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The Kraepelinian dichotomy

McDonald et al (2005) investigated the Kraepelinian dichotomy of psychosis using brain imaging. They reported distinct grey matter volumetric deficits in patients with schizophrenia and those with psychotic bipolar I disorder but common white matter abnormalities in the two disorders. Kraepelin distinguished dementia praecox and manic–depressive psychosis on the basis of symptomatology, course and outcome. He wrote that the basic disturbances in dementia praecox were the ‘impovertyishment of those feelings and stirrings which continually stoke the furnace of our will’ and ‘a loss of the internal integrity of comprehension, emotion and volition’. Furthermore, his description of manic–depressive psychosis included cases of ‘periodic and circular insanity, simple mania, melancholia and affective changes that could be regarded as rudiments of more severe disasters’ (Berner et al, 1992). This formulation is what we would today consider a spectