEN

Background First-episode psychosis intervention may improve the course and outcome of schizophrenic disorders.

Aims To describe the Danish National Schizophrenia Project and to measure the outcome of two different forms of intervention after 1 year, compared with standard treatment.

Method A prospective, longitudinal, multicentre investigation included 562 patients, consecutively referred over a 2-year period, with a first episode of psychosis. Patients were allocated to supportive psychodynamic psychotherapy as a supplement to treatment as usual, an integrated, assertive, psychosocial and educational treatment programme or treatment as usual.

Results There was a non-significant tendency towards greater improvement in social functioning in the integrated treatment group and the supportive psychodynamic psychotherapy group compared with the treatment as usual group. Significance was reached for some measures when the confounding effect of drug and alcohol misuse was included.

Conclusions Integrated treatment and supportive psychodynamic psychotherapy in addition to treatment as usual may improve outcome after 1 year of treatment for people with first-episode psychosis, compared with treatment as usual alone.

Declaration of interest None.

The first 2–3 years following a first episode of psychosis may represent a critical period during which crucial biological and psychosocial changes are imprinted in the mind of the patient, thus forming the predictors of the long-term outcome (Birchwood et al, 1998). According to this theory, psychosocial interventions counteracting the damaging effects of the negative predictors at this stage may have a disproportionate positive impact compared with interventions later in the course of the illness. The basis for a lasting result is, however, that the intervention is sustained for a period of years (Linszen et al, 2001). The Danish National Schizophrenia Project investigates precisely the effects of early, rapid and year-long sustained intervention after the first signs of psychosis.

METHOD

Study design The study was a prospective, comparative longitudinal study with a minimum intervention period of 2 years and assessments of participants at baseline and 1, 2 and 5 years after inclusion. Participants were allocated to three different treatments (Table 1).

- **Treatment 1** (*n*=119): patients were offered scheduled, manualised, supportive individual psychotherapy (one 45-min session per week, for a period of 1–3 years) and/or group psychotherapy (one 60-min session per week for a period of 1–3 years), in addition to treatment as usual. Antipsychotic medication was given in doses based on individual needs.

- **Treatment 2** (*n*=139): patients were offered an integrated treatment package – a scheduled, 2-year programme consisting of assertive community treatment, psycho-educational multifamily treatment (according to McFarlane et al (1995)), in which four to six families, including the patients, meet for 1½ h every second week for 18 months), social skills training (concerning medication, self-management, coping with symptoms, and conversational, problem-solving and conflict-solving skills) and anti-psychotic medication (low-dose strategy). This project has been described in detail elsewhere (Jorgensen et al, 2000; Nordentoft et al, 2002).

- **Treatment 3** (*n*=304): patients were offered treatment as usual, consisting of many different therapies – psychological methods, medication, medical advice and treatment by the in-patient and day hospital treatment service – administered according to patients’ needs and the available resources of the clinic at the time of treatment, not delivered in any pre-scheduled manner.
Study participants

The principal inclusion period started on 1 October 1997 and lasted 2 years. Participants were consecutively referred patients, aged 16–35 years, with a first psychotic episode of a schizophrenic spectrum disorder diagnosed by ICD–10 criteria (F20–29; World Health Organization, 1992). Written informed consent had to be obtained from all patients, although not necessarily in the initial phase of the treatment. Patients were excluded if they had a diagnosis of mental retardation or organic brain damage, or were not sufficiently proficient Danish speakers.

Patients with a first episode of psychosis, admitted to either an in-patient unit or a community mental health centre, were systematically assessed within 2 weeks and included if they fulfilled the above criteria. The assessment was conducted by members of a trained, independent research team connected to the centre. Inclusion or exclusion was decided by the team.

Treatment allocation

Two centres (52% of the sample) randomised the patients individually to either treatment 2 or treatment as usual. In three centres (13% of the sample), patients from the first part of the intake were allocated to treatment 1 and those from the second part of the intake to treatment as usual (Fig. 1). This was necessitated by the requirement to complete the treatments being studied in a relatively short period with sufficient numbers of patients. In five centres (14% of the sample), patients were only offered treatment 1 (in addition to usual treatment), and six centres (21% of the sample) offered only usual treatment to their patients.

Assessments

At baseline the following data were collected:
(a) demographic and socio-economic data;
(b) diagnosis according to ICD–10 research criteria, determined by clinical observation and judgement and confirmed by the Operational Criteria Checklist for Psychotic Illness (OPCRIT; McGuffin et al, 1991);
(c) clinical status, determined by Global Assessment of Functioning (GAF; American Psychiatric Association, 1994), the Strauss–Carpenter Outcome Scale (Strauss & Carpenter, 1974, 1977) and the Positive and Negative Syndrome Scale (PANSS; Kay et al, 1987).

The test battery was repeated in years 1 and 2, and is currently being repeated in year 5. All assessments were conducted by trained, independent interviewers.

The assessment of treatment as usual encompassed a detailed registration of the

---

Table 1  Comparison of the intervention strategies

<table>
<thead>
<tr>
<th></th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Treatment as usual</th>
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<tbody>
<tr>
<td>Medication</td>
<td>Yes, but no pre-scheduled strategy</td>
<td>Yes, non-specified low-dose strategy</td>
<td>Yes, but no pre-scheduled strategy</td>
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<td>Assertive outreach</td>
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<td>Yes</td>
<td>No</td>
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<tr>
<td>Multifamily group therapy</td>
<td>No</td>
<td>Yes (McFarlane therapy)</td>
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<tr>
<td>Social skills training</td>
<td>No</td>
<td>Yes (concerning medication, self-management, coping strategies, conversational skills, problem- and conflict-solving skills)</td>
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<tr>
<td>Individual psychotherapy</td>
<td>Yes</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td>Group psychotherapy</td>
<td>Yes</td>
<td>No</td>
<td>?</td>
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<tr>
<td>Social support</td>
<td>Yes, assertive</td>
<td>Yes</td>
<td>Yes</td>
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</table>

1. One session per week for 1–3 years.
elements of treatment for each patient during the intervention period and 3 years after, covering seven domains of the psychiatric treatment: continuity in doctor–patient relationship; treatment frames (in-patient or out-patient); medication; psychotherapy; milieu therapy; short-term family groups for the relatives; and training in daily activities.

### Intervention treatments

The two intervention treatments were conducted according to manuals. Regular supervision was provided for both kinds of intervention to enhance adherence to the manualised procedures. The manualised psychodynamic psychotherapies for group treatment (Lajer & Valbak, unpublished, available from the authors on request in Danish) and for individual treatment (Rosenbaum & Thorgaard, unpublished, available from the authors on request) aimed at a realistic cognition of psychosocial events (attitudes towards illness, realistic social goals, and emotional reactions in interpersonal relationships) and were focused on emotions, intrapsychically as well as interpersonally. The psycho-educational

### Table 2 Demographic, clinical and social baseline data

<table>
<thead>
<tr>
<th></th>
<th>Total sample (n=562)</th>
<th>Treatment 1 (n=119)</th>
<th>Treatment 2 (n=139)</th>
<th>Treatment as usual (n=304)</th>
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<td>Male</td>
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<td>65</td>
<td>60</td>
<td>66</td>
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<td>36</td>
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<td>40</td>
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<td><strong>Age, years:</strong></td>
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<td>At inclusion</td>
<td>24.1 (16.2–35.9)</td>
<td>24.6 (17.6–35.9)</td>
<td>24.5 (17.9–34.3)</td>
<td>23.9 (16.2–35.6)</td>
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<td>At onset of illness</td>
<td>21.0 (6.0–35.0)</td>
<td>21.0 (7.0–35.0)</td>
<td>21.0 (7.0–33.0)</td>
<td>20.0 (6.0–35.0)</td>
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<td>81</td>
<td>89</td>
<td>91</td>
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<td>26</td>
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<td><strong>Diagnosis, %</strong></td>
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<td>F20 (schizophrenia)</td>
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<td>72</td>
<td>73</td>
<td>65</td>
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<td>F21 (schizotypal)</td>
<td>11</td>
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<td>12</td>
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<td>F23 (transient psychosis)</td>
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<td>6</td>
<td>6</td>
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<td><strong>Hospital admission (months) during previous year (n=556), %</strong></td>
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<td>4</td>
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<td>Admitted &gt; 6 months</td>
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<td>1</td>
<td>4</td>
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<tr>
<td><strong>Symptoms (n=557), %</strong></td>
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<tr>
<td>Severe or moderate symptoms</td>
<td>78</td>
<td>74</td>
<td>81</td>
<td>79</td>
<td>0.48</td>
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<tr>
<td>GAF (n=558): median (range)</td>
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<tr>
<td>Symptoms</td>
<td>32 (10–80)</td>
<td>31 (10–75)</td>
<td>30 (10–61)</td>
<td>33 (10–80)</td>
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<tr>
<td>Function</td>
<td>36 (10–80)</td>
<td>35 (15–61)</td>
<td>40 (10–75)</td>
<td>40 (10–80)</td>
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<tr>
<td>PANSS (n=558): median (range)</td>
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<tr>
<td>Positive symptoms</td>
<td>18 (7–40)</td>
<td>18 (7–32)</td>
<td>18 (7–40)</td>
<td>18 (7–32)</td>
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<tr>
<td>Negative symptoms</td>
<td>20 (7–49)</td>
<td>21 (7–41)</td>
<td>17 (7–46)</td>
<td>20 (7–46)</td>
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<td>Drug or alcohol misuse (n=553), %</td>
<td>27</td>
<td>27</td>
<td>24</td>
<td>28</td>
<td>0.75</td>
</tr>
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</table>

GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale.
1. Values from generalised estimating equations or linear mixed models.
2. Living alone v. not living alone.
family treatment was manualised according to McFarlane et al, 1995. The focus of each session was problem-solving and the development of skills to cope with aspects of the illness. The social skills training was based on selected modules from Liberman et al (1986) and Bellack et al (1997).

**Statistical analysis**

The multicentre structure of this study had to be taken into account in the analyses since two patients treated at the same centre might not give independent observations. Logistic regression with generalised estimating equations (Hardin & Hilbe, 2003; Donner & Klar, 2004) was used for dichotomous variables and linear mixed models were used for continuous variables. These methods were used to compare the three study groups at baseline, at 1 year and for differences between baseline and 1 year. In the calculation of changes from baseline to year 1, the analysis was adjusted for baseline values.

Members of the independent research teams met twice a year and rated videotape of patient assessments. The results of 12 rating sessions were used for the calculation of reliability. It was measured for PANSS and GAF by calculating the intraclass correlation coefficient (ICC; Bartko & Carpenter, 1976). All tests were two-sided, and all analyses were executed by using SAS software version 8.2. Owing to multiple comparisons, the Bonferroni correction was used in the interpretation of the results at baseline and for the pairwise comparisons at 1 year of treatment.

**RESULTS**

A total of 562 patients (361 men and 201 women) met the inclusion criteria and gave informed consent to participation in the study. Most were of Nordic origin (92%). The socio-demographic and clinical data of the sample at inclusion are shown in Table 2. (Patients who had been admitted to the hospital system in the year preceding the outbreak of psychosis had all been given diagnoses of non-psychotic conditions.)

**Reliability of study measures**

The ICC for PANSS positive symptoms was 0.70, for PANSS negative symptoms it was 0.74, for GAF symptoms it was 0.56 and for GAF function it was 0.74. The ICC agreement is thus good for PANSS and GAF function, and moderate but acceptable for GAF symptoms.

**Comparison between the three groups at baseline**

The groups were similar at baseline in terms of age, diagnosis, PANSS positive score, GAF symptom score, GAF function score, GAF total score, and admission/non-admission to hospital during the year before inclusion in the study (i.e. admitted with a diagnosis of a psychiatric illness other than F20 psychosis). A significant lower PANSS negative symptom score for the treatment 2 group disappeared when the Bonferroni correction was used.

At year 1, data were obtained from 450 patients (80%). These participants did not differ from the group for whom data were not obtained, in terms of age, gender, diagnosis, GAF and PANSS scores. Furthermore, there was no statistical difference between the three investigated groups. In the F20 group of patients with schizophrenia, 80% participated in the rating at year 1.

**Improvement in symptoms and social function after 1 year of treatment**

At year 1, a significant improvement was found for GAF symptom score, GAF function score, GAF total score, PANSS positive score ($P<0.0001$) and PANSS negative score ($P<0.04$) when the three treatment groups were sampled together. More than half of the sample (54%) had more contact with friends in year 1 compared with the year prior to baseline, 18% had more work and 58% had fewer symptoms.

Comparing the improvements in the three groups at year 1 did not reveal any significant difference between each of the two intervention groups and the usual treatment group (Table 3). Non-significant tendencies were found for hospital admission and GAF function. The reduction in time spent in hospital ($v$: the year before inclusion) was greater in patients receiving treatment 2 or treatment as usual than in patients receiving treatment 1 ($P<0.08$), whereas treatments 1 and 2 both improved the patients’ GAF function scores more than treatment as usual ($P<0.06$). Comparisons between treatment 1 and treatment as usual were in favour of the intervention:

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Changes from baseline to year 1: results from generalised linear mixed model (odds ratio) or linear mixed model (parameter estimate), adjusted for baseline value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Treatment 1</strong></td>
</tr>
<tr>
<td></td>
<td><strong>OR/PE (95% CI)</strong></td>
</tr>
<tr>
<td>Less time in hospital in past year ($n=428$)</td>
<td>0.41 (0.15 to 1.11)</td>
</tr>
<tr>
<td>More social contact in past year ($n=427$)</td>
<td>1.55 (0.85 to 2.81)</td>
</tr>
<tr>
<td>More work in past year ($n=428$)</td>
<td>0.42 (0.20 to 0.88)</td>
</tr>
<tr>
<td>Less symptoms in past year ($n=427$)</td>
<td>1.39 (0.72 to 2.73)</td>
</tr>
<tr>
<td><strong>GAF</strong></td>
<td></td>
</tr>
<tr>
<td>Symptoms ($n=395$)</td>
<td>5.02 (–0.04 to 10.08)</td>
</tr>
<tr>
<td>Function ($n=395$)</td>
<td>4.13 (–0.06 to 8.32)</td>
</tr>
<tr>
<td><strong>Total ($n=395$)</strong></td>
<td>4.65 (0.61 to 8.68)</td>
</tr>
<tr>
<td><strong>PANSS</strong></td>
<td></td>
</tr>
<tr>
<td>Positive symptoms ($n=420$)</td>
<td>–1.06 (–2.63 to 0.51)</td>
</tr>
<tr>
<td>Negative symptoms ($n=417$)</td>
<td>–0.51 (–1.97 to 0.95)</td>
</tr>
</tbody>
</table>

GAF, Global Assessment of Functioning; OR, odds ratio; PANSS, Positive and Negative Syndrome Scale; PE, parameter estimate.
GAF total ($P=0.03$). With the Bonferroni correction, however, this difference disappeared. When we controlled for drug and alcohol misuse as a confounding factor, we found that both intervention treatments produced significant improvements in GAF function score ($P=0.02$) and PANSS negative score ($P=0.02$).

Five people died by suicide during year 1 (0.9% of the whole sample), including two unexplained deaths; no difference was found between suicide rates in the intervention groups and in the usual treatment group.

**DISCUSSION**

From clinical experience it might be assumed that the psychopharmacological treatment accounted for much of the improvement during the first year of treatment. That contributes in part to the understanding of the lack of statistical difference between the specific interventions and treatment as usual. Moreover, in the initial phase of the treatment of patients with a first episode of psychosis, in which the creation of an alliance with the patient is of major importance, the active ingredients of the specific interventions used in this study were not expected to have worked for a sufficient amount of time to make a significant difference. For instance, at the time of the year 1 assessment, only a third of the intended-to-treat patients might have only received less than 6 months of individual psychodynamic psychotherapy or of social skills training, and major changes were not expected within that time span.

Even though our study participants had only been exposed for a limited time to the specific intervention, it is an interesting (although from clinical experience not unexpected) finding that patients who do not misuse alcohol or drugs are receptive to the specific interventions to such an extent that for some variables it results in a statistically significant difference between the improvements in the intervention groups compared with treatment as usual. This may serve as a guideline to the selection of the patients who might benefit from psychotherapy in the initial phase of treatment.

The multisite study

Conducting a prospective, long-term study involving 16 centres is a laborious process with many pitfalls (Kraemer, 2000). The strengths of the multisite model in our study are the quantity of consecutively referred patients; the inclusion of different types of treatment centres (small/big, urban/rural, university/non-university) in all three groups being compared; the percentage of the Danish population covered by the study (approximately 45%); the comparison of two different therapies with standard treatment of supposedly good quality; and that the treatment was conducted mainly by therapists with standard training rather than master clinicians. The study was thus both naturalistic and realistic, and mimicked the actual conditions of the Danish national health system at the time of the health system’s development (1998–2000). This supports the generalisation of the results as well as the possibility of recommending in the future the use of both clinical measures and treatment methods in the day-to-day practice of psychiatry. Furthermore, it is in accordance with recent data emphasising that pragmatically defined public health, integrated treatment programmes and effectiveness studies in many ways are more useful in the planning of schizophrenia prevention than narrowly defined regulatory models and efficacy studies (Lebowitz & Pearson, 2001; Gilbody et al, 2002).

An additional positive element of the long-term multisite project is the establishment of a network of centres that can collaborate through adopting the same treatment methods, the same measurement scales and upholding the same treatment values. The collaboration requires an idealistic approach and has to overcome the potential lack of funding. The reward for each centre is the provision of training of interviewers in the use of psychometric scales and of therapists in the chosen methods of treatment. As a result of these collaborative efforts, the reliability of the ratings of PANSS and GAF was satisfactory.

**Comparison with other studies**

Previous studies of first-episode psychosis have found a positive outcome for various integrated treatments compared with standard treatment (Martindale et al, 2000: pp. 200–292). These integrated treatment programmes all differ in content, combination of treatment forms or length of treatment, and it is hard to compare them directly with our study. Furthermore, the active curative factors in these studies have been hard to distil. Possible curative factors in our integrated treatment programme (treatment 2) might be the rapid, consistent and long-term involvement of the treatment team; the specific targeting of the patient’s return to work, school or other educational programme; and the specific targeting of the attempt to enable in-patients to progress to out-patient treatment.

Previous studies comparing psychodynamic psychotherapy and standard treatment are few and have diverse results, some in favour of the psychodynamic treatment (Karon & VandenBos, 1981), others against (May, 1968). Positive outcome has mainly been associated with treatment by experienced therapists or master clinicians (Karon & VandenBos, 1981) and/or with the formation of a therapeutic alliance (Frank & Gunderson, 1990). However, none of the previous studies concerned patients with first-episode psychosis, and it is by no means given that we can extend the findings from these previous studies of psychotherapy of schizophrenia to our sample.

One limitation of our study is the lack of individual randomisation of all patients. It was, however, the price we had to pay in order to include many different types of centre. Another limitation to the interpretation of our results is the lack of 1-year data for 20% of the patients. This was not expected, but cannot be considered exceptionally high (Gilbody et al, 2002). No difference in adherence to the project was found between the treatment 1 group (0.86) and the treatment 2 group (0.81). However, a greater number of patients remaining in the study after 1 year might have increased the possibility of a significant effect of the interventions.

Finally, the study was constructed by the use of a limited battery of tests and by not including detailed analysis of possible factors confounding the effect of therapy, such as duration of untreated psychosis, premorbid social function, interpersonal attitude and behaviour in school. We did, however, include drug and alcohol misuse, and controlling the data for these confounding factors changed some measures in favour of the two treatment interventions.

**ACKNOWLEDGEMENTS**

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Birth dimensions and risk of depression in adulthood: cohort study of Danish men born in 1953

MERETE OSLER, MERETE NORDENTOFT and ANNE-MARIE NYBO ANDERSEN

Background  Two British cohort studies have reported birth weight to be associated with self-reported depression in adulthood, even after adjustment for socio-economic factors.

Aims  To examine the relationship between birth dimensions and discharge from a psychiatric ward with a depression diagnosis in adulthood.

Method  A cohort of 10,753 male singletons born in Copenhagen, Denmark in 1953 and for whom birth certificates had been traced in 1965 were followed from 1969 until 2002, with record linkage for date of first admission to a psychiatric ward that led to a discharge diagnosis of depression.

Results  A total of 190 men, corresponding to 1.8% of the cohort, had a discharge diagnosis of depression. The Cox's regression analyses failed to show any association between birth dimensions (birth weight and ponderal index) and risk of psychiatric ward diagnosis of depression in adulthood, even after adjustment for social indicators at birth.

Conclusions  This study does not support the existence of a relation between birth dimensions and psychiatric ward admission for depression in adults.

Declaration of interest  None.

Numerous studies have investigated the association between birth weight and health outcomes. Birth weight has been associated particularly with cardiovascular disease (Joseph & Kramer, 1996; Law & Sheil, 1996; Barker, 1998; Harding, 2001), and also with several other outcomes (Barker, 1998; Harding, 2001). Two British cohort studies have recently indicated that low birth weight might be associated with an increased risk of depression later in life after adjustment for socioeconomic circumstances (Thompson et al, 2001; Gale & Martyn, 2004). These observations are compatible with the ‘foetal origin of adult disease’ hypothesis. Poor intrauterine growth could lead to permanent alterations of the neuroendocrine system and subsequently to an increased vulnerability to depression later in life. However, not all evidence concurs with the association between birth weight and depression. Thus, the first British cohort study failed to show an association in women (Thompson et al, 2001), and the later study found no relationship in men after multiple adjustments (Gale & Martyn, 2004). In our study we examined the association between size at birth and risk of psychiatric hospital discharge with a depression diagnosis during the years 1969–2003, in a cohort of Danish men born in 1953.

METHOD

Study population

According to official statistics, 12,270 boys were born within the metropolitan area of Copenhagen during 1953. These persons formed the population of the Danish longitudinal study (Project Metropolit) which has been described in detail elsewhere (Høgh & Wolf, 1981; Osler et al, 2004). Briefly, 11,376 of this population, who were alive and living in Denmark in 1968, were registered with a unique personal identification number when the Civil Registration System (CRS) was established.

Data sources and variables

Data from birth certificates, including information on date and place of birth, birth weight and birth length, singleton or multiple birth, mother's age and marital status, and father's occupational status at time of delivery, were manually collected for all members of the original study population in 1965. In January 2002, the Metropolit cohort was followed up to ascertain vital status through record linkage with the CRS Registry; if the person was not alive and living in Denmark, we obtained information on date of death or date of emigration/disappearance. Information on date of admission to psychiatric wards (from 1969 to December 2002) and diagnosis on discharge was obtained from the Danish Psychiatric Central Register. This register has compiled computerised data on admissions to psychiatric hospitals and to psychiatric departments in general hospitals in Denmark since April 1969, with coverage close to 100% (Munk-Jørgensen & Mortensen, 1997). The personal registration number ensured that a complete history of psychiatric hospitalisation could be established for each cohort member. A total of 230 boys born as twins and triplets and 393 boys with missing birth data were excluded, leaving 10,753 cohort members for the study analyses.

Birth weight was recorded in 100 g groups and analysed as a continuous variable and in the three categories <2500 g, 2500–3499 g and ≥3500 g. Ponderal index used as a proxy measure for intrauterine growth was calculated as birth weight in kilograms ÷ (birth length in metres)3, and entered into the models in quintiles. The marital status of the mother at time of delivery was treated in three categories: married, unmarried (single, divorced or widowed) and unknown. Fathers' occupation, which was recorded in 23 categories, was re-coded into three categories: employees (self-employed and salaried employed), worker (manual and non-manual workers) and unknown.

Diagnoses were classified according to ICD–8 (World Health Organization, 1967) during the years 1969–1993 and ICD–10 (World Health Organization, 1992) from 1994. The diagnoses included for this study were manic episode and bipolar affective disorder (code numbers
296.19, 296.39 and 298.19 in ICD–8 and F30, F31, F34.0 and F38.0 in ICD–10) and depressive disorders (code numbers 296.09, 296.29, 296.89, 296.99, 300.49 and 301.19 in ICD–8 and F32, F33, F34.1 and F38.1 in ICD–10).

**Statistical analysis**

Associations between birth weight, other covariates and depression were analysed using Cox’s proportional hazards regression models with age as the underlying time scale. Entry time was age at 1 April 1969 and follow-up ended at the age of first admission with a diagnosis of depression, death, emigration or 1 January 2002, whichever came first. The proportional hazards assumption was evaluated for all variables by comparing estimated −ln(−ln) survivor curves over the different categories of the variables being investigated. In (analysis time), and by tests based on the generalisation described by Grambsch & Therneau (1994). A power calculation based on the birth weight distribution and estimated number of cases showed that the study would have adequate power (i.e. >80%) to detect a relative risk of 2.0 or greater. We performed the statistical analyses using STATA version 7 (Stata, 2001).

**RESULTS**

A total of 190 men had been discharged from a psychiatric ward with a diagnosis of depression between 1969 and 2002, of whom 39 were diagnosed as having a bipolar affective disorder. The distribution of birth dimensions and socio-economic indicators at birth are shown in Table 1, together with the unadjusted hazard ratios for depression according to these characteristics. We found no association between birth weight or ponderal index and risk of depression from age 16 to 49 years. Indicators of disadvantaged parental social position at birth (father’s occupation and mother’s marital status) were associated with increased risk of depression, with the strongest and significant estimate for single mothers. Entering the social indicators into the model changed the associations of birth weight and ponderal index with depression marginally. We repeated all analyses using data for psychiatric admission for bipolar affective disorder only. Because there were so few cases, birth weight was analysed in two categories, comparing the highest and the lowest half for this outcome. This gave nearly the same risk estimate: HR=1.02 (95% CI 0.53–1.95).

**DISCUSSION**

In this cohort of almost 11 000 Danish men born in 1953 we found no relation between birth weight or ponderal index and risk of psychiatric admission for depression in adult life, either before or after adjustment for father’s occupation and mother’s marital status at birth. The point estimates were close to 1.

### Table 1  Crude and adjusted risk ratios of depression at age 15–49 years in relation to birth characteristics (n=10 753)

<table>
<thead>
<tr>
<th>Birth weight, g</th>
<th>Total n</th>
<th>Cases of depression n</th>
<th>Crude ratio (95% CI)</th>
<th>Adjusted for maternal marital status</th>
<th>Adjusted for paternal occupation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2499</td>
<td>461</td>
<td>8</td>
<td>1.03 (0.50–2.13)</td>
<td>0.98 (0.50–2.02)</td>
<td>1.01 (0.48–2.08)</td>
</tr>
<tr>
<td>2500–3499</td>
<td>5301</td>
<td>96</td>
<td>0.97 (0.72–1.31)</td>
<td>0.96 (0.91–1.29)</td>
<td>0.97 (0.71–1.30)</td>
</tr>
<tr>
<td>≥3500</td>
<td>4987</td>
<td>86</td>
<td>1.00 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Unknown</td>
<td>27</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 100 g increase</td>
<td></td>
<td></td>
<td>1.00 (0.98–1.03)</td>
<td>1.00 (0.98–1.03)</td>
<td>1.00 (0.98–1.03)</td>
</tr>
<tr>
<td>Ponderal index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile 5 (lowest)</td>
<td>2170</td>
<td>31</td>
<td>0.76 (0.41–1.23)</td>
<td>0.77 (0.48–1.24)</td>
<td>0.77 (0.84–1.98)</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>2340</td>
<td>29</td>
<td>0.66 (0.40–1.09)</td>
<td>0.68 (0.40–1.09)</td>
<td>0.66 (0.67–1.65)</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>1967</td>
<td>40</td>
<td>1.04 (0.66–1.65)</td>
<td>1.04 (0.66–1.65)</td>
<td>1.05 (0.67–1.65)</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>2237</td>
<td>54</td>
<td>1.31 (0.86–2.00)</td>
<td>1.29 (0.85–1.98)</td>
<td>1.29 (0.84–1.98)</td>
</tr>
<tr>
<td>Quintile 1 (highest)</td>
<td>2012</td>
<td>36</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per unit increase</td>
<td></td>
<td></td>
<td>1.02 (0.99–1.03)</td>
<td>1.02 (0.99–1.05)</td>
<td>1.02 (0.99–1.05)</td>
</tr>
<tr>
<td>Maternal marital status at birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>9826</td>
<td>163</td>
<td>1 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unmarried</td>
<td>914</td>
<td>27</td>
<td>1.83 (1.00–2.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>13</td>
<td>0</td>
<td>1 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paternal occupational status at birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employee</td>
<td>4902</td>
<td>36</td>
<td>1 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worker</td>
<td>5138</td>
<td>85</td>
<td>0.93 (0.69–1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>713</td>
<td>19</td>
<td>1.56 (0.94–2.56)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Adjusted for paternal occupational status at birth.
Strengths of the study
The study population consisted of all male singletons born in a well-defined area (covering a third of the Danish population) who survived to the age of 15 years. By using the population registers we managed to obtain complete follow-up information, and consequently these results are based on birth and psychiatric admission data for more than 95% of this non-selected population. We assume that our outcome measure is valid, since it was based on diagnoses confirmed by a psychiatrist and did not depend on the individual’s ability to answer a questionnaire; we do not believe our study is subject to the selection biases that might occur when the outcome is based on self-report from a questionnaire.

Limitations
Birth weight has in this area of research been understood as a proxy measure of foetal growth. Birth weight is, however, a combined measure of at least two components: foetal growth rate and gestational age at birth (Wilcox, 2001). We had no information on gestational age, but ponderal index has been suggested as a measure of foetal growth which, in theory, should reflect intrauterine growth restriction (Joseph & Kramer, 1996). We did not find any clear indication of an association between quintiles of ponderal index and adult depression.

Depression is more common in women than in men, but women were not represented in the data-set. The risk of depression increases with age, and our study will not capture the presumed larger number of cases occurring later in life, although the follow-up covered a period of more than 30 years. On the order hand, depression at younger ages may have risk factors that differ from those of later-life depression. Some cases of bipolar disorder are first manifested and diagnosed as unipolar depression, and since our cohort was relatively young a number of diagnoses of unipolar depression will be changed to bipolar disorder at a later stage; consequently, we decided to analyse the two forms of depressive disorder together. Bipolar affective disorder is the most specific diagnosis, however, and therefore we repeated all the analyses for this outcome. The small number of cases in our study reduces the statistical power, in particular of the analyses with bipolar affective disorder as outcome. However, the number of cases of this disorder will increase as the cohort matures, and at a later stage it will also be possible to make a register-based study of the total population, when the children recorded on the computerised medical birth register (started in January 1973) have become old enough to develop severe depression leading to hospitalisation.

We only had information about affective disorders diagnosed during admission to psychiatric hospital or the psychiatric department of a general hospital. A large proportion of patients with depression are treated solely as out-patients in community mental health centres, in private specialist practice or by their general practitioner. Furthermore, no information was available on possible confounders such as maternal depression.

Comparison with other studies
In the Hertfordshire birth cohort study the relation between birth weight and depression was examined in the late 1990s among 882 men and women born between 1920 and 1930; cases were identified by means of the Geriatric Depression Scale and the Geriatric Mental State Examination (Thompson et al, 2001). There was a strong association between lower birth weight and risk of depression in men, but no such relation in women. However, in the most recent study of 8000 male and female participants in the 1970 British Birth Cohort, lower birth weight was a significant risk factor for depression (assessed by Rutter’s 24-item Malaise Inventory) at age 26 years in women, whereas there was no association between birth weight and risk of depression in men after adjustment for potential confounding factors (Gale & Martyn, 2004). In these two birth cohort studies psychiatric morbidity was assessed by means of self-completion scales. Although this approach might be more liable to misclassification than a register-based assessment of outcome, it might

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catch the less severe cases of depression treated in general practice. In two previous studies cases have been identified through hospital admission records. An Italian case-control study with 41 cases found that patients admitted to hospital with depression were more likely than controls matched by gender, age, maternal age and marital status to have been small for gestational age; cases had also lower mean birth weight, although this difference was of marginal significance (Preti et al., 2000). Further, Brown et al (2000), in an investigation of a birth cohort in The Netherlands, found that risk of major depression requiring hospitalisation was increased in groups of men and women who were exposed to famine during late gestation in the Dutch Hunger Winter of 1944–1945.

**Interpretation**

Our study provides no support for the existence of an inverse relationship between birth dimensions and discharge from a psychiatric ward with a diagnosis of depression in adult men. The fact that birth weight has been related to several unexpected outcomes points towards confounding factors as an explanation of the association (Weiss, 2001; Lawlor et al., 2004). The lack of association between birth weight and severe depressive disorders, which is known to be closely related to social circumstances during childhood, indicates that the relation found between birth size and other chronic diseases in adulthood is not just a result of residual confounding by factors related to social position.

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Care staff training in detection of depression in residential homes for the elderly

Randomised trial

A. M. H. EIsses, H. KLUITER, K. JONGENELIS, A. M. POT, A. T. F. BEEKMAN and J. ORMEL

**Background** Many people with depression in residential care homes for the elderly do not receive treatment because their depression remains undetected.

**Aims** To determine the effects of staff training on the detection, treatment and outcome of depression in residents of ten homes.

**Method** We conducted a randomised controlled trial in ten residential homes. The intervention consisted of a training programme for staff and collaborative evaluation by staff and a mental health specialist of residents with possible depression.

**Results** Recognition of depression increased more in homes where staff received the training than in the control homes. Treatment rates also increased compared with control homes, but the increase was not significant. Residents with depressive symptoms had a more favourable course when staff had received training. Moreover, the prevalence of depressive symptoms decreased, but the decrease was not significant.

**Conclusions** Training of care staff results in the increased detection of depression in the elderly, a trend towards more treatment and better outcomes.

**Declaration of interest** None. Funding detailed in Acknowledgements.

Although depressive symptoms seriously affect the quality of life of a growing proportion of elderly people in residential care homes (Koenig & Blazer, 1992; Ames, 1993; Blazer, 1994), many residents do not receive adequate antidepressant treatment (Rovner et al., 1991; Pond et al., 2002). Lack of recognition of depressive symptoms and signs by the attending staff in the residential home is a major obstacle to the provision of adequate treatment (Koenig et al., 1988; Rovner et al., 1991; Jackson & Baldwin, 1993; Bagley et al., 2000). This study evaluates the effects of a programme of care staff training in residential homes on the recognition of depression, the treatment rate and the prognosis of those with depression. Our second aim was to study whether the training programme leads to lower prevalence and incidence rates for depression, since the training might positively affect the staff’s attitude to those residents vulnerable to depression.

**METHOD**

**Design** The study was a randomised controlled trial; ten residential care homes for the elderly were randomly assigned to either an experimental or a control group. The experimental group implemented a package of interventions. To compare the intervention with standard practice in residential homes, the control group provided care as usual. Several outcome measures were assessed because we evaluated the outcome of a whole care programme. The intervention was introduced in the month following baseline assessment. Research data were collected shortly before (baseline) and 6 months after the training by interviewers especially trained for this study. To guarantee an independent assessment, the interviewers were masked to the intervention and not associated with the residential homes. The researchers did not inform care staff of findings pertaining to the residents.

The main outcome measures referred to residents with depression (recognition, treatment and prognosis). The secondary outcome measure referred to the whole group of residents (prevalence). Written informed consent was obtained prior to the study. The medical ethics committee approved the study.

**Intervention**

The intervention was directed towards the care staff and consisted of two components: (a) training in using a standardised screening instrument; (b) review of the findings of screening at a staff meeting. The training focused on the recognition of psychological symptoms in residents and the recording of observations according to the Behaviour Rating Scale for Psychogeriatric Inpatients (Dutch abbreviation GIP–28). The GIP–28 consists of three reliable and valid scales: apathy, cognitive disturbance and affective disturbance (Jonghe et al., 1997). The GIP–28 has been used in the care of the elderly for over 15 years. During daily care activities the care staff observe specific behavioural aspects of residents. The staff later indicate how often they have registered certain behaviours. The advantage of this instrument is that active participation of the resident is not required. Trainers were mental health specialists; trainees were the care staff of the residential homes. The training consisted of two sessions of 2 h. During the training, care staff learned how to observe specific behaviours, supported by video material. Special attention was given to the basic differences in behavioural manifestations of dementia and depression.

Evaluation of the intervention consisted of a discussion of the recorded observations by an experienced mental health nurse or psychologist with the care staff at a formal meeting to determine the course of action. Residents who were possibly depressed according to the GIP–28 were identified and discussed. The discussion resulted in a decision on the course of action:

- (a) alerting staff to pay more attention to the resident;
- (b) additional diagnostic assessment;
- (c) referral to the general practitioner; or
- (d) referral to a psychiatrist or mental health specialist.
The effects of the intervention (e.g. successful detection) were assessed separately from the GIP recordings. Furthermore, no feedback was given – by the researchers or anyone else – to the care staff about the success of the detection of depression.

**Selection of homes**

In The Netherlands, residential homes provide daily care to the infirm elderly over 65 years with significant limitations to daily living; if needed, they also provide basic medical care. About 5% of all those over 65 years in The Netherlands live in a residential home. Nursing homes, in which about 3% of all Dutch residents over 65 years reside, provide more specialised medical care to all ages, but mainly to the elderly.

Of the 42 residential homes in the province of Drenthe, 23 were eligible for the study. The 19 non-eligible homes were excluded because they met one or more of the following exclusion criteria:

(a) ongoing or planned relocation, merger, changes in care methods or organisational instability (10 excluded);
(b) homes for specific populations (e.g. blind elderly) (3 excluded);
(c) participation in the pilot study or working with systematic screening procedures (6 excluded).

The staff of five of these homes had no interest in participation, as they received adequate assistance from the attending psychologist of a nearby nursing home. Five homes were not interested in the study, and three homes indicated that the intervention took too much time. Ultimately, ten homes were willing to participate.

Residential homes in the province of Drenthe are comparable to those in other parts of The Netherlands: they have the same gender ratio of residents (1 male: 4 female); mean residents’ age (about 85 years); care methods; and admission criteria. However, homes in Drenthe are slightly smaller (about 85 beds) than those in other parts of the country (101 beds), and Drenthe itself consists of small towns (up to 150,000 inhabitants) and rural areas (Centraal Bureau voor de Statistiek, 1998).

**Matching and randomisation**

Since the intensity of existing care might constitute a major confounder if not well balanced over both conditions, we matched the homes on care intensity. Care intensity was defined as: (a) the presence of contact nursing (one personal carer maintains intensive contact with the resident’s family and general practitioner); and (b) care ratio (number of carers divided by the number of residents in the home). The matched homes were randomly assigned to the control or the experimental group. Control homes did not implement the intervention; they continued with standard care, comprising regular reports on residents by staff, without systematic observation or the use of rating scales.

**Selection of residents**

We visited all residents aged 65 years and above, except those receiving day care for dementia. The researchers notified residents of the study by a letter explaining the study and requesting their approval. Those who were severely cognitively impaired, indicated by a score below 15 on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), and those with severe hearing problems or aphasia were excluded. We reasoned that no valid assessments could be obtained from these residents.

**Assessments**

**Depression**

We assessed residents at baseline and follow-up with the validated Dutch version of the Geriatric Depression Scale (GDS), consisting of 30 yes/no items, which measures clinically relevant depressive symptoms (Yesavage et al., 1982; Kok, 1994). The GDS was administered at an interview between resident and trained research assistant, because many participants had serious difficulty with reading due to visual problems. The GDS does not contain any items assessing physical symptoms, hence it is an appropriate instrument for the elderly with physical illness. The GDS has been validated as a screening tool in nursing homes (McGivney et al., 1994). A score of over 10 on the GDS–30 is indicative of depression (Brink et al., 1982). Scores between 11 and 20 indicate moderate depression, and scores above 20 indicate severe depression (Brink et al., 1982).

**Recognition of depression**

Masked to the GDS results, the care staff were asked, at baseline and follow-up, to rate each resident as probably depressed or probably not depressed. The staff’s ratings were compared with the scores of the residents on the GDS (above/below threshold). The GDS was the ‘gold standard’ in this study. Both sensitivity and specificity were calculated.

**Treatment of depression**

Treatment (yes/no) was defined as the prescription of antidepressant medication or counselling by a professional (e.g. general practitioner, psychologist or social worker). Interviews with care managers and medical records were used to obtain such information.

**Statistical analysis**

To determine prognosis, we compared residents from both experimental and control groups assessed as depressed (GDS > 10) at baseline. To examine whether the intervention led to improvement of recognition, treatment and a lower prevalence of depression, data were required on all residents present at baseline and on all residents present at follow-up. Thus, for these analyses, ‘new’ residents were included at follow-up (new inhabitants, as well as those who were ill or refused participation at baseline).

Sensitivity refers to the proportion of residents with depression (GDS > 10) correctly identified by the care staff. Specificity refers to the proportion of residents without depression (GDS ≤ 10) correctly identified by the care staff.

For the statistical evaluation of differences in proportions between experimental and control homes, taking into account baseline differences, Newcombe’s method 10 for independent proportions was used (Newcombe, 2001). Differences in means were evaluated by t-tests. Where appropriate effect sizes were reported according to Cohen (1992).

**RESULTS**

**Baseline characteristics**

**Homes**

Ten homes participated; five were assigned to the experimental group and five to the control group. The mean number of beds in each home was 75 (range 45–132) and did not differ between groups. The mean number of residents participating in each home was 41 (range 26–82). The ratio of care staff to residents, reflecting the intensity of care available, did not differ between the experimental group and the control group (t-test = 0.181, P = 0.861).
Residents

There were 426 residents included at baseline; 41 residents were excluded because of severe cognitive impairment, 13 were physically too ill to participate, 5 had died shortly before the interviews and 2 residents could not be visited. There were 52 residents who refused to participate at baseline. Table 1 describes the baseline characteristics of the sample, divided into control and experimental groups. Most respondents were female (74.2%). The mean age of the men was 84.8 years (s.d.=7.4, range 65–98 years). The mean age of the women was 85.6 years (s.d.=6.1, range 69–101 years). At baseline, 12.7% of the male residents suffered from depressive symptoms and 14.9% of the female residents. There were no significant baseline differences between the control and experimental groups.

Table 2 shows the inclusion at baseline, the loss to follow-up and the inclusion of ‘new’ residents. Figure 1 presents a flow chart of inclusion and attrition rates at baseline and follow-up. At follow-up, data were available on 173 residents in the experimental group and 187 in the control group. Most residents were female (76.9%). Of the men, 10.8% had a GDS score above 10; 11.9% of the women had a score above 10.

In the experimental group 27 residents had depressive symptoms at baseline. Of these, 12 residents were also investigated at follow-up (15 were lost to follow-up: 7 refused, 5 died, 2 were too ill and 1 was too deaf). In the control group, 19 of the 34 GDS-positive residents at baseline participated at follow-up (15 were lost to follow-up: 3 died, 7 refused, 2 were too cognitively impaired and 3 were too ill).

Analyses of those who dropped out (n=146) and those who were assessed twice (n=280) revealed that the mean score on the GDS at baseline was significantly higher in those who dropped out (7.29, s.d.=5.13) compared with those who were assessed twice (5.60, s.d.=4.24, t-test=3.422, P=0.001). There were no age and gender differences between those who dropped out and those who were assessed twice. At follow-up, the mean GDS score of those assessed twice and new participants did not differ statistically (6.07, s.d.=4.36 v. 5.60, s.d.=4.45, t-test=−0.843, P=0.400).

There was no difference in mean GDS score of those who dropped out from the control and experimental groups (7.22, s.d.=5.24 v. 7.36, s.d.=5.05; t-test=0.161, P=0.871) or the mean score of those assessed twice in the two groups (t-test=−1.008, P=0.314). There was, however, a difference in mean scores of ‘newcomers’. The newcomers in the control group had a higher mean GDS score (6.91, s.d.=4.895) than those in the experimental group (4.73, s.d.=3.95; t-test=−2.102, P=0.040).

The mean GDS scores did not differ between the groups (t-test=−0.458, P=0.647). The average GDS scores at baseline did not differ among the ten homes (ANOVA F=1.645, P=0.100).

Care staff

The sample of staff at baseline (42 in the control and 43 in the experimental group) included 10% nurses, 33% orderlies, 50% geriatric helpers and 7% others. These care
Effects of intervention

Effect on recognition

Table 3 shows the staff ratings (depressed/not depressed) compared with the GDS score (screen positive, GDS > 10; screen negative, GDS ≤ 10). Table 4 shows the recognition rates (sensitivity and specificity). The improvement in sensitivity is significantly greater in the experimental group than in the control group where it actually decreased (Z = 1.6722, P = 0.0472).

Effect on treatment for depression

The treatment rate of residents with depressive symptoms showed a large difference at baseline in favour of the control group: 33.3% (11 out of 33) received treatment compared with 3.8% (1 out of 26) in the experimental group. The treatment rate in the experimental group increased (up to 23.1%, 3 out of 13), but remained stable in the control group (31%, 9 out of 29). Although substantial, the difference in increase of treatment rate was not statistically significant (Table 4).

Effect on the course of depressive symptoms

We defined the course of depression as favourable if the GDS score at follow-up fell into a less severe category than at baseline. In the experimental group, 58.3% (7 out of 12) improved v. 15.8%

average 9.5 years in the homes under study (s.d. = 5, range 10 months to 23 years, median = 10 years). The samples are representative of the staff in Dutch homes for the elderly.

Fig. 1 Flow-chart of inclusion and attrition of respondents in the experimental and control groups at baseline and follow-up. *The number of respondents excluded at baseline because of illness, absence or refusal, but that did participate at follow-up.

Table 3 Recognition of depression in the experimental group before (baseline) and after training (follow-up) compared with the untrained control group (number of residents)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Experimental</td>
<td>Control</td>
</tr>
<tr>
<td>Staff —/GDS—</td>
<td>138/143</td>
<td>137/128</td>
</tr>
<tr>
<td>Staff+/GDS+</td>
<td>12/19</td>
<td>8/13</td>
</tr>
<tr>
<td>Staff+/GDS—</td>
<td>30/39</td>
<td>22/29</td>
</tr>
<tr>
<td>Staff —/GDS+</td>
<td>15/11</td>
<td>5/16</td>
</tr>
<tr>
<td>Totals</td>
<td>195/212</td>
<td>172/186</td>
</tr>
</tbody>
</table>

+, Depressed according to GDS > 10 or care staff; −, not depressed according to GDS ≤ 10 or care staff.

Table 4 Sensitivity, specificity, positive predictive value, negative predictive value, treatment rate, improvement and prevalence of depressive symptoms (%) in the experimental and control groups at baseline and follow-up

<table>
<thead>
<tr>
<th></th>
<th>Experimental group</th>
<th>Control group</th>
<th></th>
<th>Z-score¹</th>
<th>P (one-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td>Baseline</td>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>44.4</td>
<td>61.5</td>
<td>63.3</td>
<td>44.8</td>
<td>1.6722</td>
</tr>
<tr>
<td>Specificity</td>
<td>82.1</td>
<td>86.2</td>
<td>78.6</td>
<td>81.5</td>
<td>0.1787</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>26.6</td>
<td>26.7</td>
<td>32.8</td>
<td>31.0</td>
<td>-0.0069</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>90.2</td>
<td>96.5</td>
<td>92.9</td>
<td>88.9</td>
<td>2.3123</td>
</tr>
<tr>
<td>Treatment rate</td>
<td>3.8</td>
<td>23.1</td>
<td>33.3</td>
<td>31.0</td>
<td>1.3677</td>
</tr>
<tr>
<td>Improvement of depressive symptoms</td>
<td>NA</td>
<td>58.3</td>
<td>NA</td>
<td>15.8</td>
<td>2.4682</td>
</tr>
<tr>
<td>Prevalence of depressive symptoms</td>
<td>13.6</td>
<td>7.5</td>
<td>14.9</td>
<td>15.5</td>
<td>-1.4022</td>
</tr>
<tr>
<td>Incidence of depressive symptoms</td>
<td>NA</td>
<td>3.5</td>
<td>NA</td>
<td>5.9</td>
<td>-0.8593</td>
</tr>
</tbody>
</table>

¹ Z-score of the difference in proportions between baseline and follow-up. The Z-score of ‘improvement of depressive symptoms’ refers to the difference between proportions in both conditions (Newcombe, 2001).
We also examined the decrease in depressive symptoms for participants with a positive GDS score at baseline (GDS > 10). In the experimental group the GDS decreased by a mean of -4.50 GDS units (s.d.=4.76) but increased by 0.684 GDS units (s.d.=4.12) in the control group. The corresponding effect size was -1.18 (95% CI -1.93 to -0.38) suggesting that the GDS scores of residents who were depressed at baseline (GDS > 10) decreased significantly more in the experimental than in the control group.

**Effect on the prevalence and incidence of depression**

We also investigated whether the whole sample benefited from the intervention. The prevalence of depressive symptoms (GDS > 10) at baseline was similar in both groups, with 13.6% in the experimental group and 14.9% in the control group. At follow-up, the prevalence of depressive symptoms in the experimental group decreased to 7.5% but remained at 15.5% in the control group. Although substantial, the difference between the groups was not significant (Table 4). We also compared the decrease in depressive symptoms between baseline and follow-up. The mean difference score was 0.1360 (s.d.=3.4) in the experimental group and 0.7419 (s.d.=3.2) in the control group. The effect size was -0.18 (95% CI -0.42 to 0.005) (NS).

Moreover, the incidence of depressive symptoms (GDS > 10) at follow-up in residents without depression at baseline was 3.5% in the experimental group and 5.9% in the control group. There is a suggestion that the intervention contributes to the prevention of depressive symptoms, but the difference was not statistically significant (Z=-0.8593, P=0.1951).

**DISCUSSION**

**Methodological considerations**

In the current study, a self-rating instrument of depression was used instead of a diagnostic interview. This may have included false positives, but 'adequate diagnosis of depression by care staff' was not the goal of the intervention. We were interested in the education of care staff in the recognition of those residents apparently suffering from depressive symptoms.

The two groups of care homes were well-balanced with respect to degree of care. However, we did not succeed in creating two equivalent groups at baseline with regard to recognition and treatment rates. Although we have carefully checked the procedures, we can not explain the difference. We are reassured that the baseline difference was coincidental, but would have preferred all baseline indices to be (roughly) equivalent. With ten homes there is a considerable probability of baseline inequality. In this type of intervention the number of randomisable units is by implication always lower than one would wish from a statistical and a design point of view. Unlike many studies at the institutional level we applied baseline assessments; by doing this we were able to correct for baseline non-equivalence and calculate the change in scores brought about by the intervention.

The study had high rates of loss to follow-up of residents with depression. Hence, only small numbers of residents with depression were available for analyses of improvement. The loss to follow-up reflects the vulnerability of residents with depression.

Newcomers in the control group were more depressed than those in the experimental group, but there was no overall difference in symptom rates between new participants and residents assessed twice. This may be a result of support of newly arrived residents by the care staff. An attentive and supporting attitude may be enhanced by training.

The effects we found were not large. This is because the number of residents with depression in our study was much smaller than expected from previous prevalence studies. Such a small number restricts the maximum effect attainable, through the phenomenon of 'restriction of range'. The intervention may be more effective in populations with higher prevalences (Nunnally, 1976).

Furthermore, the sensitivity decreased in the control group at follow-up, probably because of a reduction in awareness or demoralisation owing to not having received the training. These phenomena are documented in the literature on research methodology of intervention studies (Cook & Campbell, 1979).

**Effect on recognition**

Recognition of depression in the elderly in residential homes is undoubtedly difficult; difficulties result from the high prevalence of multiple physical disorders and functional impairments in residents (Koenig et al, 1993). The intervention under study brought about an increase in the recognition rates (sensitivity). At the same time, the specificity remained high and stable, implying that the care staff improved their recognition of depression, without wrongly rating non-depressed residents as depressed. Furthermore, the positive predictive value of the judgements of care staff remained stable in both groups between baseline and follow-up, whereas the negative predictive value increased after the intervention.

Judgements of care staff are without doubt valuable in the recognition of depression, but before psychological or pharmacological treatment for the depression may be provided, screening instruments and clinical assessments by, for example, general practitioners are still mandatory.

**Effect on treatment for depression**

The treatment rate of residents with depressive symptoms increased after the intervention. The increase was substantial but not statistically significant. This supports the results of another recent randomised controlled trial carried out in long-term care facilities: the frequency of treatment or referral to mental health services by primary care physicians increased when they were informed about the results of a depression screen (GDS) (Soon & Levine, 2002).

**Effect on the course of depressive symptoms**

Residents with depressive symptoms improved more in the homes where the intervention had been implemented than in the control homes. Our results are in line with those reported by Cuijpers & van Lammeren (2001), who applied a quasi-experimental design. They reported favourable patient outcome as a result of a comprehensive training programme in residential homes focusing on caregivers, residents and relatives. Beneficial effects of training and education of care staff on the course of depressive symptoms have also been reported by Proctor and colleagues (1999). Rabins et al (2000) also found positive effects of an intervention on the reduction of psychiatric symptoms in the elderly. They taught staff to find cases, to perform assessment in the residents' apartments and to provide care if necessary. This
method compares well with that used in our study.

**Effect on the prevalence and incidence of depression**

Our findings suggest that the intervention contributes to the prevention of depressive symptoms, since in the experimental group: (a) the prevalence rates of depressive symptoms showed a greater decrease between baseline and follow-up (NS); and (b) the incidence of depressive symptoms was lower compared with the control group (NS).

In summary, we have found support for the beneficial effects of a programme of staff training in improving detection, treatment and the course of depression in normal practice. The care staff appreciated the training, the systematic observation procedures and the meetings with the mental health worker. They indicated that they received valuable tools to deal with vulnerable residents. The intervention has now been implemented successfully in several parts of The Netherlands.

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A. M. H. EiSSeS, MsC, H. KlUJTER, PhD, Department of Psychiatry, Medical Faculty, University of Groningen; K. JOnGENeLis, M.D, A. M. PoT, PHD, A. T. F. BeeKMAN, M.D, PHD, EMGO Institute, Free University Amsterdam; J. ORMeL, PHD, Department of Psychiatry, Medical Faculty, University of Groningen, The Netherlands

(First received 24 February 2004, final revision 1 November 2004, accepted 5 November 2004)

**CLINICAL IMPLICATIONS**

- Training care staff in systematic observation contributed to the improvement of detection, treatment and course of depressive symptoms in the elderly living in residential homes.
- Improvement of sensitivity was achieved with high stable specificity. Hence, unnecessary treatment of non-depressed residents was avoided.
- Focused involvement of care staff in detecting mental health problems is feasible, desirable and worthwhile.

**LIMITATIONS**

- Despite matching and randomisation, the experimental and control groups had unequal starting points with regard to recognition and treatment rates.
- A self-rating instrument of depression was used instead of a diagnostic interview.
- The study had restricted numbers of residents with depressive symptoms which limits the maximum effects achievable.

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**REFERENCES**


**Distinctive neurocognitive effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy in major depression**

SVENJA C. SCHULZE-R AUŞCENBACH, UTA HARMS, THOMAS E. SCHLAEPFER, WOLFGANG MAIER, PETER FALKAI and MICHAEL WAGNER

**Background**
Studies have compared electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) with regard to clinical efficacy in the treatment of depression, but no study has yet addressed the differential impact on cognition.

**Aims**
To compare the neurocognitive effects of unilateral ECT and rTMS.

**Method**
Thirty patients with treatment-refractory non-psychotic major depression received an average of ten treatments with either unilateral ECT or left prefrontal rTMS and were assessed for objective and subjective cognitive impairments before and about a week after treatment.

**Results**
Treatment response was comparable (46% of the ECT group and 44% of the rTMS group showed a reduction of 50% or more in Hamilton Rating Scale for Depression scores). In patients treated with rTMS, cognitive performance remained constant or improved and memory complaints alleviated, whereas in the ECT group memory recall deficits emerged and memory complaints remained.

**Conclusions**
In contrast to unilateral ECT, rTMS has no adverse memory effects.

**Declaration of interest**
None.

Electroconvulsive therapy (ECT) is highly effective in the treatment of severe depression (UK ECT Review Group, 2003). During the past decade, transcranial magnetic stimulation has emerged as a new antidepressant treatment (e.g. Berman et al, 2000). Some randomised trials suggest that repetitive transcranial magnetic stimulation (rTMS) might be as effective as ECT in the treatment of non-psychotic depression (Grunhaus et al, 2000, 2003; Janicak et al, 2002). However, recent reviews and meta-analyses show temperate enthusiasm for transcranial magnetic stimulation as an alternative to ECT (e.g. Martin et al, 2003; Schlaepfer et al, 2003) and emphasise the need for further studies.

In weighing the benefits and risks of different treatment methods, cognitive side-effects are an important issue. Electroconvulsive therapy has been shown to induce anterograde amnesia, retrograde amnesia and subjective memory complaints (e.g. Squire & Slater, 1983; Lisman et al, 2000). Although such deficits tend to cease within weeks to months, a review of patients’ perspectives on ECT (Rose et al, 2003) indicates that persistent memory impairment following this therapy may be more frequent than is evident from testing with standard neuropsychological batteries. In contrast, rTMS seems not to have any substantial cognitive side-effects (e.g. Triggs et al, 1999). However, a comprehensive comparison of cognitive side-effects is lacking so far.

**METHOD**

**Participants**
Thirty patients referred to the Psychiatric University Hospital of Bonn with treatment-resistant, non-psychotic major depressive disorder participated in the study. All patients met the following inclusion criteria:

- a DSM-IV diagnosis of major depressive disorder (American Psychiatric Association, 1994), as assessed by an experienced clinical psychiatrist;
- no additional Axis I diagnosis;
- unsuccessful treatment response to at least two different types of antidepressants, each given in a sufficient dosage range for at least 4 weeks;
- age over 18 years;
- no previous treatment with ECT or rTMS.

The patient sample consisted of 16 men and 14 women; the average age was 47 years (range 25–69) (Table 1).

All patients were referred for ECT or rTMS at the University Hospital of Bonn after prior treatments with antidepressant drugs had failed. The department offers both of these therapies, and is one of only a few specialised treatment centres in Germany to do so. All participants approached our clinic with the specific wish – or a referring doctor’s recommendation – to receive either rTMS or ECT, and received the treatment of their choice if no clinical exclusion criterion was present. The study consisted of consecutively admitted cases within a specified period, going into either the rTMS or the ECT group with comparable likelihood. Fourteen patients were treated with ECT and 16 received rTMS. The two groups did not show significant differences on any of the variables measured; most importantly, they were comparable with regard to age, gender, level of depression, level of education and verbal IQ (Table 1). Furthermore, the cognitive status levels of the two groups at baseline were almost identical, allowing us to study the changes induced by ECT or rTMS. All participants gave informed consent to repeated neuropsychological assessment.

In order to disentangle treatment-related changes in performance from test repetition effects, a control group of 15 healthy volunteers, matched by age, gender, level of education and verbal IQ to the patient groups (see Table 1), was also assessed twice, with the same interval between testings as the patients.

**Clinical ratings and neuropsychological tasks**
Patients and controls were assessed with an extensive test battery before and about a week after completion of the treatment.
Table 1  Demographic and clinical variables

<table>
<thead>
<tr>
<th></th>
<th>ECT group (n=14)</th>
<th>rTMS group (n=16)</th>
<th>Control group (n=15)</th>
<th>ECT v. rTMS Patients v. controls p\textsuperscript{i}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years: mean (s.d.)</td>
<td>46.7 (11.0)</td>
<td>47.7 (13.1)</td>
<td>48.9 (13.8)</td>
<td>0.828\textsuperscript{b} 0.672\textsuperscript{b}</td>
</tr>
<tr>
<td>Gender, n</td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
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<td>9</td>
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<td>Female</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>HRSD score: mean (s.d.)</td>
<td>22.3 (3.0)</td>
<td>21.3 (3.5)</td>
<td></td>
<td>0.393\textsuperscript{a}</td>
</tr>
<tr>
<td>Level of education, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No graduation</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Elementary school</td>
<td>6</td>
<td>9</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Secondary school</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>A-levels</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>A-levels and course of studies</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Verbal IQ (WST score):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (s.d.)</td>
<td>101.9 (17.0)</td>
<td>99.9 (16.6)</td>
<td>108.2 (17.5)</td>
<td>0.779\textsuperscript{a} 0.187\textsuperscript{a}</td>
</tr>
</tbody>
</table>

ECT, electroconvulsive therapy; HRSD, Hamilton Rating Scale for Depression; rTMS, repetitive transcranial magnetic stimulation; WST, Wortschatztest (Schmidt & Metzler, 1992).
1. All P values not significant.
2. t-test.
3. \(\chi^2\) test.

Pre-treatment testing took place 1–3 days before the first treatment session, and the post-treatment testing was done 8.8 days on average after the last ECT or rTMS session with equal intervals between the last treatment and post-treatment testing for both groups (P=0.68, NS). The clinical effects of ECT and rTMS were assessed using the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967; German version by the Collegium Internationale Psychiatriae Scalarum, 1978) and the Beck Depression Inventory (BDI; Beck et al, 1961; German version by Hautzinger et al, 1994). The ratings were made by the treating clinical psychiatrist. Cognitive effects of ECT and rTMS were assessed with a comprehensive neuropsychological battery (see Appendix) with special emphasis on memory functions. Cognitive testing was done by a psychologist masked to the treatment assignments.

**Treatments**

**Electroconvulsive therapy**

Electroconvulsive therapy was given in accordance with current clinical guidelines (American Psychiatric Association, 1990; Folkerts, 1997), using a Thymatron III DG stimulator (Somatics Inc., Illinois, USA), which delivers a brief-pulse bidirectional current. All treatments were given under anaesthesia with propofol (2 mg/kg), muscle relaxation with suxamethonium (1 mg/kg) and 100% oxygenation. Medication was not changed during treatment. Antidepressants, low-potency neuroleptics and non-benzodiazepine hypnotics were allowed. Stimulation was always unilateral on the right hemisphere (all patients were reported to be right-handed for several manual activities). Seizure threshold was determined by a titration method and was age-based. Stimulation intensity was 2–2.5 times the seizure threshold. Therapy was given twice-weekly with a minimum interval of 48 h between treatments. Decisions concerning the number of treatments were made by the psychiatrist in attendance; participants received a mean of 9.9 (s.d.=2.7) treatments.

**Transcranial magnetic stimulation**

Transcranial magnetic stimulation was given with a Magstim Rapid machine (Magstim Co. Ltd, Whitland, UK). To make the frequencies of ECT and rTMS comparable, patients were treated two or three times per week; they received a mean of 10.8 (s.d.=1.4) treatments. Medication was kept constant as well. Stimulation was applied over the left dorsolateral prefrontal cortex with an intensity of 100% and a frequency of 10 Hz (20–30 trains of 2 s duration per treatment session, 5 s intertrain interval). Stimulation frequency was identical to that in previous studies comparing rTMS and ECT (Grunhaus et al, 2000, 2003; Janicak et al, 2002).

**Data analysis**

Data analysis was done using the Statistical Package for the Social Sciences, for Windows version 10.0. To compare the two treatment methods, analyses of variance (ANOVA) with repeated-measures, between-group t-tests (Welch-corrected for unequal variances) and within-group t-tests were performed. In addition, the numbers of responders in both groups were compared using a chi-squared test. Patients were considered to be responders to treatment if their HRSD scores had decreased by at least 50% from baseline levels. One person in the ECT group withdrew from the study because of severe orientation and memory problems after two ECT treatments; these data were not included in the analysis.

**RESULTS**

**Clinical effectiveness**

Both treatment methods resulted in a marked reduction of depression, as assessed by HRSD score, BDI score and response rates. In the ECT group the mean HRSD scores decreased by 35% from 22.4 (s.d.=3.1) to 14.5 (s.d.=5.7), P<0.001. In the rTMS group the mean HRSD score decreased by 39%, from 21.3 (s.d.=3.5) to 13.0 (s.d.=4.9), P<0.001 (Fig. 1). The ANOVA showed a significant time effect (\(F_{1,27}=65.25, P<0.001\)), but no group effect and no interaction. Similar results were found for self-ratings of depression on the BDI. In the ECT group the mean BDI scores decreased by 7.6 points (24%) and in the rTMS group the decrease was 6.4 points (27%). The ANOVA revealed a significant time effect (\(F_{1,24}=8.40, P<0.008\)), but no significant group effect and no interaction.

Patients were considered to be responders to treatment if their final HRSD score had decreased by 50% or more from baseline. According to this criterion, 46% of the ECT group and 44% of the rTMS group were treatment responders (\(\chi^2(1)=0.02, P=0.90\), NS).

**Neuropsychological effects**

Before treatment, the two groups with depressive disorder did not differ from each other on any of the neuropsychological measures (Table 2). After treatment, significant differences between the ECT and rTMS treatment groups emerged for specific memory functions; these differences
Clinical improvement shown by reductions in Hamilton Rating Scale for Depression (HRSD) scores following (a) electroconvulsive therapy (ECT) and (b) transcranial magnetic stimulation (rTMS).

Table 2  Cognitive measures in the three study groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control group</th>
<th>ECT group</th>
<th>rTMS group</th>
<th>t-test: ECT vs. rTMS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Learning and anterograde memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVLT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall (trials 1–5)</td>
<td>59.4 (10.0)</td>
<td>62.0 (11.0)</td>
<td>42.1 (8.5)</td>
<td>46.7 (8.5)</td>
</tr>
<tr>
<td>Recall after interference (trial 5 minus trial 6)</td>
<td>1.2 (1.2)</td>
<td>0.8 (1.3)</td>
<td>2.8 (2.2)</td>
<td>3.9 (1.9)</td>
</tr>
<tr>
<td>Recall after delay (trial 5 minus trial 7)</td>
<td>1.1 (1.6)</td>
<td>0.1 (0.6)</td>
<td>2.4 (1.8)</td>
<td>4.2 (1.6)</td>
</tr>
<tr>
<td>Recognition hits</td>
<td>14.4 (1.4)</td>
<td>14.1 (2.0)</td>
<td>12.8 (2.1)</td>
<td>12.7 (1.8)</td>
</tr>
<tr>
<td>Recognition false alarms</td>
<td>0.3 (1.3)</td>
<td>0.1 (0.4)</td>
<td>4.4 (5.8)</td>
<td>4.9 (6.1)</td>
</tr>
<tr>
<td>MPT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recall trial 3</td>
<td>20.3 (4.9)</td>
<td>20.3 (4.5)</td>
<td>11.4 (5.9)</td>
<td>10.7 (5.9)</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>18.9 (5.3)</td>
<td>19.2 (4.1)</td>
<td>9.5 (4.7)</td>
<td>8.2 (4.5)</td>
</tr>
<tr>
<td>Retrograde memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Retrograde AVLT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recall</td>
<td>4.3 (3.7)</td>
<td>*</td>
<td>2.5 (2.6)</td>
<td>1.7 (2.2)</td>
</tr>
<tr>
<td>Recognition hits</td>
<td>12.5 (2.1)</td>
<td>10.8 (2.5)</td>
<td>9.3 (3.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Recognition false alarms</td>
<td>1.8 (1.6)</td>
<td>5.0 (3.0)</td>
<td>1.1 (1.1)</td>
<td>NA</td>
</tr>
<tr>
<td>Four-card task</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Free recall</td>
<td>2.0 (1.4)</td>
<td>0.4 (0.5)</td>
<td>1.4 (1.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Recognition</td>
<td>3.1 (0.7)</td>
<td>2.3 (0.7)</td>
<td>2.6 (0.5)</td>
<td>NA</td>
</tr>
<tr>
<td>AMI</td>
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<td></td>
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<tr>
<td>Recall score</td>
<td>27.3 (2.2)</td>
<td>27.9 (2.3)</td>
<td>26.9 (1.8)</td>
<td>26.6 (2.4)</td>
</tr>
<tr>
<td>Subjective memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSMQ</td>
<td>2.7 (10.2)</td>
<td>2.3 (8.0)</td>
<td>–20.7 (19.0)</td>
<td>–15.2 (25.2)</td>
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<tr>
<td>Other cognitive functions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>29.1 (1.0)</td>
<td>29.2 (1.1)</td>
<td>27.9 (1.7)</td>
<td>28.3 (1.3)</td>
</tr>
<tr>
<td>Trail Making Test A</td>
<td>37 (19)</td>
<td>36 (18)</td>
<td>56 (24)</td>
<td>53 (23)</td>
</tr>
<tr>
<td>Trail Making Test B</td>
<td>82 (39)</td>
<td>76 (34)</td>
<td>162 (134)</td>
<td>144 (96)</td>
</tr>
<tr>
<td>Digit span (WAIS–R)</td>
<td>17.1 (4.8)</td>
<td>18.1 (4.6)</td>
<td>12.6 (3.0)</td>
<td>13.7 (4.1)</td>
</tr>
<tr>
<td>Letter–number span</td>
<td>18.2 (2.7)</td>
<td>18.9 (3.4)</td>
<td>14.1 (3.4)</td>
<td>13.9 (3.6)</td>
</tr>
<tr>
<td>Word fluency (LPS)</td>
<td>40.0 (15.1)</td>
<td>39.9 (14.7)</td>
<td>29.6 (11.2)</td>
<td>27.9 (10.1)</td>
</tr>
</tbody>
</table>

ECT, Auditory Verbal Learning Test; rTMS, repetitive transcranial magnetic stimulation; SSMQ, Squire Subjective Memory Questionnaire; WAIS–R, Wechsler Adult Intelligence Scale – Revised.

1. See Appendix for details.
2. Contrasts at baseline and about 1 week after treatment.
and $F_{(1,23)}=15.56$, $P=0.001$), whereas the effects of time and group were not significant (Fig. 2(a)).

**Retrograde memory function**

After treatment, participants in the ECT group made significantly more errors than those in the rTMS group in recognising words learned before treatment ($P=0.025$). After treatment, they also recalled significantly fewer items from the visual card task administered before treatment, compared with the rTMS group ($P=0.012$) (Fig. 2(b)).

**Subjective memory complaints**

After treatment, participants given ECT reported no change in memory problems compared with before treatment ($P=0.38$, NS), whereas the rTMS patients judged their own memory much more positively after treatment ($P=0.002$). The ANOVA of the subjective memory measure showed a significant time effect ($F_{(1,23)}=11.04$, $P=0.003$) and a group × time interaction approaching significance ($F_{(1,23)}=3.68$, $P=0.067$) in the absence of any group effect (Fig. 2(c)).

In summary, significant between-group differences were found in anterograde verbal memory, in two retrograde memory parameters and in participants' subjective estimation of their own memory abilities. In contrast to memory, other cognitive functions measured remained constant in both treatment groups; we found no significant group, time or interaction effect in these variables (Table 2).

**Association of memory and depression**

Weiner et al (1986) found no relationship between subjective and objective memory measures in patients given ECT, and concluded that self-rated memory changes may be more a function of clinical symptoms than of objectively demonstrable changes in memory function. We explored this issue, correlating the subjective memory complaints, rated with the Squire Subjective Memory Questionnaire (Squire et al, 1979), with the level of depression (BDI and HRSD scores) and with the assessed neuropsychological variables. The patients’ memory complaints correlated with depression as well as with several cognitive measures. The patients’ self-ratings of memory functions correlated significantly with their self-ratings of depression (BDI: $r=-0.67$, $P<0.01$), but less so with the clinician ratings of depression (HRSD: $r=-0.31$, $P=0.13$). Self-rating of memory also correlated with the ability to learn and recall new verbal and visual material (AVLT sum of trials 1–5: $r=0.42$, $P<0.05$; AVLT trial 7 after delay: $r=0.46$, $P<0.05$; Memory for Persons Test, delayed recall, $r=0.48$, $P<0.05$), and with the ability to correctly recognize words learned before treatment (retrograde AVLT, false alarms: $r=0.61$, $P<0.05$), but not with their autobiographical memory ($r=0.07$, $P=0.75$, NS). Importantly, the correlations between subjective and objective memory did not change markedly when controlling for self-rated (BDI) depression by partial correlations.

**Comparison with healthy controls**

The group of healthy controls was included to control for test repetition effects and to see whether (and which) impaired cognitive functions would return to normal levels after treatment in both groups. A comparison of the cognitive functions of the participants with depression and the healthy controls at baseline showed highly significant deficits on the part of the patients in almost all measures. Repeated-measures ANOVAs comparing each treatment group separately with the healthy control group revealed that the performance gap between the ECT and control groups with regard to anterograde memory increased (group × time interaction, $P<0.05$ for recall after interference and $P<0.001$ for recall after delay). In contrast, the difference between the rTMS and control groups remained unchanged (the group × time interactions were not significant).

After treatment, the ECT and control groups differed considerably in their ability to remember words or cards from pre-treatment testing (retrograde AVLT: $P=0.049$; four-card task: $P=0.001$), whereas the rTMS group showed retrograde memory functions identical to those of the control group (retrograde AVLT: $P=0.33$, NS; four-card task: $P=0.26$, NS). Similarly, the self-rating of memory functions by the rTMS group differed significantly from that in the control group only before treatment ($P=0.001$); after treatment the rTMS group rated their memory functions to be as good as those of the healthy group ($P=0.69$, NS). In contrast, the ECT group rated their memory abilities more negatively than the control group both before ($P=0.001$) and after treatment ($P=0.039$). The group × time interaction in the ANOVA comparing control and rTMS groups was significant ($P<0.001$), but this interaction was not significant in the ANOVA comparing the control and ECT groups ($P=0.30$, NS).

**DISCUSSION**

The major conclusion to be drawn from this study pertains to the cognitive effects of unilateral ECT and left prefrontal rTMS in patients with severe depression, since this study was designed to assess these effects...
with sensitive neuropsychological measures. Because the antidepressant effect of both treatments was identical, and the groups did not differ prior to treatment, the cognitive changes over time and the post-treatment group differences can be attributed to the different treatments. In the ECT group, not a single cognitive variable improved after treatment, and the recall of newly learned material even became worse. In the rTMS group, some objective memory measures and the subjective memory rating improved in parallel with the improvement in mood, and reached normal performance levels.

Clinical effectiveness of ECT and rTMS

The two treatments appeared to be clinically equivalent in this group of patients with treatment-resistant, non-psychotic depression. Although the study was not randomised, its finding of comparable antidepressant efficacy of ECT and rTMS is in line with the results of all three randomised comparison studies published so far (Grunhaus et al, 2000, 2003; Janicak et al, 2002). The rates of those responding to unilateral ECT are in the expected range for medication-resistant non-psychotic depression (McCall, 2001), but might have been higher if a higher ECT dosage had been used (Sackeim et al, 2000). However, a higher dosage would probably increase the risk of cognitive adverse effects. A definitive answer to the question of clinical equipotency of ECT and rTMS will have to await further studies.

Anterograde memory

Patients treated with ECT showed more anterograde memory problems at the post-treatment assessment than did either patients treated with rTMS or healthy controls. In particular, they remembered fewer words only after learning the interference word list of the Auditory Verbal Learning Test (between Trials 5 and 6 of the AVLT), indicating a recall deficit rather than a working memory or learning deficit. This extends findings by Hasse-Sander et al (1998), who reported impaired verbal delayed recall 1–2 days after unilateral ECT (no longer follow-up was made), and of Cronholm & Ottosson (1961), who described specific deficits in the delayed recall of newly learned words, figures and persons 1 week after bilateral ECT. For the rTMS group, the lack of anterograde memory effects is in line with previous studies (e.g. Triggs et al, 1999).

Retrograde memory

The ECT patients, in contrast to the patients treated with rTMS or the control group, also showed retrograde memory problems after treatment. They remembered fewer of the pictures and made more errors in recalling words learned before treatment. No difference emerged for autobiographical memory, which is in line with previous studies demonstrating deficits in recall of past events only after bilateral ECT, not after unilateral therapy (Squire et al, 1981; Weiner et al, 1986; Lisanby et al, 2000). The verbal and visual retrograde memory tasks used here might be more sensitive to ECT-induced impairments than the Autobiographical Memory Interview, possibly because recent memory traces formed during the days before treatment are more vulnerable to ECT effects than are more remote memories (Squire et al, 1981; Lisanby et al, 2000).

Subjective memory

After treatment, the ECT patients complained more about memory problems than the rTMS patients and the controls. Squire et al (1979), Freeman et al (1980) and Squire & Slater (1983) also found subjective cognitive side-effects after ECT. After rTMS the patients’ subjective memory ratings equalled those of the healthy controls, whereas after ECT the patients’ ratings were very negative. This group difference cannot be explained by different clinical effects of the two treatment methods. At least in part, this group difference in subjective memory appears to be related to subjectively measurable memory impairments after ECT, because the subjective memory functions not only correlated with the level of depression, which is a common finding (e.g. Weiner et al, 1986), but also with several objective memory measures (even when statistically controlling for the level of depression). Associations between subjective and objective memory measures after ECT have often found to be lacking (e.g. Prudic et al 2000), but some studies suggest that such a relationship may exist, at least for certain forms of memory and for specific periods after ECT (e.g. Freeman et al, 1980). Thus, complaints of patients about memory deficits (metamemory) may partly result from the experience of objective memory failures after ECT, and should not be dismissed as being simply a sign of depressive complaints.

Clinical implications

With regard to objective and subjective memory function, patients with severe depression appear to be cognitively better off 1 week after a course of rTMS than 1 week after a course of unilateral ECT, despite (in this study) an indistinguishable antidepressive effect of the two treatments. Adverse memory effects after ECT may fully resolve after a longer interval, usually after several months (Weeks et al, 1980); nevertheless, if rTMS evolves into an alternative treatment for some forms of medication-resistant depression, clinicians and patients should be aware of its reduced risk for adverse memory effects, compared with unilateral ECT. Future comparison studies of ECT, rTMS and magnetic seizure therapy (Kosel et al, 2003) should include sensitive memory assessments and longer follow-up intervals to evaluate fully the ratio of benefits and risks of these treatment methods.

Limitations

Because our study lacked a sham-treated patient control group and patients were not randomly assigned to treatments, no conclusion should be drawn regarding the absolute or relative antidepressant effectiveness of rTMS or ECT. Although the pattern of cognitive findings, in line with previous work, suggests that unilateral ECT, in contrast to rTMS, specifically impairs several aspects of memory for at least a week after a treatment series, the small number of participants in our study renders this a preliminary finding requiring confirmation in other samples.

APPENDIX

Neurocognitive test battery

Learning and anterograde memory function

(a) Auditory Verbal Learning Test (AVLT; Rey, 1964); German version by Helmstaedter et al (2001).

(b) Memory for Persons Test (Bulla-Hellwig & Spanhofer, 1996); a German visual memory test in which each of 12 different faces has to be associated with a name and an occupation.

Retrograde memory function

(a) Autobiographical Memory Interview (Kapelman et al, 1990); shortened German version.
(b) Retrograde AVL T: at the post-treatment assessment, participants were asked to recall the 15 AVL T words they had learned before treatment. The task involved a free recall and a recognition task. This measure was introduced after the study began, therefore only data from 13 patients (6 receiving electroconvulsive therapy, 7 repetitive transcranial magnetic stimulation) and 15 controls were available.

(c) Four-card task: before treatment, participants were asked to reproduce a demonstrated arrangement of four picture cards from the Rivermead Behavioural Memory Test (Wilson et al., 1991); after treatment they were asked details about the ‘test with cards’ (number of cards, kind of task, recall and recognition of depicted objects), and the number of correct details was scored.

Subjective memory function
Squire Subjective Memory Questionnaire (Squire et al., 1979): this 18-item self-rated scale of memory functions comprises items such as ‘My ability to hold in my memory things that I have learned is...’. Respondents were asked to compare their present memory with their memory before they became ill (patients) or with their memory 1 year ago (controls), on a nine-point scale from −4 (worse than before) to +4 (better than before).

Other neurocognitive functions
(a) Mini-Mental State Examination (Folstein et al., 1975): German version by Kessler et al (1990).
(b) Trail Making Test A and B (Reitan, 1979).
(c) Digit span: Wechsler Adult Intelligence Scale – Revised (Wechsler, 1981).
(d) Letter–number span (Gold et al., 1997).
(e) Word fluency: Leistungs-Prüf-System (Horn, 1983).

REFERENCES

CLINICAL IMPLICATIONS
- In people with treatment-resistant depression, even unilateral electroconvulsive therapy (ECT) is associated with memory deficits 1 week after the last treatment.
- Repetitive transcranial magnetic stimulation is not accompanied by such memory impairments.
- Self-reported memory impairments after ECT can be related to objective memory deficits and must not be dismissed as being depressive complaints only.

LIMITATIONS
- Patient groups were not randomised and no patient control group was assessed, limiting conclusions about clinical efficacy.
- Sample sizes were small.
- There was no long-term follow-up.

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Mental health inequalities in Wales, UK: multi-level investigation of the effect of area deprivation

PETROS SKAPINAKIS, GLYN LEWIS, RICARDO ARAYA, KELVYN JONES and GARETH WILLIAMS

Background Geographical variation in the prevalence of common mental disorders has not been explained adequately.

Aims To investigate whether regional mental health differences in Wales would persist after having taken into account the characteristics of individuals and regional social deprivation.

Method Data from the 1998 Welsh Health Survey were used. Common mental disorders were assessed with the mental health index included in the Short-Form 36 health survey (SF–36). The data were analysed using a multi-level linear regression model.

Results Of the total variance in the mental health index, 1.47% occurred at the between-region level (95% CI 0.56–2.38). Adjustment for individual characteristics did not explain the between-region variation. A higher area deprivation score was associated with a higher score on the mental health index.

Conclusions Mental health differences in Wales are partly explained by the level of regional social deprivation.

Declaration of interest None.

Geographical variation in the prevalence of common mental disorders has been observed for many years in Britain (Lewis & Booth, 1992; Weich et al., 2001). Traditionally this variation has been attributed to differences in the population composition rather than in the contextual characteristics. The advent of the statistical technique of multi-level analysis has made it possible to investigate the effect on mental health of both compositional and contextual variables in the same model. The few studies carried out so far have generally found negative results for the effect of place (Duncan et al., 1995; Weich et al., 2003a; further details available from G.L. on request). From the risk factors studied, measures of aggregate deprivation failed to reach statistical significance after adjustment for the individual-level (compositional) variables (Reijneveld & Schene, 1998; Weich et al., 2003b). However, this is a relatively new field and further research is required. In the present study we investigated whether differences in mental health in Wales would persist after taking into account the individual characteristics. We also tested the hypothesis that individuals living in more deprived areas would have worse mental health.

METHOD

Description of the data-set

The 1998 Welsh Health Survey (National Assembly for Wales, 1999) was a cross-sectional postal survey carried out in Wales with the aim of collecting information on various aspects of the physical and mental health of adults aged 18 years and over living in Wales. The research instrument used in the survey included the Short-Form 36 health survey (SF–36) (Ware & Sherbourne, 1992). The sample was drawn from electoral registers of the 22 regional unitary authorities of Wales. Small authorities were slightly oversampled to achieve the required sample size. The current study included 26,710 individuals who had data on the SF–36. The response rate was 60%, with a range across regions of between 50.4% in Wrexham and 65.4% in Powys. The main fieldwork was carried out between May and August 1998.

Information on Wales

Wales occupies a broad peninsula on the western side of Great Britain, with a total area of 20,760 square kilometres and a population of approximately 2.9 million in 2001. The average population density is lower than that in England but in the industrialised south is comparable to other highly populated areas in Britain. The median population (mid-year estimates in 2001) in the 22 regional unitary authorities was 122,850, with a range between 55,900 in Merthyr and 305,200 in Cardiff.

Measures

Assessment of common mental disorders

The main outcome used in the present study was psychiatric morbidity, as measured by the mental health index included in the SF–36. The SF–36 (Ware & Sherbourne, 1992) is an instrument widely used to assess the health status of patients and it has also been used in community studies. The psychometric properties of the SF–36 were tested in a study in the UK general population and the mental health index showed good internal consistency (Cronbach’s $\alpha=0.83$; Jenkinson et al., 1993). In addition, a study carried out in Wales compared the mental health index with the 12-item General Health Questionnaire (GHQ–12), an instrument commonly used to assess common mental disorders in the community, and found it to be comparable (Winston & Smith, 2000).

The mental health index is a set of five questions asking about the presence of negative (three questions) or positive (two questions) feelings during the past 4 weeks. The five questions used for the index are:

(a) Have you been a very nervous person?
(b) Have you felt so down in the dumps that nothing could cheer you up?
(c) Have you felt calm and peaceful?
(d) Have you felt downhearted and low?
(e) Have you been a happy person?

Each of the questions has six response categories ranging from ‘all of the time’ to
'none of the time'. For the purposes of the present paper we reversed the order of scoring for the three negative questions and therefore a higher score on the index represents greater psychiatric morbidity. We then transformed the raw scores (ranging from 5 to 30) on a scale from 0 (no morbidity) to 100 (high morbidity). In our analysis we used the transformed scores as a continuous variable. It should be noted that this simple instrument assumes that common mental disorders represent a single dimension. Several epidemiological studies have confirmed the usefulness of this assumption for the common mental disorders of depression or anxiety (Goldberg & Huxley, 1992).

**Individual characteristics**

Information on the following individual-level variables was available: age, gender, marital status (coded in four categories: single; divorced; widowed; married/living as couple), employment status (coded in four categories: employed full-time or part-time; unemployed or unable to work because of long-term disability; retired; economically inactive), the Registrar General’s social class based on the participant’s present or most recent occupation (coded in five categories: I/II; III, non-manual; III, manual; IV/V; missing values), and housing tenure status (either owner or tenant).

**Deprivation at the authority level**

Levels of deprivation across regions were estimated with the Welsh Index of Multiple Deprivation (National Assembly for Wales, 2004). This is a composite measure developed by the local government data unit with the aim of modelling levels of deprivation in Wales and supporting policy development and targeting of resources. The data used in the derivation of the index are based on direct measures of deprivation at the small-area level (the electoral division level). Data from the following domains were included: income, employment, health, education, housing and geographical access to services. Detailed information for the derivation of this index is given elsewhere (National Assembly for Wales, 2004). For the purposes of the present paper we used the average electoral division rank. This was a number between 104 for the most deprived area and 708 for the least deprived area. For easier interpretation of the index we subtracted the actual score from 1000 and therefore the new score has a median of 558 and a range of 292–896, with a higher score meaning a higher level of deprivation. The 22 regions were categorised further into three groups according to their deprivation score, as follows: low level of deprivation (scores of 292–490), middle level of deprivation (491–651) and high level of deprivation (652–896). The cut-offs chosen were the 25th (490) and 75th (651) percentiles of the transformed score on the deprivation index.

**Statistical analysis**

Analyses were carried out with MLWin software (Rasbash et al, 2001). The score on the mental health index was used as the continuous dependent variable in a hierarchical linear regression model. The estimation procedure applied was the restricted iterative generalised least-squares method (Goldstein, 1995), which leads to unbiased estimates of the random parameters. The P values were based on Wald’s test (two-sided). Our strategy for the analysis consisted first of fitting a simple variance component model (null model) to identify the two components of variation: that between regions (level 2 variance) and that between individuals within a region (level 1 variance). The next step was to include all level 1 variables in the model. The level 1 variables were entered as fixed effects, which assumes that they are related to the mental health index in the same way across level 2 units. The degree to which the estimated level 2 variance decreased after entering the explanatory level 1 variables indicated how well the model explained the between-region variance. To examine whether deprivation at the regional level was associated independently with the mental health of the individuals, we first entered the deprivation variable into the null model (to obtain crude estimates) and then adjusted for all level 1 variables. The deprivation index was entered as a categorical variable, using dummy variables for the categories of middle and high level of deprivation. We also explored graphically whether differences in mental health between regions persisted after taking into account the individual characteristics and regional deprivation, by plotting the 22 residuals in the null model after adjustment for individual variables and after adjustment for both individual variables and regional deprivation.

**RESULTS**

A greater proportion of the participants were female (54.8%, n=14 629), married/living as a couple (66.4%, n=17 730) and employed full-time/part-time (51.9%, n=13 831). The mental health index had a mean of 27.96 (s.d.=18.97).

Table 1 shows the hierarchical structure of the data and the crude regional averages of the mental health index. Regions have been arranged in rank order of their social deprivation indices. There are differences between regions, with a high average of 32.7 (s.d.=20.5) in Blaenau Gwent and a low of 25.1 (s.d.=17.6) in Monmouthshire. There is a strong relationship between the rank order of regional deprivation and the rank order of the mental health index, with Spearman’s r=0.60 (P=0.003).

**Null model**

The intercept-only model is presented in Table 2. The constant value of 27.85 (s.e.=0.51) represents the average mental health score across regions. This value does not remain constant across regions and the random effect variances are presented. Most variance occurs at level 1 (individuals) and only 1.47% of the total (unexplained) variance occurs at level 2 (95% CI 0.56–2.38). Although small, this amount of variation at the regional level is statistically significant (P=0.002).

**Inclusion of individual characteristics and regional deprivation**

Model 1 in Table 2 shows the degree to which the two variances are decreased after entering the individual characteristics into the model. It can be seen that the total unexplained variance at level 2 is reduced by 32.6% but is still significant. Further adjustment for regional deprivation (model 2) led to a 50% reduction in the total unexplained variance at level 2, but this remained significant (P=0.005).

**Association between regional deprivation and common mental disorders**

Table 3 shows the association between level 2 deprivation and scores on the mental health index before and after adjustment for individual-level socio-demographic characteristics. It can be seen that the regional
Variance and percentage of total unexplained variance at the individual and regional level in mental health index scores (Welsh Health Survey, 1998)

<table>
<thead>
<tr>
<th>Region</th>
<th>Mean (s.d.) MHIC (rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monmouthshire</td>
<td>25.1 (17.6)</td>
</tr>
<tr>
<td>Vale of Glamorgan</td>
<td>25.6 (17.3)</td>
</tr>
<tr>
<td>Flintshire</td>
<td>26.8 (18.3)</td>
</tr>
<tr>
<td>Powys</td>
<td>25.3 (18.3)</td>
</tr>
<tr>
<td>Cardiff</td>
<td>28.4 (18.9)</td>
</tr>
<tr>
<td>Ceredigion</td>
<td>26.0 (18.0)</td>
</tr>
<tr>
<td>Conwy</td>
<td>25.9 (18.2)</td>
</tr>
<tr>
<td>Denbighshire</td>
<td>26.2 (19.1)</td>
</tr>
<tr>
<td>Swansea</td>
<td>27.3 (18.9)</td>
</tr>
<tr>
<td>Newport</td>
<td>29.1 (19.0)</td>
</tr>
<tr>
<td>Wrexham</td>
<td>28.1 (19.5)</td>
</tr>
<tr>
<td>Bridgend</td>
<td>28.6 (18.2)</td>
</tr>
<tr>
<td>Pembrokeshire</td>
<td>25.2 (18.0)</td>
</tr>
<tr>
<td>Torfaen</td>
<td>31.1 (20.4)</td>
</tr>
<tr>
<td>Gwyrnedd</td>
<td>25.4 (17.1)</td>
</tr>
<tr>
<td>Isle of Anglesey</td>
<td>25.0 (17.1)</td>
</tr>
<tr>
<td>Carmarthenshire</td>
<td>27.5 (18.6)</td>
</tr>
<tr>
<td>Rhondda Cynon Taff</td>
<td>30.2 (19.4)</td>
</tr>
<tr>
<td>Caerphilly</td>
<td>30.9 (20.2)</td>
</tr>
<tr>
<td>Neath Port Talbot</td>
<td>29.2 (19.7)</td>
</tr>
<tr>
<td>Blaenau Gwent</td>
<td>32.7 (20.5)</td>
</tr>
<tr>
<td>Merthyr Tydfil</td>
<td>32.6 (21.0)</td>
</tr>
</tbody>
</table>

1. A higher score means more deprivation.
2. Mental health index: measures current psychiatric morbidity, with a higher score meaning higher morbidity.

### Table 1

The hierarchical structure of the data-set

<table>
<thead>
<tr>
<th>Level 2: local unitary authorities (n=22)</th>
<th>Welsh Index of Multiple Deprivation (rank)</th>
<th>Level 1: individuals (n=26710)</th>
<th>Mean (s.d.) MHIC (rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monmouthshire</td>
<td>251</td>
<td>1062</td>
<td>25.1 (17.6)</td>
</tr>
<tr>
<td>Vale of Glamorgan</td>
<td>256</td>
<td>1052</td>
<td>25.6 (17.3)</td>
</tr>
<tr>
<td>Flintshire</td>
<td>268</td>
<td>1040</td>
<td>26.8 (18.3)</td>
</tr>
<tr>
<td>Powys</td>
<td>253</td>
<td>1132</td>
<td>25.3 (18.3)</td>
</tr>
<tr>
<td>Cardiff</td>
<td>284</td>
<td>1132</td>
<td>28.4 (18.9)</td>
</tr>
<tr>
<td>Ceredigion</td>
<td>260</td>
<td>890</td>
<td>26.0 (18.0)</td>
</tr>
<tr>
<td>Conwy</td>
<td>259</td>
<td>958</td>
<td>25.9 (18.2)</td>
</tr>
<tr>
<td>Denbighshire</td>
<td>262</td>
<td>879</td>
<td>26.2 (19.1)</td>
</tr>
<tr>
<td>Swansea</td>
<td>2061</td>
<td>252</td>
<td>27.3 (18.9)</td>
</tr>
<tr>
<td>Newport</td>
<td>1118</td>
<td>29.1 (19.0)</td>
<td></td>
</tr>
<tr>
<td>Wrexham</td>
<td>934</td>
<td>28.1 (19.5)</td>
<td></td>
</tr>
<tr>
<td>Bridgend</td>
<td>1127</td>
<td>28.6 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Pembrokeshire</td>
<td>1034</td>
<td>25.2 (18.0)</td>
<td></td>
</tr>
<tr>
<td>Torfaen</td>
<td>908</td>
<td>31.1 (20.4)</td>
<td></td>
</tr>
<tr>
<td>Gwynedd</td>
<td>1076</td>
<td>25.4 (17.1)</td>
<td></td>
</tr>
<tr>
<td>Isle of Anglesey</td>
<td>888</td>
<td>25.0 (17.1)</td>
<td></td>
</tr>
<tr>
<td>Carmarthenshire</td>
<td>1281</td>
<td>27.5 (18.6)</td>
<td></td>
</tr>
<tr>
<td>Rhondda Cynon Taff</td>
<td>1980</td>
<td>30.2 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Caerphilly</td>
<td>1426</td>
<td>30.9 (20.2)</td>
<td></td>
</tr>
<tr>
<td>Neath Port Talbot</td>
<td>1245</td>
<td>29.2 (19.7)</td>
<td></td>
</tr>
<tr>
<td>Blaenau Gwent</td>
<td>874</td>
<td>32.7 (20.5)</td>
<td></td>
</tr>
<tr>
<td>Merthyr Tydfil</td>
<td>783</td>
<td>32.6 (21.0)</td>
<td></td>
</tr>
</tbody>
</table>

1. The mental health index measures current psychiatric morbidity and was entered as the dependent variable in a two-level linear regression model.
2. Individual-level variables included age, gender, marital status, employment status, social class and housing tenure status.
3. Regional deprivation refers to the score on the Welsh Index of Multiple Deprivation.

#### DISCUSSION

**Main findings**

In this cross-sectional postal survey we found significant differences in psychiatric morbidity, as measured by a brief self-completed questionnaire, between the 22 administrative regions of Wales. These differences persisted (although they were reduced) after taking into account the characteristics of the individuals. Regional deprivation was associated independently with psychiatric morbidity and explained part of the variation at the regional level.

**Limitations of the study**

Certain limitations should be considered before interpreting these results. First, it has been pointed out by others that there is a lack of theory on the mechanisms that link area of residence and health in general, or mental health in particular (Macintyre et al., 2002; O’Campo, 2003). The study of the effects of area of residence on mental health is so limited that our study is mainly exploratory in nature. Although we hypothesised that a measure of deprivation at the regional level would be associated with common mental disorders, our findings should be interpreted more as a preliminary effort that can help the generation of new hypotheses, rather than as an indication that this specific factor might ‘explain’ mental health differences across regions.

Second, we used large administrative areas...
as our higher level of aggregation, and our analysis included only two levels. We did not have data on other intermediate levels, such as the electoral ward. However, for the specific hypothesis of our study this design is adequate. Third, the cross-sectional design is certainly limited and issues related to reverse causality and duration of exposure can be dealt with only by longitudinal designs. Fourth, we assessed common mental disorders in a crude way, using a simple five-item self-reported measure. Although this measure has been found to be comparable with other similar instruments, such as the GHQ–12, a degree of random misclassification will be inevitable and may have biased our results in either direction. Finally, this was a postal survey with an average response rate of 60%. The most likely effect of this relatively low response is type II errors, but if there were an association between regional deprivation, common mental disorders and probability of response to the survey, the results could be biased in either direction.

**Area effects**

Previous research that aimed to investigate the effect of area of residence on mental health has observed generally that, once individual characteristics have been taken into account, the amount of variation attributed to the higher levels is very small and not significant (Duncan et al., 1995; Weich et al., 2003; further details available from G.L. on request). Our own estimates are somewhat higher and statistically significant. A number of reasons may explain this discrepancy: the choice of instruments to measure psychiatric morbidity (other studies mainly have used the General Health Questionnaire) may have contributed to this difference; and the power of previous studies to find a statistically significant difference may have been compromised by the choice of the higher level. With regard to the latter, it has been argued (Snijders & Bosker, 1999; Diez Roux, 2004) that the power to detect the higher level variance component is influenced by the number of individual observations in each group. A greater number of higher level groups with relatively few individual observations per group will yield large standard errors and may have insufficient power to detect a significant variance component at this level (although it will maximise the power to detect an association between a higher level risk factor and the individual outcome). It is interesting to note that most previous studies have used either the postcode or the electoral ward as the higher level and this resulted in a small number of observations per group in the range of 14–23 persons. In contrast, our own study had a mean of 1214 individual observations per region. The study by Duncan et al. (1995) used the regions in Britain as the higher level but this study failed to find a significant result even in the null model.

Our study consisted of two levels of analysis whereas previous studies included a third intermediate level, most commonly the household level, and this may be a further reason for our significant results (or the non-significant results of previous studies) on the variation attributed to the higher levels. It should be noted that previous studies had selected more than one individual per household and this made necessary the inclusion of the household level to take account of the clustering of observations. In our own study only one individual per household was selected. Failure to include the household level in multi-level studies of mental health has been criticised.

![Fig. 1 Mental health differences across the 22 regions of Wales, UK. The bars show the residuals from a two-level linear regression in the null model, after adjustment for individual socio-demographic characteristics (model 1) and after additional adjustment for regional deprivation (model 2). Significant residuals in the full model (model 2) are noted by asterisks.](image)
in the past (Weich et al, 2003b). However, inclusion of an intermediate level will also increase the chances of overadjustment, which is considered an important problem in multi-level research (Diez Roux, 2004). For example, if the effects of area of residence on individual mental health are mediated through unknown household factors, then inclusion of this level will reduce the reported associations at the higher level (Davie Smith et al, 1998).

All studies that have investigated the effect of area of residence on several health outcomes generally have found small size effects, in the range of 1–5% of the total (unexplained) variance (Boyle & Willms, 1999). Our own result of 0.9% confirms these findings. Do these small figures have any public health importance? To answer this question one should take into account the possible ways in which a higher level context may affect an individual outcome. Blakely & Woodward (2000) have discussed this issue in detail. Contextual factors may have a direct effect on individual mental health or they may influence other intervening variables that mediate their effect. It has been argued that a direct effect is not possible because it will require a final reduction to an individual process. However, as Blakely & Woodward (2000) rightly pointed out, such reductionism is not helpful in public health terms because knowledge of one component of a causal chain may be sufficient for public health interventions. In addition, modifications of higher level risk factors are more efficient from a public health perspective compared with interventions that target individuals. Certainly, further research is needed to understand better what constitutes an adequate amount of explained variation (Boyle & Willms, 1999).

Association of deprivation with mental health

Our hypothesis that an index of regional deprivation would be associated with common mental disorders was confirmed in this data-set. The few previous studies that have investigated the same issue generally have found negative results, after taking into account the individual characteristics (Rejneveld & Schene, 1998; McCulloch, 2001; Weich et al, 2003b). As mentioned before, the choice of levels of analysis and the problems of overadjustment may have contributed to this discrepancy. In addition, selection bias could be an alternative explanation. Individuals select the places they live and the (unidentified) individual factors that influence this selection may be responsible for the reported association. The resulting bias, however, could be in either direction (Duncan et al, 2004).

Regional residuals

Analysis of the 22 regional residuals (Fig. 1) may shed more light on the reported association between regional deprivation and common mental disorders. The residuals reflect the unexplained variability between regions and from Fig. 1 several points can be made. First, adjustment for the individual variables generally had little effect on reducing the differences between regions. In contrast, further adjustment for regional deprivation had a significant effect and only 7 out of 22 regions had residuals significantly different from zero. Second, for most regions, adjustment for deprivation reduced the value of the residual. This effect was more evident in regions where there was a strong association between deprivation and common mental disorders. It can be seen from the figure that for Merthyr, Blaenau Gwent, Caerphilly and Rhondda Cynon Taff regional deprivation explained most of the variation. Third, for some regions (e.g. Cardiff and Newport) adjustment for regional deprivation had the opposite effect and the value of the residual was increased, indicating that other higher level variables, possibly related to the urban environment (Weich et al, 2003b), may be more relevant. Fourth, Pembrokeshire, Gwynedd and the Isle of Anglesey differed in that they had significant negative residuals even though they had more than the average regional deprivation. Whether this discrepancy is owing to the rural/urban difference in rates of common mental disorders is not known, but certainly requires further research.

Interpretation of the association between regional deprivation and common mental disorders is not easy. Regional deprivation is most probably a proxy for other unmeasured regional attributes and the pathways involved are likely to be complex and include feedback loops (Diez Roux, 2004). Longitudinal studies may be of particular importance. However, clarification of these pathways will certainly require a combination of methods, both qualitative and quantitative.

ACKNOWLEDGEMENTS

The study was funded by the National Assembly for Wales. However, the views expressed in this report are those of the authors alone. We thank Dr Kate Chamberlain of the Welsh local government data unit for providing us with information on the Welsh Index of Multiple Deprivation.

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Common mental disorders were assessed with a simple five-item questionnaire and this may have resulted in measurement bias.

Limitations

- Research into the effect of area of residence on mental health is still limited and our study is mainly of an exploratory nature.
- The contextual effects may vary with the number of levels used and our choice of levels may have influenced our results in either direction.
- Common mental disorders were assessed with a simple five-item questionnaire and this may have resulted in measurement bias.

Clinical implications

- Mental health differences between regions in Wales persisted even after adjustment for individual characteristics.
- An index of regional deprivation was found to be associated independently with common mental disorders, even after adjustment for individual-level variables.
- Although the effect of area of residence on mental health appears to be small, it may be important from a public health perspective.

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(First received 3 March 2004, final revision 14 September 2004, accepted 30 September 2004)
Misdiagnosis of post-traumatic stress disorder following severe traumatic brain injury

RUTH E. SUMPTER and TOM M. McMILLAN

Background The incidence of post-traumatic stress disorder (PTSD) after traumatic brain injury is unclear. One issue involves the validity of diagnosis using self-report questionnaires.

Aims To compare PTSD ‘caseness’ arising from questionnaire self-report and structured interview.

Method Participants (n=34) with traumatic brain injury were recruited. Screening measures and self-report questionnaires were administered, followed by the structured interview.

Results Using questionnaires, 59% fulfilled criteria for PTSD on the Post-traumatic Diagnostic Scale and 44% on the Impact of Events Scale, whereas using structured interview (Clinician-Administered PTSD Scale) only 3% were ‘cases’. This discrepancy may arise from confusions between effects of PTSD and traumatic brain injury.

Conclusions After traumatic brain injury, PTSD self-report measures might be used for screening but not diagnosis.

Declaration of Interest None.

There is growing acceptance that post-traumatic stress disorder (PTSD) can occur after traumatic brain injury (McMillan et al, 2003), but the reported incidence varies widely (0–56%), making service planning difficult. Such variability may arise because of methodological difficulties (Bryant, 2001), but in addition, the effects of traumatic brain injury might lead to inaccurate reporting or interpretation of responses. For example, people with traumatic brain injury can focus on the memory gap resulting from coma and post-traumatic amnesia without great distress and this might be inappropriately labelled as ‘intrusive’; they may avoid tasks and situations because of incapacity rather than fear; and often their lives have been significantly altered by traumatic brain injury (McMillan, 2001). Personality change, including impulsiveness, reduced insight, rigid thinking, reduced motivation, and impaired learning and concentration resulting from traumatic brain injury, may also cause some complaints to be mislabelled as PTSD symptoms. McMillan (2001) reported a severe case of traumatic brain injury that appeared to have PTSD on the basis of the Post-traumatic Diagnostic Scale (PDS), but clearly did not at clinical interview. The present study examines McMillan’s finding in a group of severe cases of traumatic brain injury.

METHOD

Permission was obtained from the local research ethics committee.

Participants

A total of 34 participants were recruited from community out-patient and rehabilitation services, and voluntary organisations. A power calculation based on proportions of people with severe traumatic brain injury reaching PTSD ‘caseness’ on the Impact of Events Scale (IES) and Clinician-Administered PTSD Scale (CAPS) (Turnbull et al, 2001) indicated n=30, needed for 80% power, with α set at 0.05 and β 0.2. Participants were >17 years, with a severe traumatic brain injury (post-traumatic amnesia >1 day) at least 3 months before interview. Exclusion criteria were scores <27 on the Mini-Mental State Examination (Folstein et al, 1975), severe dysphasia or dyslexia, or current treatment for psychosis.

Measures

PTSD

(i) IES, a 15-item self-report questionnaire, providing ratings of avoidance and intrusion (Horowitz et al, 1979). Total IES scores >25 determined ‘caseness’ (Cornell et al, 1999).

(ii) PDS, a 49-item self-report questionnaire based on the 17 DSM-IV (American Psychiatric Association, 1994) symptoms, with ratings of duration, onset and impact on social and occupational functioning. For all definitions, criterion A need not be met in a population with severe traumatic brain injury given the co-occurrence of loss of consciousness and post-traumatic amnesia.

(iii) CAPS, a structured clinical interview assessing the 17 DSM-IV symptoms, their duration and impact. A symptom is ‘present’ when the frequency is >0 and intensity >1 (Blake et al, 1995). Two definitions of caseness were used to consider difficulties that might arise if CAPS is administered by an unsupervised and inexperienced clinician:

(a) CAPS–without judgement requires DSM-IV criteria B–F to be fulfilled.

(b) CAPS–with clinical judgement in addition requires the clinician to adjudge that the symptoms are related to the trauma.

Other

(i) The Hospital Anxiety and Depression Scale (HADS) has two sub-scales (anxiety and depression); scores >7 were rated abnormal (Zigmond & Snaith, 1983).

(ii) The Rivermead Post Concussion Symptoms Questionnaire (RPQ) is a 14-item self-report questionnaire (King et al, 1995).
(iii) The Glasgow Outcome Scale–Extended (GOS–E) is a clinician-rated scale of social and functional disability after traumatic brain injury (Wilson et al., 1998).

(iv) Post-traumatic amnesia duration estimates severity of traumatic brain injury and was carried out retrospectively (McMillan et al., 1996).

(v) The Mini-Mental State Examination was used to assess ability to consent to participate (Folstein et al., 1975).

(vi) The Speed of Comprehension Test (SCT) assesses speed and accuracy of information processing (Baddeley, 1992).


Procedure

Demographic and injury information were obtained at interview. Screening measures and self-report questionnaires were administered, and then the clinician-rated GOS–E and the structured interview (CAPS).

RESULTS

Demographic and descriptive measures

Thirty male and four female participants were recruited from community services. The average age at interview was 40 years (s.d.=11, range 20–60 years) and years of education 12 (s.d.=2, range 10–20). Average premorbid intelligence quotient (IQ) (National Adult Reading Test [NART]) was 100 (s.d.=14, range 69–121) and time since injury 6 years (s.d.=7, range 0.6–34). Average duration of post-traumatic amnesia was 11 weeks (s.d.=13 weeks, range 26 h to 52 weeks). Cause of injury was road traffic accident (16), fall (11), assault (6) or sports accident (1). Compensation claims or legal proceedings were ongoing in 12 cases. GOS–E scores ranged from lower-severe to upper-moderate disability, with 53% in the lower-moderate category. RPQ scores ranged from 3 to 60 (mean=30, s.d.=14). Average SCT scaled scores were <25th percentile (Baddeley et al, 1992), (mean=–6, s.d.=–2.7, range 1–12).

Diagnostic measures (Table I)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Range</th>
<th>Mean</th>
<th>s.d.</th>
<th>Interpretation of mean score</th>
<th>PTSD caseness (%)</th>
<th>PTSD caseness criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>HADS–anxiety</td>
<td>0–18</td>
<td>9</td>
<td>5</td>
<td>Mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS–depression</td>
<td>0–16</td>
<td>8</td>
<td>4</td>
<td>Mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDS–number of symptoms</td>
<td>2–17</td>
<td>9.74</td>
<td>4.22</td>
<td>–</td>
<td>20 (59)</td>
<td></td>
</tr>
<tr>
<td>PDS–symptom severity score</td>
<td>2–45</td>
<td>21.18</td>
<td>11.11</td>
<td>Moderate–severe</td>
<td></td>
<td></td>
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<tr>
<td>IES–total score</td>
<td>0.59</td>
<td>24.35</td>
<td>16.77</td>
<td>Mild</td>
<td>15 (44)</td>
<td></td>
</tr>
<tr>
<td>IES–intrusion score</td>
<td>0–29</td>
<td>10.71</td>
<td>8.31</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES–avoidance score</td>
<td>0–36</td>
<td>13.65</td>
<td>9.72</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPS–total (frequency plus intensity)</td>
<td>13–59</td>
<td>29.35</td>
<td>11.95</td>
<td>–</td>
<td>6 (18)</td>
<td></td>
</tr>
<tr>
<td>CAPS–frequency</td>
<td>7–30</td>
<td>16.21</td>
<td>6.42</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPS–intensity</td>
<td>6–29</td>
<td>13.09</td>
<td>5.02</td>
<td>–</td>
<td>1 (3)</td>
<td></td>
</tr>
</tbody>
</table>

Table I Assessment measure scores, interpretation and caseness criteria

COPS, Clinician-Administered Post-traumatic Stress Disorder Scale; HADS, The Hospital Anxiety and Depression Scale; IES, Impact of Events Scale; PDS, Post-traumatic Diagnostic Scale; PTSD, Post-traumatic Stress Disorder.

3. Criteria B–F are fulfulled (minimum score of 1 for frequency and 2 for intensity) (B, 1 symptom; C, 3 symptoms; D, 2 symptoms; E, duration >1 month; F, symptoms have social and occupational impact).

DISCUSSION

People with severe traumatic brain injury met PTSD criteria for ‘caseness’ more often using self-report questionnaires than structured interview. Significantly more (false positive) ‘cases’ were identified using questionnaires, even compared with interview without clinical judgement guiding the relevance of responses to trauma. ‘Cases’ were not identified at interview that were not also identified by questionnaire, supporting the use of questionnaires as screening tools, perhaps tentatively given that only one participant was diagnosed with PTSD at...
DIAGNOSING PTSD AFTER BRAIN INJURY

Clinical implications

- Structured interview is necessary for diagnosis of PTSD after severe traumatic brain injury.
- Questionnaire self-report can be useful to screen for PTSD symptoms after traumatic brain injury.
- The true incidence of PTSD after severe brain injury has yet to be determined.

Limitations

- Findings may not extend to minor brain injury.
- Understanding of how people with traumatic brain injury make errors on questionnaires may be improved by qualitative data.
- Although similar demographically to cohort studies, the sample was not recruited consecutively.

References


Psychological investigation of the structure of paranoia in a non-clinical population

DANIEL FREEMAN, PHILIPPA A. GARETY, PAUL E. BEBBINGTON, BENJAMIN SMITH, REBECCA ROLLINSON, DAVID FOWLER, ELIZABETH KUIPERS, KATARZYNA RAY and GRAHAM DUNN

Background

Previous studies of paranoia have assessed only limited numbers of paranoid thoughts, and have not considered the experience from a multidimensional perspective or examined the relationship between different suspicious thoughts.

Aims

To assess a wide range of paranoid thoughts multidimensionally and examine their distribution, to identify the associated coping strategies and to examine social—cognitive processes and paranoia.

Method

Six questionnaire assessments were completed by 1202 individuals using the internet.

Results

Paranoid thoughts occurred regularly in approximately a third of the group. Increasing endorsement of paranoid thoughts was characterised by the recruitment of rarer and odder ideas. Higher levels of paranoia were associated with emotional and avoidant coping, less use of rational and detached coping, negative attitudes to emotional expression, submissive behaviours and lower social rank.

Conclusions

Suspiciousness is common and there may be a hierarchical arrangement of such thoughts that builds on common emotional concerns.

Declaration of interest

None.

It is possible that paranoid ideation is almost as common as symptoms of anxiety and depression (e.g. van Os & Verdoux, 2003; Johns et al, 2004). For many people, thoughts that friends, acquaintances or strangers might be hostile, or deliberately watching them, appear to be an everyday occurrence. This may parallel the findings of earlier studies that a level of obsessive thinking is normal in the general population (Rachman & de Silva, 1978). In one way this is not surprising, because being wary of the intentions of others is adaptive in some situations. At a cultural level, a fear of others is variably incorporated into the political and social climate. In general such thoughts are not a clinical problem, becoming so only when they are excessive, exaggerated or unfounded, and cause distress. Paranoid thoughts in non-clinical populations are phenomena of interest in their own right and may inform our understanding of delusions.

This study provides information on the frequency in a non-clinical sample of paranoid ideation, and the associated levels of conviction and distress. Such information can be useful to present to patients in the clinical setting, but no comparable research examining a wide range of paranoid thoughts, or considering such thoughts from a multidimensional perspective, has hitherto been published. There is no published evidence on, for example, the weekly frequency of paranoia in the general population. We predicted that the distribution of suspicious thoughts would be similar to that of affective symptoms, with many people having a few suspicious thoughts and a few people having many (Melzer et al, 2002). Moreover, as with affective symptoms, increasing symptom counts will be characterised by the recruitment of rarer and odder ideas (Sturt, 1981). There may be a hierarchy of paranoid thoughts. The study also had the aim of identifying how individuals in the general population cope with paranoid thoughts. We wished to identify the coping strategies that were associated with the most and the least distress. Finally, we examined potential connections between paranoia and three social–cognitive processes: attitudes to emotional expression, social comparison and submissive behaviours.

METHOD

Participants and procedure

An anonymous internet survey was considered to provide a safe environment for survey participants to disclose suspicious thoughts. Internet research has been found to reach the same conclusions as laboratory-based studies (Birnbaum, 2001). Students at King’s College London, the University of East Anglia and University College London were e-mailed the address of a website where they could take part in a survey of ‘everyday worries about others’. The study had received the approval of local research ethics committees. Completion of each questionnaire was timed, and one submission completed too quickly (<45 s) was deleted. Paranoia Checklist questionnaires with more than five pieces of missing data (i.e. completion rate less than 90%) were not included; consequently, the percentage of the Paranoia Checklist data that were prorated was minimal (≤0.5%). The final sample comprised 1202 people. After providing demographic information, participants were presented with six questionnaires.

Questionnaires

Paranoia Scale

The 20-item, self-report Paranoia Scale (Fenigstein & Vanable, 1992) was developed to measure paranoia in college students. Each item is rated on a five-point scale (1 not at all applicable, 5 extremely applicable). Scores can range from 20 to 100, with the higher scores indicating greater paranoid ideation. It is the most widely used dimensional measure of paranoia. However, the scale contains many items that are not clearly persecutory (e.g. ‘My parents and family find more fault with me than they should’) and does not provide an estimate of the frequency or distress of paranoid thoughts. The Paranoia Checklist was therefore developed specifically for this study.
Paranoia Checklist
The Paranoia Checklist was devised to investigate paranoid thoughts of a more clinical nature than those assessed in the Paranoia Scale and to provide a multidimensional assessment of paranoid ideation. The checklist has 18 items, each rated on a five-point scale for frequency, degree of conviction, and distress. We report the convergent validity of the Paranoia Checklist in relation to the Paranoia Scale in the results section.

Coping Styles Questionnaire
The Coping Styles Questionnaire (CSQ; Roger et al., 1993) builds upon the Ways of Coping Checklist (Folkman & Lazarus, 1980), and was validated with a UK student sample. The questionnaire comprises 60 coping strategies rated on a four-point frequency scale. Participants were asked to complete the questionnaire for how they typically react to the worries assessed in the Paranoia Checklist. There are four factors: rational coping, detached coping, emotional coping and avoidance coping. The former two factors are considered by the questionnaire developers as adaptive and the latter two as maladaptive.

Attitudes to Emotional Expression Questionnaire
On the Attitudes to Emotional Expression Questionnaire (Joseph et al., 1994) respondents were asked to rate how much they agree on a five-point scale (1 agree very much, 2 agree slightly, 3 neutral, 4 disagree slightly, 5 disagree very much) with four attitudes to emotional expression (e.g. ‘I think you should always keep your feelings under control’). Higher scores indicate more positive attitudes to emotional expression.

Social Comparison Scale
On the Social Comparison Scale (Gilbert & Allan, 1994) participants rate, by selecting a number between 1 and 10, whether they generally feel in relation to others: inferior—superior; less competent—more competent; less likeable—likeable; more reserved—less reserved; left out—accepted. Higher scores indicate higher perceived social rank.

Submitive Behaviours Scale
The Submissive Behaviours Scale (Allan & Gilbert, 1997) is a 16-item scale assessing a number of behaviours considered as submissiveess (e.g. ‘I agree that I am wrong, even though I know I’m not’). Each behaviour is rated on a five-point scale (0 never, 4 always). Higher scores indicate greater use of submissive behaviours.

Analysis
Analyses were conducted using the Statistical Package for the Social Sciences, SPSS for Windows, version 11.0 (SPSS, 2001). Significance test results are quoted as two-tailed probabilities.

RESULTS
Demographic data
There were more women (n=821) than men (n=371) among the respondents. Although the World Wide Web was once considered predominantly a male preserve, studies have found that more women than men participate in online psychological studies (Birnbaum, 2001). The average age was 23.0 years (s.d.=6.1, range 17–61, interquartile range 5). The respondents reported their ethnicity predominantly as White (n=1001), followed by Asian (n=98) and ‘other’ (n=70). There were few Black African (n=9) and African-Caribbean (n=9) respondents.

Reliability and validity of the Paranoia Checklist
Cronbach’s α for each of the three dimensions of the Paranoia Checklist was 0.9 or above, indicating excellent internal reliability. As would be expected, time taken to complete the Paranoia Checklist had a small positive correlation with a total score for frequency, conviction and distress (r=0.10, P<0.001). The Paranoia Scale was completed by 1016 of the Paranoia Checklist respondents. The mean Paranoia Scale score of the total group was 42.7 (s.d.=14.3), which is comparable with that reported by Fenigstein & Vanable (1992). There was convergent validity of the checklist with the Paranoia Scale: higher Paranoia Scale scores correlated with Paranoia Checklist frequency (r=0.71, P<0.001), conviction (r=0.62, P<0.001) and distress scores (r=0.58, P<0.001).

Prevalence of thoughts with a paranoid content
The frequencies, conviction and distress associated with the suspicious thoughts assessed in the Paranoia Checklist are displayed in Tables 1–3. There was appreciable endorsement of the checklist items. The 1-week prevalence of the individual thoughts ranged from 3% (‘I can detect messages about me in the press/TV/radio’) to 52% (‘I need to be on my guard against others’) (Table 1). The mean frequency score was 11.9 (s.d.=10.5, range 0–64; 25th percentile 4.0, 50th percentile 9.0, 75th percentile 16.0). Between 2% and 7% of participants adhered to individual thoughts with a level of absolute conviction (Table 2). If we consider levels of belief of ‘somewhat’ or greater, there is more variation between the individual items (4–56%). The mean conviction score was 16.7 (s.d.=12.1, range 0–72; 25th percentile 8.0, 50th percentile 14.0, 75th percentile 22.0). Between 1% and 7% of participants found individual thoughts very distressing (Table 3). Again, there was more variation between the thoughts if distress was taken as ‘at least somewhat distressing’ or greater (3–42%). The mean distress score was 14.6 (s.d.=12.2, range 0–70; 25th percentile 5.0, 50th percentile 12.0, 75th percentile 21.0).

The different dimensions of the Paranoia Checklist were positively correlated. Frequency scores were correlated with conviction (r=0.75, P<0.001) and distress (r=0.66, P<0.001), and conviction and distress scores were also positively correlated (r=0.65, P<0.001). There were no differences between men and women in the frequency (t=0.66, d.f.=1190, P=0.51) or conviction (t=1.03, d.f.=1190, P=0.30) with which paranoid thoughts were experienced. Females did report a significantly higher level of distress associated with the thoughts (t=2.72, d.f.=1190, P=0.007, mean difference =-2.07, 95% CI -3.60 to -0.58), although it can be seen that this difference is very small.

In Tables 4 and 5 the levels of conviction and distress associated with each suspicious thought are reported for the individuals experiencing such ideas at least weekly. Here it can be seen that the rarer and more implausible paranoid items (e.g. ‘There is a possibility of a conspiracy against me’) are held with the strongest levels of conviction and associated with
the most distress. This is confirmed by high negative correlations between the frequency of (at least weekly) endorsement of questionnaire items and the percentage of people who believed the thought absolutely \((n=18; r = -0.74, P < 0.001)\) and with the percentage of people who found the thought very distressing \((n=18; r = -0.75, P < 0.001)\). In other words, the less frequently experienced thoughts were held with proportionately more conviction and distress.

To examine whether people who endorsed the rarer items also endorsed the more common suspicious thoughts with
higher conviction and distress, we split the sample into those who endorsed at least one rare item (items with frequency less than 10%) (n=277) and those who did not endorse a rare item (n=925). The two groups were then compared on levels of conviction and distress for the eight most common items (endorsement rates of over 20%). Each one of these comparisons was made only for the individuals in the two groups who had endorsed the item (i.e. experienced the thought at least weekly).
The rarer item group had significantly higher conviction rates for seven of the eight common suspicious thoughts and significantly higher distress levels for five of the eight common suspicious thoughts \((P<0.05)\). It seems that individuals with the rarer thoughts were also experiencing the commoner thoughts more strongly.

We predicted that suspiciousness in the general population would have a profile similar to that of affective symptoms. First, there would be a single population distribution rather than evidence of a bimodal distribution (i.e. between ‘clinical paranoia’ and ‘non-clinical paranoia’). Second, the rarer ideas would be associated with the presence of many other suspicions; put another way, the relationship between rare symptoms and common symptoms would be non-reflexive, in that the former would be more predictive of the latter than vice versa. The total number of checklist items endorsed by each person was first calculated (endorsement referring to weekly occurrence or above). The count of suspicious thoughts could therefore range from 0 to 18. The distribution of the count is displayed in Fig. 1. It can be seen that the suspicious thought count follows a single continuous model (Melzer et al, 2002). The distribution closely fits an exponential curve. To examine whether the rarer thoughts were associated with a higher rate of endorsement of other checklist items, the mean difference for the suspicious thought count was calculated between those with and those without each suspicious thought (correcting for the contribution due to that item; Sturt, 1981). The mean difference (i.e. the excess of endorsement associated with each item) was significantly associated with the frequency of item endorsement \((n=18; \ r=-0.75, \ P<0.001)\). Thus, the rarer checklist items were associated with a higher total score than were the

![Graph showing exponential distribution](image)

**Fig. 1** Percentage of the study population v. total number of Paranoia Checklist items endorsed, with fitted exponential curve.

---

**Table 5** Level of distress for those who experienced the thought at least weekly

<table>
<thead>
<tr>
<th>Thought</th>
<th>n</th>
<th>Not distressing (%)</th>
<th>A little distressing (%)</th>
<th>Somewhat distressing (%)</th>
<th>Moderately distressing (%)</th>
<th>Very distressing (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I need to be on my guard against others</td>
<td>621</td>
<td>19</td>
<td>34</td>
<td>26</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>There might be negative comments being circulated about me</td>
<td>499</td>
<td>10</td>
<td>28</td>
<td>25</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>People deliberately try to irritate me</td>
<td>306</td>
<td>18</td>
<td>34</td>
<td>25</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>I might be being observed or followed</td>
<td>230</td>
<td>16</td>
<td>29</td>
<td>25</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>People are trying to make me upset</td>
<td>148</td>
<td>5</td>
<td>22</td>
<td>35</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>People communicate about me in subtle ways</td>
<td>315</td>
<td>19</td>
<td>32</td>
<td>27</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Strangers and friends look at me critically</td>
<td>574</td>
<td>13</td>
<td>29</td>
<td>27</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>People might be hostile towards me</td>
<td>343</td>
<td>9</td>
<td>29</td>
<td>30</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>Bad things are being said about me behind my back</td>
<td>360</td>
<td>8</td>
<td>22</td>
<td>29</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>Someone I know has bad intentions towards me</td>
<td>155</td>
<td>9</td>
<td>23</td>
<td>30</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>I have a suspicion that someone has it in for me</td>
<td>97</td>
<td>11</td>
<td>23</td>
<td>28</td>
<td>13</td>
<td>25</td>
</tr>
<tr>
<td>People would harm me if given an opportunity</td>
<td>94</td>
<td>6</td>
<td>14</td>
<td>33</td>
<td>15</td>
<td>32</td>
</tr>
<tr>
<td>Someone I don’t know has bad intentions towards me</td>
<td>91</td>
<td>12</td>
<td>22</td>
<td>26</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>There is a possibility of a conspiracy against me</td>
<td>58</td>
<td>9</td>
<td>24</td>
<td>22</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>People are laughing at me</td>
<td>393</td>
<td>17</td>
<td>25</td>
<td>25</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>I am under threat from others</td>
<td>131</td>
<td>8</td>
<td>19</td>
<td>30</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>I can detect coded messages about me in the press/TV/radio</td>
<td>29</td>
<td>24</td>
<td>17</td>
<td>21</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>My actions and thoughts might be controlled by others</td>
<td>100</td>
<td>12</td>
<td>28</td>
<td>24</td>
<td>17</td>
<td>19</td>
</tr>
</tbody>
</table>

The distribution closely fits an exponential curve. To examine whether the rarer thoughts were associated with a higher rate of endorsement of other checklist items, the mean difference for the suspicious thought count was calculated between those with and those without each suspicious thought (correcting for the contribution due to that item; Sturt, 1981). The mean difference (i.e. the excess of endorsement associated with each item) was significantly associated with the frequency of item endorsement \((n=18; \ r=-0.75, \ P<0.001)\). Thus, the rarer checklist items were associated with a higher total score than were the
Coping with paranoid thoughts

A total of 1046 participants also completed the CSQ. Higher levels of emotional and avoidant coping were associated with higher levels of paranoia (Table 6). In contrast, higher levels of detached coping were associated with lower levels of paranoia. Higher levels of rational coping were associated with lower levels of paranoia frequency and distress, but not significantly with paranoia conviction. In Table 7 we highlight the coping strategies most strongly correlated with paranoia frequency.

Social–cognitive processes and paranoid thoughts

There were significant but generally modest associations between the social–cognitive processes and the dimensions of paranoia. Negative attitudes to emotional expression, lower social comparison (particularly feeling left out) and greater use of submissive behaviours were significantly associated with greater paranoia (Table 8).

DISCUSSION

Study limitations

There are methodological constraints that need to be acknowledged when interpreting our results. Foremost, the sample was not epidemiologically representative. It was self-selected, restricted to university students and recruited by e-mail. The gender ratio was certainly skewed, perhaps...
in consequence of our methods. People who self-select for questionnaires of this type may be more prone to psychological disturbance, or the stigma of appearing so might skew the sample in the opposite direction. Thus, our investigation in a selected group indicates a need for more elaborate and more truly epidemiological studies. There are also issues concerning whether the experiences assessed are actually unfounded; questionnaire studies may include an unknown proportion of paranoia that is realistic and therefore well judged and appropriate. It is also unknown whether any of the participants had received treatment for a psychiatric disorder, and what the level of substance use was in the group. The study was also limited by the cross-sectional questionnaire design, which limits the conclusions that can be drawn concerning the causal direction of the relationships between associated variables.

### Hierarchy of paranoia

Our survey clearly indicates that suspicious thoughts are a weekly occurrence for many people: 30–40% of the respondents had ideas that negative comments were being circulated about them and 10–30% had persecutory thoughts, with thoughts of mild threat (e.g. ‘People deliberately try to irritate me’) being more common than severe threat (e.g. ‘Someone has it in for me’). In contrast, only a small proportion (approximately 5%) of respondents endorsed the checklist items that were the most improbable (e.g. that there was a conspiracy). Nevertheless, the rarer and odder suspicions – characteristic of clinical presentations – occurred in tandem with the more common and plausible experiences. The rarer the thought, the higher the total score indicated by its presence. There has been no previous examination of paranoia in this way.

The findings indicate a hierarchy of paranoia (Fig. 2): the most common type of suspiciousness is that of a social anxiety or interpersonal worry theme; ideas of reference build upon these sensitivities; persecutory thoughts are closely associated with the attributions of significance; as the severity of the threatened harm increases, the less common the thought; and suspiciousness involving severe harm and organisations and conspiracy is at the top of the hierarchy. The implication is that severe paranoia may build upon common emotional concerns, consistent with a recent cognitive model of persecutory delusions (Freeman et al., 2002; Freeman & Garety, 2004). The interesting questions therefore concern the identification of the additional factors that contribute to the development of severe paranoia and whether there are qualitative shifts in experience at the top end of the hierarchy (note that individuals at the higher end of the hierarchy tended to endorse all their suspicious thoughts with high levels of conviction and distress). The survey findings also indicate that there is a continuous (exponential) distribution of total number of suspicious thoughts in the general population, although the thoughts appear in a hierarchical arrangement. No distinct sub-population was identified. This therefore demonstrates correspondence to common mental health disorders such as depression and anxiety.

Interestingly, the ideation captured in this survey did not seem to be restricted to passing thoughts that were dismissed almost in the same instant that they occurred. Approximately 10–20% of the survey respondents held paranoid ideation with strong conviction and significant distress. It is likely that the survey identified a significant group of people who were having distressing experiences that they managed on their own. We believe that there is a reticence in the general population about discussing the occurrence of suspicious thoughts, partly arising from the negative connotations associated with the term

### Table 8  Social cognitive processes and paranoia

<table>
<thead>
<tr>
<th>n</th>
<th>Paranoia Checklist</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>P</td>
<td>Frequency</td>
<td>Conviction</td>
<td>Distress</td>
</tr>
<tr>
<td>1049</td>
<td>0.291 &lt; 0.001</td>
<td>0.335 &lt; 0.001</td>
<td>0.161 &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Social comparison</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean score</td>
<td>1035 - 0.265 &lt; 0.001</td>
<td>-0.193 &lt; 0.001</td>
<td>-0.270 &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Inferior–superior</td>
<td>966 - 0.149 &lt; 0.001</td>
<td>0.091 0.005</td>
<td>-0.179 &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Less competent–more competent</td>
<td>980 - 0.117 &lt; 0.001</td>
<td>-0.089 0.005</td>
<td>-0.190 &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Less likeable–likeable</td>
<td>934 - 0.038 0.251</td>
<td>-0.051 0.001</td>
<td>-0.010 0.763</td>
<td></td>
</tr>
<tr>
<td>More reserved–less reserved</td>
<td>938 - 0.092 0.005</td>
<td>-0.058 0.074</td>
<td>-0.081 0.013</td>
<td></td>
</tr>
<tr>
<td>Left out–accepted</td>
<td>970 - 0.374 &lt; 0.001</td>
<td>-0.271 &lt; 0.001</td>
<td>-0.333 &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Submissive behaviour</td>
<td>1027 0.392 &lt; 0.001</td>
<td>0.295 &lt; 0.001</td>
<td>0.385 &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

![Fig. 2 The paranoia hierarchy.](image)
paranoia and a lack of recognition of how common these experiences actually are. The provision of the type of information obtained in this survey may help to normalise paranoia and set the stage for making the experience understandable. This is an important element in the development of alternative explanations of experiences (Freeman et al., 2004).

Coping with paranoid thoughts

If paranoia is an everyday phenomenon, which many people manage well, then it provides an opportunity to gain clinically useful information on optimal ways of coping. More frequent and distressing paranoia was associated with becoming isolated, giving up activities, and feelings of powerlessness and depression. Conversely, less frequent paranoia was associated with not catastrophising and by gaining sufficient (meta-cognitive) distance to consider the situation dispassionately. More broadly, coping with paranoia may resemble coping with other stressful or negative events: rational (or task-oriented) coping and detachment from the situation are more helpful than emotional or avoidant coping. It is not clear to what extent poor coping encourages paranoia, and to what extent strong paranoia interferes with effective coping.

Social–cognitive factors

There has been a re-emergence of the study of the influence of social factors on psychosis by examining their impact at the cognitive level of explanation (Garety et al., 2001). In our survey associations were found between paranoia and social–cognitive processes that could plausibly exacerbate suspiciousness. Thus, we found evidence that not expressing feelings to others may increase suspiciousness. This follows early research on the psychological consequences of the Herald of Free Enterprise ferry disaster, which indicated that negative attitudes to emotional expression in survivors were associated with higher levels of anxiety (Joseph et al., 1997).

There was a significant association of paranoia with submissive behaviours. As Allan & Gilbert (1997) note, people who have difficulties in asserting themselves – which these authors conceptualise within an evolutionary framework as having low dominance and inferior social rank – can be vulnerable to a number of psychological problems. Further, these authors report that submissiveness is associated with paranoid thoughts and with angry thoughts and feelings. Attritions that others have negative intentions underlie feelings of anger. We think that in some cases anger may contribute to the attribution of intent in persecutory ideation. However, rather than expressing anger or resentment towards others, individuals may instead ruminate and feel aggrieved owing to timidity or submissiveness. This will maintain a state in which external attributions and anomalous experiences are more likely, thus leading to the persistence of persecutory ideation.

We also found that respondents who felt left out, inferior or less competent in relation to others displayed higher levels of suspiciousness. Birchwood et al. (2000) reported a connection between social comparison and the experience of hearing voices. We suggest that a lack of social self-confidence might make people feel vulnerable to attack and hence contribute to the occurrence of paranoia. This is consistent with experimental evidence that interpersonal sensitivity predicts persecutory ideation (Freeman et al., 2003). It is of note, however, that in our study the associations of paranoia with many of the variables were of small to medium effect size. This is unsurprising, and is consistent with the view that paranoia is a complex phenomenon likely to arise from a number of social, cognitive and biological factors.

Interventions for paranoid thoughts

Our study has practical implications for clinical interventions in paranoia. Interventions may be more effective if they include recognition of the ubiquity of

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**CLINICAL IMPLICATIONS**

- Having suspicious thoughts is a common experience and provision of this information may help reduce patient distress.
- Feelings of hopelessness and lack of control may contribute to the occurrence of more suspicious thoughts, whereas gaining distance from such thoughts and evaluating them may reduce such experiences.
- Not talking to others about suspicious thoughts, feeling vulnerable and behaving timidly with others may be factors in the development of paranoia.

**LIMITATIONS**

- An epidemiologically representative sample was not recruited.
- The group mainly comprised young adults who may have higher rates of suspiciousness.
- Only cross-sectional associations between paranoia, coping strategies and social–cognitive processes were examined.

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suspiciousness; encourage talking about such experiences with others; improve self-esteem; help people in negotiating relationships with others; and encourage detachment and feelings of control over the situation. These are all central components of cognitive–behavioural interventions for psychosis (e.g. Fowler et al., 1993; Chadwick et al., 1996).

ACKNOWLEDGEMENTS

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Community study of knowledge of and attitude to mental illness in Nigeria

OYE GUREJE, VICTOR O. LASEBIKAN, OLUSOLA EPHRAIM-OLUWANUGA, BENJAMIN O. OLLEY and LOLA KOLA

Background The improvement of community tolerance of people with mental illness is important for their integration. Little is known about the knowledge of and attitude to mental illness in sub-Saharan Africa.

Aims To determine the knowledge and attitudes of a representative community sample in Nigeria.

Method A multistage, clustered sample of household respondents was studied in three states in the Yoruba-speaking parts of Nigeria (representing 22% of the national population). A total of 2040 individuals participated (response rate 74.2%).

Results Poor knowledge of causation was common. Negative views of mental illness were widespread, with as many as 96.5% (s.d. = 0.5) believing that people with mental illness are dangerous because of their violent behaviour. Most would not tolerate even basic social contacts with a mentally ill person: 82.7% (s.e. = 1.3) would be afraid to have a conversation with a mentally ill person and only 16.9% (s.e. = 0.9) would consider marrying one. Socio-demographic predictors of both poor knowledge and intolerant attitude were generally very few.

Conclusions There is widespread stigmatisation of mental illness in the Nigerian community. Negative attitudes to mental illness may be fuelled by notions of causation that suggest that affected people are in some way responsible for their illness, and by fear.

Declaration of interest None.

Mental illness often constitutes a double jeopardy for those affected because of stigmatisation by members of the community (Corrigan & Watson, 2002). Studies conducted in North America and western Europe suggest that stigma is a major problem in the community (Taylor & Dear, 1980; Brockington et al., 1993; Huxley, 1993; Jorm et al., 1999; Crisp et al., 2000). Negative views such as those implying that people with mental illness are irresponsible and therefore incapable of making their own decisions, or are dangerous and are to be feared, are widespread. Since negative beliefs often lead to discrimination, there is little wonder that studies have also shown that people with mental health problems living in the community experience rampant harassment (Kelly & McKenna, 1997; Berzins et al., 2003). Some studies conducted in Africa have suggested that the experience of stigma by people with mental illness may be common (Awaritefe & Ebie, 1975; Shibire et al., 2001), but there is no information on how widespread negative attitudes to mental illness may be in the community. As noted by Corrigan & Watson (2002), it is unclear whether the lack of empirical data partly explains the speculation that stigmatisation of mental illness may be less common among Africans (Fabrega, 1991).

METHOD

Sample characteristics

The survey was conducted in three Yoruba-speaking states in south-western Nigeria (Ogun, Oyo and Osun) between March and August 2002. The survey on stigma was a segment of a much larger survey of mental disorders in the community (the Nigeria Survey of Mental Health and Well-being) and was administered by trained lay interviewers from the Department of Psychiatry, University of Ibadan. Both studies were approved by the University of Ibadan and University College Hospital joint ethics committee.

The study was based on a stratified, multistage clustered probability sample of household residents aged 18 years or older in the selected states. First, stratification was based on states (three categories) and size of the primary stage units, which were the local government areas (two categories). The second stage was to select two primary stage units per stratum, with probability of selection proportional to size. The third stage was the random selection of four enumeration areas from each local government area; these are geographical units demarcated by the National Population Commission, each consisting of about 60–80 household units. We enumerated the households in each selected area and randomly selected the number of households required to meet our desired sample size. One resident aged 18 years or over was approached for participation in each selected household. We used the Kish method to identify the potential respondent (Kish, 1995) and no replacement was made for refusals. A total of 2040 persons participated in the survey on stigma, representing a response rate of 74.2%. The results presented here have been weighted to reflect the within-household probability of selection and to incorporate a post-stratification adjustment such that the sample is representative of the age by gender distribution of the projected population of Nigeria in 2000.

Income was categorised into four groups: 'low' (defined as less than or equal to median or the pre-tax income per household), 'low average' (greater than 'low' up to twice the median value), 'high average' (greater than 'low average' up to three times median value) and 'high' (greater than 'high average'). Residence was classified as rural (fewer than 12,000 households), semi-urban (12,000–20,000 households per local government area) and urban (more than 20,000 households).

Assessment

A modified version of the questionnaire developed for the World Psychiatric Association Programme to Reduce Stigma and Discrimination Because of Schizophrenia was used (Stuart & Arboleda-Florez, 2001; World Psychiatric Association, 2002). The questionnaire is focused mainly on knowledge of and attitude to schizophrenia. It was modified largely to take
account of the focus of this survey, which was on mental illness rather than schizophrenia. Thus, in addition to substituting the term 'mental illness' for 'schizophrenia', specific items relating to the symptoms of schizophrenia were deleted. The questionnaire was translated into Yoruba by a panel of four bilingual mental health research workers using the iterative back-translation method. In the translation, particular care was made to convey a broad idea of 'mental illness' (arun opolo), differentiating it from psychosis (iwin or were) and mental retardation (ode or odoyo).

Analysis

Simple cross-tabulations were used to calculate proportions and their distributions in different groups. To take account of the sampling procedure, with clustering and weighting of cases, standard errors of proportions were estimated with the jack-knife method implemented in the STATA software (StataCorp, 2001). Statistical significance was evaluated at the 0.5 level and was based on two-sided design-based tests.

RESULTS

Table 1 shows the socio-demographic attributes of the sample. In keeping with the demographic and economic profile of Nigeria, the sample was predominantly young and most came from low or low average income households. The population of Nigeria is predominantly rural, but the south-western area where the study was conducted is more urban than the rest of the country and this is reflected in the table.

Most respondents expressed the view that substance misuse (alcohol or drugs, but mainly the latter) could result in mental illness (Table 2). The next most commonly endorsed cause of mental illness was a belief that it could be due to possession by evil spirits. Following this, trauma, stress and heredity were about equally ascribed as possible causes. Only about one in ten respondents believed that biological factors or brain disease could be the cause of mental illness. Confirming a stronger belief in supernatural causation, over 9% thought mental illness could result from punishment from God, whereas only about 6% thought poverty could cause mental illness.

The views about mental illness were generally negative (Table 3). People with mental illness were believed to be mentally retarded, to be a public nuisance and to be dangerous. Less than half of the respondents believed that such people could be treated outside hospital and only about one-quarter thought they could work in regular jobs. Poor knowledge about mental illness seemed to pervade all segments of the community: no consistent association was observed between the predominantly negative views of mental illness on the one hand and gender, age, education, income or residence on the other hand.

Table 4 shows that most respondents were unwilling to have social interactions with someone with mental illness. Most would be afraid to have a conversation and would be disturbed to work with a person with mental illness. Only a few would be willing to maintain a friendship and fewer still would consider marrying such a person. There were also inconsistent associations of socio-demographic attributes with negative attitudes to mental illness. As shown in Table 4, apart from evidence of a somewhat more liberal attitude of men and those residing in urban areas, negative attitude to mental illness seems to be highly prevalent across many different groups in the community.

DISCUSSION

To our knowledge, this is the first large-scale study of knowledge of and attitudes towards mental illness in sub-Saharan Africa. Previous studies have either been on a much smaller scale (Awaritefe & Ebie, 1975; Odejide & Olatawura, 1979), or have examined the perception of stigma by relatives of people with mental illness (Shibre et al, 2001) or the views of mental illness among special groups (Binitie, 1970). Large-scale community studies have been lacking. Such studies are of obvious importance for any policy aimed at promoting better knowledge and tolerance of mental illness by the public.

Caveats in interpreting the findings

In interpreting the results of the survey, cognisance should be taken of its limitations. Even though the sample was selected to be representative of the adult population of the Yoruba, who make up about 22% of the Nigerian population, the views expressed may not necessarily reflect the views of the other ethnic groups in the country. Nigeria is a culturally diverse

<table>
<thead>
<tr>
<th>Cause</th>
<th>Proportion endorsing cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug or alcohol misuse</td>
<td>80.8 (1.1)</td>
</tr>
<tr>
<td>Possession by evil spirits</td>
<td>30.2 (1.0)</td>
</tr>
<tr>
<td>Traumatic event or shock</td>
<td>29.9 (1.0)</td>
</tr>
<tr>
<td>Stress</td>
<td>29.2 (0.9)</td>
</tr>
<tr>
<td>Genetic inheritance</td>
<td>26.5 (0.9)</td>
</tr>
<tr>
<td>Physical abuse</td>
<td>14.7 (0.72)</td>
</tr>
<tr>
<td>Biological factors (other than</td>
<td></td>
</tr>
<tr>
<td>brain disease or genetic</td>
<td></td>
</tr>
<tr>
<td>inheritance)</td>
<td></td>
</tr>
<tr>
<td>God’s punishment</td>
<td>9.3 (0.6)</td>
</tr>
<tr>
<td>Brain disease</td>
<td>9.2 (0.5)</td>
</tr>
<tr>
<td>Poverty</td>
<td>6.2 (0.5)</td>
</tr>
</tbody>
</table>
Table 3 Views of respondents about people with mental illness

<table>
<thead>
<tr>
<th>Item</th>
<th>Overall Proportion endorsing item, % (s.e.)</th>
<th>Gender Proportion endorsing item, % (s.e.)</th>
<th>Age group, years Proportion endorsing item, % (s.e.)</th>
<th>Education years Proportion endorsing item, % (s.e.)</th>
<th>Household income Proportion endorsing item, % (s.e.)</th>
<th>Urbanicity Proportion endorsing item, % (s.e.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can be treated outside hospital</td>
<td>45.0 (1.4)</td>
<td>Male 42.6 (2.1)</td>
<td>Female 47.2 (1.8)</td>
<td>18–25 42.6 (2.3)</td>
<td>26–40 45.9 (2.2)</td>
<td>41–64 45.7 (3.0)</td>
</tr>
<tr>
<td>Tend to be mentally retarded</td>
<td>91.5 (0.8)</td>
<td>Male 90.5 (1.2)</td>
<td>Female 92.4 (1.1)</td>
<td>18–25 93.0 (1.8)</td>
<td>26–40 90.6 (1.0)</td>
<td>41–64 91.5 (1.3)</td>
</tr>
<tr>
<td>Are a public nuisance</td>
<td>95.2 (0.6)</td>
<td>Male 95.5 (0.8)</td>
<td>Female 95.0 (0.9)</td>
<td>18–25 92.7 (1.2)</td>
<td>26–40 95.8 (1.1)</td>
<td>41–64 97.5 (0.8)</td>
</tr>
<tr>
<td>Can work in regular jobs</td>
<td>25.5 (0.8)</td>
<td>Male 26.7 (1.5)</td>
<td>Female 24.3 (1.5)</td>
<td>18–25 22.6 (2.8)</td>
<td>26–40 28.4 (1.6)</td>
<td>41–64 24.7 (1.9)</td>
</tr>
<tr>
<td>Are dangerous because of violent behaviour</td>
<td>96.5 (0.5)</td>
<td>Male 95.6 (0.9)</td>
<td>Female 97.2 (0.6)</td>
<td>18–25 96.1 (1.2)</td>
<td>26–40 96.2 (0.7)</td>
<td>41–64 97.3 (0.7)</td>
</tr>
</tbody>
</table>

1. Categorised as low (L), low average (LA), high average (HA) and high (H).
<table>
<thead>
<tr>
<th>Item</th>
<th>Overall</th>
<th>Proportion endorsing item, % (s.e.)</th>
<th>Proportion endorsing item, % (s.e.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gender</td>
<td>Age group, years</td>
<td>Education years</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>18-25</td>
<td>26-40</td>
</tr>
<tr>
<td>Afraid to have a conversation</td>
<td>82.7 (1.3)</td>
<td>84.5</td>
<td>82.4</td>
</tr>
<tr>
<td></td>
<td>(2.1)</td>
<td>(1.8)</td>
<td>(2.5)</td>
</tr>
<tr>
<td></td>
<td>$\chi^2=21.64$, $P&lt;0.001$</td>
<td>$\chi^2=2.66$, $P=0.59$</td>
<td>$\chi^2=25.23$, $P&lt;0.005$</td>
</tr>
<tr>
<td>Upset or disturbed about working on the same job</td>
<td>78.1 (1.1)</td>
<td>85.1</td>
<td>76.4</td>
</tr>
<tr>
<td></td>
<td>(1.4)</td>
<td>(1.4)</td>
<td>(2.3)</td>
</tr>
<tr>
<td></td>
<td>$\chi^2=4.03$, $P=0.05$</td>
<td>$\chi^2=30.54$, $P&lt;0.01$</td>
<td>$\chi^2=15.4$, $P=0.28$</td>
</tr>
<tr>
<td>Could maintain a friendship</td>
<td>16.9 (0.9)</td>
<td>15.5</td>
<td>15.7</td>
</tr>
<tr>
<td></td>
<td>(1.3)</td>
<td>(1.2)</td>
<td>(2.1)</td>
</tr>
<tr>
<td></td>
<td>$\chi^2=3.16$, $P=0.10$</td>
<td>$\chi^2=6.65$, $P=0.18$</td>
<td>$\chi^2=8.69$, $P=0.14$</td>
</tr>
<tr>
<td>Unwilling to share a room</td>
<td>81.2 (1.1)</td>
<td>85.0</td>
<td>78.1</td>
</tr>
<tr>
<td></td>
<td>(1.7)</td>
<td>(1.9)</td>
<td>(1.7)</td>
</tr>
<tr>
<td></td>
<td>$\chi^2=0.16$, $P=0.81$</td>
<td>$\chi^2=12.97$, $P&lt;0.05$</td>
<td>$\chi^2=0.56$, $P=0.87$</td>
</tr>
<tr>
<td>Ashamed if people knew</td>
<td>82.9 (0.7)</td>
<td>86.0</td>
<td>83.3</td>
</tr>
<tr>
<td>someone in your family has been diagnosed with mental illness</td>
<td>$\chi^2=2.46$, $P=0.20$</td>
<td>$\chi^2=11.72$, $P=0.014$</td>
<td>$\chi^2=3.64$, $P=0.45$</td>
</tr>
<tr>
<td>Could marry someone with mental illness</td>
<td>3.4 (0.6)</td>
<td>3.8</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>(0.7)</td>
<td>(0.5)</td>
<td>(0.6)</td>
</tr>
<tr>
<td></td>
<td>$\chi^2=0.99$, $P=0.17$</td>
<td>$\chi^2=2.87$, $P=0.34$</td>
<td>$\chi^2=4.63$, $P=0.31$</td>
</tr>
</tbody>
</table>

1. Categorised as low (L), low average (LA), high average (HA) and high (H).
country and its various parts are dissimilar in their access to mental health services (Ayonrinde et al., 2004), both of which factors may affect views about and attitude to mental illness. Nevertheless, a few studies conducted among other ethnic groups in Nigeria, albeit on a much smaller scale, suggest that the findings here with regard to widespread poor knowledge of and attitude towards mental illness may not be peculiar to the Yoruba ethnic group (Binitie, 1970; Awaritefe & Ebie, 1975). Also, we have focused on mental illness generally, not on specific mental disorders. In answering questions about mental illness, respondents might have done so with a mind-set on a particular group of mental disorders, probably psychotic disorders, even though our translation sought to capture the specific focus of our interest on mental illness. Although this might have biased their responses in one direction, it would still be remarkable if the public view of what constitutes mental illness was a narrow one.

Causes of mental illness
The common views about what causes mental illness provide a basis for setting other findings of our study in context. This is because views about causation are strongly associated with stigmatising attitudes to mental illness (Bhugra, 1989; Hayward & Bright, 1997; Haghhighat, 2001). Our results suggest that knowledge about mental illness is very poor in the Nigerian community. The widespread belief that misuse of drugs is the cause of mental illness may be regarded as good, in view of its possible restraining effect on the use of illicit or psychoactive substances. However, since this is only true for a very limited number of mental disorders, and since the public often views the misuse of substances as a moral failing, this belief may translate to a notion of mental illness as being self-inflicted. Such a view is more likely to elicit condemnation rather than understanding or sympathy (Weiner et al., 1988). Other than alcohol, the most commonly used psychoactive substance in Nigeria is cannabis. It is not uncommon for the public in Nigeria to make the assumption that anyone using cannabis will have a mental illness or that anyone with mental illness has used cannabis. Indeed, criminality is also often included in the causal link. Thus, the use of cannabis is often seen as implying a criminal predisposition and vice versa. Next in importance in the list of possible causes of mental illness was a belief that it could be due to possession by evil spirits, and this view was expressed by as many as a third of our respondents. Also, almost one in ten in the community thought mental illness might be a divine punishment. Such views, apart from further implying that people with mental illness might in some way be deserving of their lot, have important ramifications for the seeking of medical care by persons affected. A supernatural view of the origin of mental illness may imply that orthodox medical care would be futile and that help would be more likely to be obtained from spiritualists and traditional healers. Indeed, previous studies in Nigeria have suggested that care for mental illness is most often sought from these providers (Gureje et al., 1993) and that a view about supernatural causation of mental illness is shared by them. In professing a ‘biological’ or ‘brain disease’ causation for mental illness, our respondents could have meant any of several things. Poisoning, either deliberate or by eating dangerous herbs, is commonly seen as a possible cause of mental illness. There is also a cultural understanding that some emotionally trying traditional rites or rituals could lead to mental illness in those who are not psychologically or physically prepared. Childbirth can also upset the body mechanisms and lead to mental health problems.

Views about mental illness
Negative views about individuals with mental illness were widely held. Less than half of the respondents thought that people with mental illness could be treated outside a hospital or other health facility, implying a belief that community-based care is unlikely to be feasible and might even be dangerous for the public. Only about a quarter thought that mentally ill people could work in regular jobs. Most respondents thought that people with mental illness were mentally retarded, were a public nuisance and were dangerous because of their violent behaviour. These negative views were uniformly expressed by all groups in our study, and there was no clear gender, age, educational or economic correlate of poor knowledge. Negative views of mental illness have been reported in some studies to be more common among the poorly educated, those of low social class and persons aged 50 years and above (Wolff et al., 1996); our study did not identify such associations.

Attitudes towards people with mental illness
The negative views expressed by respondents were indicative of the degree of tolerance they might have of people with mental illness. In particular, views such as those of dangerousness and low intelligence have been found to fuel community resentment of people with mental illness (Hayward & Bright, 1997; Corrigan & Watson, 2002). Consequently, the attitudes of our survey respondents to people with mental illness were not surprising. We found that most people in the community would be afraid to have a conversation with someone known to have a mental illness and only a few would consider such a person for friendship. The closer the intimacy required for the interaction, the stronger the community’s desire to keep a distance. Thus, less than 4% would consider marrying anyone with mental illness. Here again, the associations with demographic or residential features were very few indeed. Other than a somewhat more tolerant attitude to people with mental illness shown by respondents residing in urban areas and by men, there was no interpretable relationship between negative attitudes to those who are mentally ill on the one hand, and age, education or income on the other hand. Previous studies of selected groups in Nigeria have suggested that negative attitude to mental illness may be less pervasive among the well educated (Odejide & Olatuwura, 1979). Our findings suggest that the attitudes of such groups do not reflect those of the community at large.

The universality of stigma
The findings of this survey do not support the claim that mental illness is less stigmatised in developing countries (Fabrega, 1991). Although developing countries constitute a diverse group in terms of culture and social norms, it is nevertheless true that our findings are in broad agreement with the observations made by others working in places such as India and Ethiopia (Thara & Sinivasan, 2000; Shibire et al., 2001). Indeed, as noted by Murthy (2002), stigmatisation of mental illness probably exists everywhere, even though the form and nature of it may differ across cultures. Our observations suggest that poor knowledge of the causes of mental illness, especially an
1. The need for the development of a well-articulated mental health policy has been identified for most African countries where none exists (Gureje & Alem, 2000). Findings such as those of our study suggest that a strong emphasis on public education should be an important component of any such policy.

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Migration, family dysfunction and psychotic symptoms in children and adolescents

LUIS R. PATINO, JEAN-PAUL SELTEN, HERMAN VAN ENGELAND, JAN H. M. DUYX, RENE S. KAHN and HUIBERT BURGER

Summary  A cross-sectional study of 3426 referred children and adolescents showed that the presence of both migration history and family dysfunction was associated with a fourfold (95% CI 2–9) higher risk of psychotic symptoms compared with the absence of these factors. The relative risk was 2 (95% CI 1–4) for migration history only. Interaction between migration history and family dysfunction accounted for 58% (95% CI 5–91%) of those with psychotic symptoms. These results suggest a relationship between family dysfunction and migration in the development of psychosis.

Declaration of interest  None.

The association between migration history and psychotic disorders has been demonstrated repeatedly, but there has been no satisfactory explanation to date (Cantor-Graae et al., 2003). As seen in African–Caribbean immigrants to the UK, the effect of migration may depend on socio-environmental variables (Mallett et al., 2002). We investigated whether the relationship between migration history and psychosis is modified by family dysfunction in a sample of children and adolescents referred to a tertiary mental healthcare centre.

METHOD

Between 1982 and 1998, a total of 5253 patients aged 6–18 years were evaluated at the Child and Adolescent Department of the University Medical Center Utrecht, The Netherlands. From these, an unselected sample of 3426 patients were assessed with the Maudsley Child and Adolescent Psychiatric Rating Scale, a semi-structured psychiatric interview (Thorley, 1982).

There were 86 children and adolescents who definitely had hallucinations, delusions, ideas of reference or morbid ideas of persecution. This corresponds to a state of psychosis or probable psychosis. The interviews were performed by trainees in child and adolescent psychiatry who were supervised by board-certified specialists. Patients with symptoms of organic origin were excluded (n=4).

Migration history was defined as foreign birth (first generation) or foreign birth of at least one parent (second generation). In total 404 migrants (239 of the first generation) were identified.

Family dysfunction was recorded when at least three of the following seven problems were reported: poor relationship between adults in the household; lack of warmth between parents and child; overt disturbance of father–child relationship; overt disturbance of mother–child relationship; overt disturbance of sibling–child relationship; parental overprotection; and child abuse.

Relative risks of psychotic symptoms for individuals with a history of migration were quantified using logistic regression (Statistical Package for the Social Sciences, version 11.0 for Windows) and were expressed as odds ratios with 95% confidence intervals. Age, gender, psychiatric illness in at least one of the parents and educational level of the breadwinner (usually the father) were considered potential confounding variables. To determine whether the relationship between migration history and psychosis is modified by family dysfunction, the study population was divided according to family dysfunction and the analyses were repeated. Modification was quantified by calculating the interaction between these variables according to Rothman (1986). Corresponding 95% confidence intervals were calculated by bootstrapping as described by Assmann et al. (1996).

RESULTS

Characteristics of the study population

In those with and without a migration history, the frequencies of family dysfunction were 56% and 52%, the frequencies of psychiatric illness in a parent were 22% and 25%, the proportions of parents that were university graduates were 37% and 28% and the proportions that did not complete formal education were 13% and 8%, respectively.

Migration as a risk factor for psychotic symptoms

Table 1 summarises the results. Overall, migration was associated with an approximately twofold increased risk of psychotic symptoms. When family dysfunction was absent, this increase was substantially lower and no longer statistically significant, indicating a lack of independence of the

<table>
<thead>
<tr>
<th>Odds ratio for psychotic symptoms</th>
<th>Crude (95% CI)</th>
<th>Adjusted* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migration history†</td>
<td>1.8 (1.1–3.2)</td>
<td>2.4 (1.3–4.3)</td>
</tr>
<tr>
<td>Migration history and no family dysfunction†</td>
<td>1.2 (0.5–3.2)</td>
<td>1.5 (0.6–3.9)</td>
</tr>
<tr>
<td>Family dysfunction and no migration history†</td>
<td>1.5 (0.9–2.5)</td>
<td>1.3 (0.7–2.1)</td>
</tr>
<tr>
<td>Migration history and family dysfunction†</td>
<td>4.0 (2.0–8.2)</td>
<td>4.1 (1.9–8.5)</td>
</tr>
<tr>
<td>AP interaction†</td>
<td>0.59 (0.02–0.93)</td>
<td>0.58 (0.05–0.91)</td>
</tr>
</tbody>
</table>

* CI, Confidence interval.
† Adjusted for age, gender, psychiatric illness of a parent and educational level of breadwinner.
‡ Reference category is no migration history and no family dysfunction.
§ Attributable proportion (AP) of cases owing to the interaction of migration history and family dysfunction.
effects of migration and family dysfunction. Adjustment for confounding variables did not substantially change the results.

To quantify the interaction between family dysfunction and migration, relative risks were calculated for exposure to both migration and family dysfunction, to family dysfunction only and to migration only, with no migration and no family dysfunction as the reference. The effect when both variables were present was larger than the sum of their independent effects, indicating causal interaction. The proportion of cases attributable to the interaction between migration history and family dysfunction was 58%.

**DISCUSSION**

**Summary of findings**
The relationship between migration and psychotic symptoms was considerably stronger for children and adolescents from dysfunctional families than for those who did not report family dysfunction. The interaction between migration and family dysfunction accounted for the majority of individuals with psychotic symptoms. The relationships were independent of age, gender, the presence of psychiatric illness in the parents and the educational level of the breadwinner.

**Interpretation**
In the current study, family dysfunction may have acted as a psychosocial stressor upon susceptible individuals (i.e. those with a history of migration), thus precipitating psychotic symptoms. This is in agreement with findings from the Finnish Adoptive Family Study of Schizophrenia (Wahlberg et al, 1997; Tienari et al, 2004), which demonstrate that susceptible individuals, in this study who adopted children born to a biological mother with schizophrenia, are more sensitive to the effects of an adverse family environment. Our results support the hypothesis that the psychosocial environment plays a role in the increased incidence of psychotic disorders in subjects with a history of migration (Mallett et al, 2002).

**Study limitations**
Since family dysfunction and psychotic symptoms were measured simultaneously, it is possible that family dysfunction was a result of the psychotic symptoms rather than its cause. A second limitation is the definition of psychosis. Patients were categorised according to the presence of probable or definite psychotic symptoms, and not DSM–IV or ICD–10 categories. However, this is in accordance with the evidence that the boundaries of the psychosis phenotype extend beyond the clinical concept of a psychotic disorder (van Os et al, 2000). Importantly, psychotic symptoms in childhood and adolescence are often followed by psychotic disorders in adult life (Yung et al, 1998).

Third, the educational level of the breadwinner is not a reliable indicator of socio-economic status. Current evidence, however, increasingly indicates that the risk for schizophrenia is not associated with parental socio-economic status (Byrne et al, 2004). Finally, information bias and referral bias have to be considered. Information bias can only explain the interaction observed if the interviewers systematically scored family dysfunction more frequently in migrant patients than in non-migrant patients, and if this occurred specifically in patients with psychotic symptoms. Likewise, referral bias can only explain our results if referral of subjects from dysfunctional families was more likely for migrants than for non-migrants, and if this applied specifically to psychotic symptoms. Hence, we regard information and referral bias as unlikely explanations of our results. However, the findings of this cross-sectional study need confirmation in longitudinal population-based studies.

In conclusion, in children and adolescents the increased risk of psychotic symptoms associated with a history of migration is considerably larger in the presence of family dysfunction. This suggests that migration history and family dysfunction act in a synergistic manner. Psychosocial stress associated with family dysfunction may contribute to the development of psychosis in migrants.

**REFERENCES**


Language lateralisation in schizophrenia

Dr Sommer and colleagues (2004) reported decreased language lateralisation measured with functional magnetic resonance imaging (fMRI) in 12 monozygotic twin pairs discordant for schizophrenia compared with 12 healthy monozygotic twin pairs. The authors did not find significant differences in language lateralisation between affected twins and their co-twins without schizophrenia. In the December 2003 issue of the Czech peer-reviewed psychiatric journal Psychiatrie, we published preliminary data from a study (supported by grant NF 6794-3/2001 from the Internal Grant Agency of the Czech Republic) that examined hemispheric dominance for language processing by means of fMRI in four monozygotic twin pairs discordant for schizophrenia. Although the activation paradigm (a verbal fluency task) differed from the one employed by Dr Sommer et al, the lateralisation index was calculated according to the same method within identical volumes of interest. The results indicated that language processing was significantly less lateralised in affected twins compared with their co-twins without schizophrenia ($P<0.05$, Wilcoxon signed ranks test, robustness assessed by analysis of 10,000 Monte Carlo permutations; mean laterality index 0.90 (s.d. = 0.12) for unaffected twins and 0.73 (s.d. = 0.17) for affected twins). There were no statistical differences in the laterality index during the verbal fluency paradigm between unaffected twins from the discordant monozygotic twin pairs and the four control monozygotic twin pairs (unpublished data). The explanation of the discrepancies could lie in the participants enrolled in our study. Since the aim of our work was to assess relative contribution of non-genetic factors in previously reported decreased language lateralisation in schizophrenia, the exclusion criterion was (in contrast to Dr Sommer’s study) any family history of schizophrenia or other major psychiatric disorder. This particular study strategy allowed selection of an extreme population presumably represented by sporadic forms of the disease. In addition, stringent diagnostic criteria were used in that only participants with schizophrenia were enrolled in the study. The occurrence of psychiatric disorders in co-twins without schizophrenia and the fact that the participants were not controlled for family history of psychosis suggest a substantial degree of genetic predisposition for schizophrenia in unaffected co-twins expressed as overall decrease in language lateralisation within the discordant twin group studied by Dr Sommer and her colleagues.


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Authors’ reply: We read with interest the results of the study by Dr Spaniel et al. In parallel to our findings, they reported decreased language lateralisation in (twin) patients with schizophrenia compared with healthy (twin) controls. However, they did not report whether the decreased lateralisation in the patients resulted from increased activation of the right hemisphere, or from decreased activation of the left hemisphere. This is an essential point, since decreased activation of frontal, temporal and parietal language areas in the left hemisphere of schizophrenia patients is frequently associated with decreased task performance (as reported by Artiges et al, 2000). Increased language-related activation of right cerebral areas, in contrast, may reflect a failure to establish cerebral dominance, which may be a genetic predisposition to develop schizophrenia.

In our study (Sommer et al, 2004), the language tasks employed were selected to be very simple in order not to cause a difference in performance between patients and healthy subjects. Left hemispheric language activation was not lower in patients than in their co-twins, which, in our opinion, reflects equal task performance.

In the Spaniel et al study, a verbal fluency task was employed, which is known to generate a difference in performance between schizophrenia patients and controls, and generally yields decreased activation of left frontal areas in patients (Curtis et al, 1999). This may explain why Spaniel et al found lower lateralisation in patients compared with their co-twins.

Spaniel et al mentioned that selection of co-twins without schizophrenia and of control pairs may have caused the difference between their results and ours, since the control twin pairs in their sample were selected not to have relatives with schizophrenia. This was, however, also the case in our sample. The second point of difference raised by Spaniel et al is that the co-twins in their study had no psychiatric disorder. However, in our article we described an additional analysis comparing twins with schizophrenia with their co-twins after exclusion of all pairs from which the co-twins had psychiatric pathology, which yielded the same results as the analysis including the entire sample.

In sum, we find Dr Spaniel et al’s study an interesting contribution; in our opinion it is differences in the language activation tasks, rather than differences in sample selection, that are the cause of the differences in outcome between the studies.


Cognitive–behavioural interventions in schizophrenia

Hodgins & Müller-Isberner (2004) in their clinical implications assert that schizophrenia patients with antisocial behaviour ‘require cognitive–behavioural interventions aimed at changing antisocial behaviours…’; yet the paper itself can only quote evidence of effectiveness of these techniques in offenders who are not mentally ill (McGuire, 1995). It therefore seems unclear why they then suggest that these techniques will be effective in reducing antisocial behaviours in people with schizophrenia and should be regarded as ‘required’. Unfounded assumptions like these may be quoted by others referencing this paper and lead people to assume, mistakenly, an evidence base for this assertion. Providing cognitive–behavioural therapy to this client group may therefore provide no benefit but divert resources that may have benefited others. While I agree that reducing antisocial behaviour in this client group is desirable, we should not hasten to assume, in the absence of evidence, that cognitive–behavioural therapy will provide a panacea.


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Authors’ reply: Thank you for your interest in our work. It is important to note that we proposed that cognitive–behavioural interventions that have been shown to reduce offending could be adapted to treat a subgroup of offenders with schizophrenia. This subgroup shares with the offenders who have benefited from these interventions a history of antisocial behaviour since childhood, and antisocial attitudes and ways of thinking.

Dr Huda makes the presumption that interventions proven to reduce offending would not have a similar effect among offenders with schizophrenia. In our view, this presumption is unfounded. For example, treatments for medical conditions proven to be effective in people without schizophrenia are used with equal success with those with schizophrenia. We also disagree with Dr Huda’s presumption because, generally, effective treatments target specific problems, not a disorder. This is true in the case of schizophrenia where different treatments have been shown to have a positive impact on positive and negative symptoms, substance misuse, life skills, social skills and employment skills (Bloom et al, 2000).

As we noted, compliance with medication is a prerequisite to participating in interventions aimed at reducing offending. Furthermore, these interventions need to be adapted for use with people with schizophrenia and their effectiveness evaluated. This has been done recently, for example, with interventions that targeted substance misuse. Programmes that were adapted to patients with schizophrenia and integrated with their other treatments are reported to be effective (Mueser et al, 2003).

We agree with Dr Huda that evidence for the effectiveness of cognitive–behavioural programmes in reducing offending among persons with schizophrenia is still sparse. It is presently limited to naturalistic follow-up studies with non-random assignment of participants (T. Fahy, personal communication, 2004; Kunz et al, 2004).

In our view, however, the available evidence is encouraging and sufficient to undertake randomised controlled trials of these interventions with the subgroup of offenders with schizophrenia who display a stable pattern of antisocial behaviour from an early age. Given the potential of these interventions to prevent criminal activity, improve the individual patient’s life, and reduce costs to both the health and criminal justice system, such trials are urgently needed.


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Suicide and antidepressant sales

Helgason et al (2004) reported that the dramatic increase in the sales of antidepressants in Iceland had not had any impact on suicide rates. While the sales of antidepressants increased fivefold from 14.9 defined daily doses per 1000 persons per day in 1989 to 72.7 in 2000, the suicide rate remained quite stable (around 11/1000 000 persons per year). The data were, however, not analysed separately by gender.

Based on the World Health Organization database on national suicide rates, Levi et al (2003) compared the periods 1980–84 and 1995–99, and found that suicide rates in Iceland decreased by 1.7% in males during the whole period (17.9 to 17.6) and by 46.7% in females (from 6.0 to 3.2). In spite of the fact that the time periods investigated by Helgason et al (2004) and Levi et al (2003) are not exactly identical, the general trends should be similar. Given this extremely great (27-fold) difference in the decrease in suicide rates between males and females, it would be interesting to see the data on the use of antidepressants in Iceland between 1989 and 2000 for males and females separately. Perhaps the increase in the use of antidepressants was more pronounced in women than in men, as for example in Australia (Hall et al, 2003)?

A significant negative correlation between antidepressant prescription and national suicide rates has been reported from Sweden, Denmark, Finland and Norway (Isacsson, 2000) as well as from Hungary (Rihmer, 2004), countries where suicide rates have been traditionally high. Statistical association, of course, does not necessarily imply causality, but considering the strong relationship between untreated depression and suicide, the national trends mentioned above point in the expected direction. On the other hand, however, if a marked increase in antidepressant
utilisation is not accompanied by a substantial decline in the suicide rate, it does not mean that better and more widespread treatment of depression is not helpful for preventing many suicides. While the overall suicide rate of Australia and Northern Ireland (two countries with traditionally low suicide rates) have not substantially decreased during the past 10 years, a significant association between increased antidepressant use and decreased suicide rates in different age cohorts has been reported (Hall et al., 2003; Kelly et al., 2003).


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Authors’ reply: We have data on the suicide rates by gender from 1978 to 2000. The average rate for that period is about 19 per 100 000 for men and about 5 for women. The yearly data for women is a sequence of numbers varying from 3 to 14. Because of the small number of female suicides they can vary considerably. Even 5-year averages would have large standard deviations. If an over-dispersion coefficient of 2 is assumed, the size of the standard deviation in 5-year averages should be around 1.4 for women and 2.6 for men. Therefore, observed 5-year averages of 4–7 for women and 17–22 for men could be expected. Average rates may vary according to choice of 5-year periods (Fig. 1). The rates during 1995–1999 were 18.1 for men and 4.6 for women, but 21 for men and 5 for women during 1996–2000. The rates quoted in Isacsson’s letter for 1995–1999 are actually for 1995–1996 (Levi et al., 2003) and too low. Taking 5-year averages is a waste of information because it ignores the time series structure in the data. With such limited data the number of suicides in Iceland it is vital to use statistical techniques that use data as efficiently as possible. In this case the dynamics of suicide rates seemed to be similar for both genders, so data on them was pooled. In our opinion time series methods should be used for these data as they take advantage of the time series structure of the data. Furthermore, a time series approach leads to improved P values and decreases the possibility of spurious regression (Granger & Newbold, 1974).

In our paper (Helgason et al., 2004a) we mentioned that suicide rates had not decreased in Norway since 1995 in spite of increasing antidepressant sales.

In 1989 the amount of antidepressants prescribed was 13.9 defined daily doses per 1000 per day for men and 27.6 for women aged ≥15 years (Helgason et al., 1997). The amount prescribed in 2001 had increased to 66.8 and 119.1 defined daily doses per 1000 per day for men and women, respectively (Helgason et al., 2004b), i.e. a slightly greater increase for men without affecting suicide rates for either gender.


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Transcranial direct current stimulation

Kuruppuarachchi & Wijeratne (2004) support the use of innovative and cheaper treatments for depression in developing countries. In Brazil, for instance, antidepressants are scarcely available in the public sector and the delivery of these drugs is irregular, hence hindering long-term treatment. A recent study showed that only 17% of primary care patients with current depressive disorder in Brazil received any treatment for their depression. In comparison, 49% and 34% of patients with similar conditions in Australia and the USA, respectively, received treatment for
depression (Simon et al., 2004). The main reason for this disparity is the lack of resources in poor countries. We therefore propose that a type of brain stimulation – transcranial direct current stimulation (tDCS) – may be a satisfactory alternative to increase access to adequate antidepressant treatment.

Electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) are examples of brain stimulation therapy that are effective in treating depression. However, these treatments are expensive and might be associated with adverse effects (Hasey, 2001). In recent years, a simple technique of brain stimulation that seemed long forgotten has received renewed attention – tDCS. This treatment is inexpensive, easy to administer, non-invasive and painless (Nitsche et al., 2003). There are few past reports of tDCS in treating depression (Lolas, 1977). However, at the time of those trials much less was known about the methodological aspects and physiological effects of tDCS and the results were quite variable.

Preliminary, unpublished data from a randomised, sham-stimulation controlled and double-blind trial evaluating the effects of anodal stimulation of the left dorso-lateral prefrontal cortex in people with depression suggest that tDCS is an effective treatment for major depression (further details available from the authors on request).

Thus, we have come to believe that tDCS might be a reasonable alternative treatment for depression in low- and middle-income countries. The device to deliver tDCS is simple, can cost less than US$100.00 and can be manufactured locally. The equipment is fully reusable and utilises one standard battery that can last several weeks. Furthermore, this treatment is easy to administer, and can be applied by technicians following appropriate instruction and training. Although further studies evaluating this method are warranted, tDCS might help to improve mental health in areas with poor resources.


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NICE recommendations for valproate treatment are unhelpful

The National Institute for Clinical Excellence (NICE) guidelines for treatment of mania recommend that consideration be given to olanzapine and semisodium valproate as first-line treatments (NICE, 2003). They state that valproate can rarely cause severe liver damage and assert that liver function should be assessed before and during therapy, saying ‘tests that reflect protein synthesis, particularly prothrombin time are most relevant’. They continue: ‘Blood tests (blood cell count, including platelet count, bleeding time and coagulation tests) are therefore recommended’. Most readers will be familiar with the concept of the bleeding time only through the immortal lines delivered by James Roberton Justice in the film Doctor in the House (1954). It is a rarely indicated test of platelet function which requires making a 3 cm cut on a patient’s forearm and timing how long it takes for the bleeding to stop. Clearly such a test would not be acceptable to a substantial proportion of patients with mania.

The recommendation seems a non sequitur. Saying that valproate can cause liver damage and that ‘therefore’ these investigations should be performed does not make sense because, with the exception of the coagulation tests, they are not indicators of hepatic function. In fact, the investigations are not recommended by the British National Formulary (BNF) but in the summary product characteristics for semisodium valproate (available at http://emc.medicines.org.uk). It is here that it is stated that valproate can cause the frequent occurrence of thrombocytopenia, and it is here that the investigations listed are recommended.

It would strain credulity to believe that British doctors routinely measure bleeding time prior to initiating valproate therapy. Yet if a patient were to suffer all effects, then having ignored recommendations found both in the summary product characteristics and in NICE guidelines could make an action for negligence difficult to defend.

Even setting aside the bleeding time, the advice to perform more straightforward investigations remains problematic. Faced with a manic patient, one is unlikely to feel enthusiastic about holding off treatment until a prothrombin time has been obtained. Instead, one will be tempted to choose an alternative treatment which can be started immediately, such as haloperidol. The BNF does not recommend that these blood tests be performed before starting valproate and there is no evidence base to show that carrying them out pre-treatment will produce a better outcome. The advice seems to have been included in the NICE guidelines in a thoughtless way, without regard to the possibility that unnecessary investigations will make a particular treatment option less acceptable to both doctors and patients. If recommendations about treatment are to be evidence-based, then so must be the recommendations about accompanying investigations.


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Combating editorial racism

Peter Tyrer (2005) has set out a number of ways by which the British Journal of Psychiatry will attempt to minimise editorial racism and he acknowledges that this is only the beginning of a long journey. Nevertheless, he ought to be congratulated for his vision. His proposal to increase the number of corresponding editors from low- and middle-income countries is commendable, although I would like to see an
increase in peer reviewers who have, like corresponding editors, an understanding of the issues in these countries. Otherwise, reviewers, who I am sure are fair-minded professionals, will continue to judge papers from poorer countries on the same basis as those submitted from rich countries, thereby perpetuating the problem of disproportionate publication. Surely there must be reviewers who will undertake this task – if not, appropriate professionals need to be encouraged to get involved so that they can make a significant contribution to ending editorial racism. Additionally, their participation will also encourage greater opportunities for publications from researchers from poorer countries which in itself, I believe, is a worthy cause.


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Reading habits of British psychiatrists

Jones et al’s (2004) reassuring article that British psychiatrists read British journals may indicate the preoccupation of the British with British services. It would not be surprising to find that British people use the Royal Mail, watch the BBC or ITV, read British newspapers, fly British Airways (I wonder)! Tables 1 and 2, however, reveal another interesting observation, which the authors did not address in their otherwise interesting article. Advances in Psychiatric Treatment was more often read by those without academic commitments, in all the age groups. The difference in the adult psychiatric group is quite marked – 17% of psychiatrists without academic commitments read Advances, compared with only 2% of those with academic commitments, a difference which may even be statistically significant. These trends are maintained in Table 2, where another difference between academic and non-academic psychiatrists emerges: academic psychiatrists ranked the American Journal of Psychiatry, Archives of General Psychiatry, Biological Psychiatry and the Journal of Psychopharmacology higher than did psychiatrists without academic commitments. One could infer that psychiatrists without academic commitments preferred journals like Advances in Psychiatric Treatment, which have practical, management-related reviews and updates, and psychiatrists with academic commitments preferred research-based journals. Or these differences could confirm the Editor’s hunch that Advances in Psychiatric Treatment will gradually become more popular (Tyre, 2004).


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One hundred years ago

‘Kinds of insanity’

The preparation of a new set of statistical tables by the Medico-Psychological Association of Great Britain and Ireland for the annual recording of the vast clinical and pathological data and returns of all public asylums in the future has brought forward the inevitable question of the nomenclature and classification of the insanities. Dr. C. A. Mercier, in an article in the Journal of Mental Science for January, deals with the “kinds of insanity” which he thinks fulfil the necessary conditions of true diseases. The arrangement suggested is first to separate congenital from non-congenital cases of insanity. The congenital cases would include all idiots and most imbeciles. The classification of these is a matter of subordinate importance, whereas the division of the insanities proper into natural groups is the main desideratum in mental science and the most important aid to clearness of thought of diagnosis, and of prognosis. Cases of insanity are proposed to be considered in one of two classes – viz., general paralysis (paralytic dementia) and non-paralytic insanity. Dr. Mercier suggests that the latter class contains “diseases sufficiently distinct that merit the same separation that is given to general paralysis…. As to general paralysis the symptoms are so distinct that it is recognizable at every stage in its progress. It has a definite history, runs a definite course, and forms a complete clinical picture separable from that of any other form of insanity.” Examining other varieties of insanity and their titles or claims to be called diseases, Dr. Mercier would admit “acute delirious mania” owing to its characteristic symptoms and its course as a definite variety of insanity. “The clinical picture of acute delirious mania is distinct and prevents it from being confused with any other type of insanity. On the contrary,” he says, “puerperal insanity presents us with no distinct clinical picture. The very fact that it has been divided into puerperal mania and puerperal melancholia is proof of what I say. Puerperal insanity is acute insanity occurring within an uncertain time of childbirth, and if the antecedent of childbirth is disregarded there is nothing whatever in the clinical picture of the disease that is different from other causes of acute insanity that have no connexion with the puerperium or even in acute insanity occurring in men.” The insanity of pregnancy is regarded as having a much better right to be considered a disease, “for the fact of pregnancy is a continuing feature in the clinical picture, a feature which at once marks off the case from all other cases of insanity.” What is true of the insanity of pregnancy, he adds, is emphatically true of the insanity of lactation. It is an insanity of exhaustion – of innutrition – and differs in no respect from other cases of insanity of similar origin. Few cases of insanity occurring at the menopause in women deserve recognition as a separate variety.
of insanity. Similar cases may occur at other times of life and present the same clinical picture. The definite form of insanity of the menopause “with its special facies” is, says Dr. Mercier, rare. Senile insanity has no right to a special place in nosology. “The term means, it appears, insanity not assigned to any distinct category except by its occurrence in advanced age. It would, in my opinion, be unreasonable to base the differentia of the disease on so slender a foundation.” The insanity of epilepsy is admitted to have “a good title to the denomination of a disease.” Cases of insanity associated with bodily diseases, whether the latter be regarded as a cause or not, in no case present a clinical picture of sufficient distinctness to entitle them to separate rank as diseases. Dr. Mercier would admit the claims of a stupor, paranoia, recurrent and alternating insanity, and the two forms of insanity occurring in adolescents or young adults known as hebephrenia and katatonia. Causes of fixed delusion would also find a place in classification, being further subdivided as the delusions are persecutory, exalted, and personal. Alcoholic insanity would be recognised in its subdivisions of mania a potu, delirium tremens (acute forms), or alcoholic insanity proper of the chronic form. This threefold subdivision of alcoholic insanity would exclude all cases in which alcohol was not the main actuating cause of the malady. The above-named varieties of insanity, concluded Dr. Mercier, “have claim to the title of distinct diseases from the distinct clinical pictures they present; all other cases must be lumped together under the heading of insanity simpliciter.”

**REFERENCE**


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**Corrigendum**


After publication of this paper, the authors became aware of errors in the original analysis. These are explained in a data supplement to the online article, located at http://bjp.rcpsych.org/cgi/content/full/184/47/s94/DC1.
From the Editor’s desk

PETER TYRER

THIS MONTH’S ISSUE: THE GREATER THE KNOWLEDGE, THE GREATER THE DOUBT

Goethe’s 200-year-old observation well describes this issue. One of my medical students told me recently that she liked psychiatry because everything in it could be challenged. After sparring for a short time I had to agree with her, but suggested a lesser degree of impertinence when she is being examined. So in this issue some better-known assumptions, sometimes elevated to the status of fact, are challenged, not particularly by questioning of past support, but by new knowledge that is beginning to replace the old. The dichotomy of bipolar affective psychosis and schizophrenia introduced by Kraepelin has for some years been looking ragged at the edges, but now Craddock & Owen (pp. 364–366), with some well-placed sword thrusts delivered from genetic epidemiology, slice it up and leave it bare, although it holds on to a smidgen of respectability from the brain volumetric studies of McDonald et al (pp. 369–377). Freeman and his colleagues (pp. 427–435) go further into normal function by showing that paranoia is a widespread symptom not confined to psychosis with a majority admitting to ‘I need to be on my guard against others’; so perhaps Stalin was not that unusual in his thinking. Similarly, greater knowledge about foetal development and the hypothalamic–pituitary–adrenal axis has led to re-evaluation of obstetric complications as a hypothesis for schizophrenia (O’Keane & Scott, pp. 367–368), but assessment of these developmental risks is not easy and simple birth dimensions not an adequate substitute, at least with regard to depression (Osler et al, pp. 400–403).

Schizophrenia continues to puzzle every researcher but what is now increasingly clear is that its prodrome or pre-manifestation period is a long one, with both affective/perceptual symptoms (Owens et al, pp. 386–393) and memory impairment (McIntosh et al, pp. 378–385) presenting early. This supports the results of Tuulio-Henriksson et al (2004, 185, 215–219) and encourages the notion that the differences between bipolar disorder and schizophrenia might best be investigated in the early stages of illness. Our final area of doubt is illustrated by post-traumatic stress disorder. It is always troubling when a diagnostic label purports to explain both cause and symptoms. Sumpter & McMillan (pp. 423–426) show that the detection of traumatic brain injury is in danger of being suppressed by the expansion of a diagnosis that tends to change like a chameleon to fit its current background (Jones et al (2003), 182, 158–163) and so great care is needed in assessment when brain injury is suspected.

EDITORIAL RACISM IN THE JOURNAL INVESTIGATED BY YOUL-RI KIM

I have received some private comments about our efforts to be fairer to authors from low and middle income (LAMI) countries. Several of these can be paraphrased along the lines of: ‘Don’t get diverted into political correctness. You know perfectly well that most papers from poorer countries are not worth a hill of beans so get rid of them as soon as possible and save yourself, and their authors, from wasting everybody’s time’.

My Korean colleague, Dr Youl-Ri Kim, has been helping to investigate this HOB (hill of beans) hypothesis by looking at the fate of papers from LAMI countries and comparing them with those from high income (HI) ones. The study was carried out to determine whether the rejection rate of manuscripts submitted to the Journal was greater for those from LAMI countries than from richer ones, and whether rejected papers were less likely to be accepted in journals with high impact factors. The HOB hypothesis would support both of these. Only a small proportion (164) of the total of 1370 manuscripts during the years 2002 and 2003 have been analysed to date. The eventual publication status of these rejected manuscripts was searched using the ISI Web of Knowledge database. The impact factor of each journal was derived from the JCR Science Edition in the year of publication. Classification of the first author’s country was decided from 2002 World Bank data.

Although conclusions from the results can only be tentative in view of the relatively small numbers, the results offer only very limited support to the HOB hypothesis. Among 164 original papers submitted, 136 manuscripts (82.9%) were rejected. The Journal’s rejection rate of LAMI papers was 88.9% (8 out of 9); the rejection rate of HI papers was 82.6% (128 out of 155) ($\chi^2$=0.239, $P=0.625$, NS). Of the rejected 136 manuscripts, 78 were subsequently published in other journals (57.4%). The mean impact factor of these journals was 2.05 (s.d.=2.3). The resubmitted publication rate of LAMI papers was 37.5% (3 out of 8); the rate for HI papers was 58.6% (75 out of 128) ($\chi^2$=1.37, $P=0.242$, NS). The mean impact factor of resubmitted LAMI articles published in other journals was 1.99 (range 1.394–3.188); the mean impact factor of HI articles was 2.050 (range 0.125–6.458) ($P=0.94$, NS). Five papers from HI countries were published in a journal with a higher impact factor than that of the British Journal of Psychiatry but none of the LAMI papers achieved this. I think the message here is that the LAMI countries are contributing well to the psychiatric literature and that, as far as the British Journal of Psychiatry is concerned, the common exhortation in school reports, ‘could try harder’, applies.

But please keep looking at this column; more will follow.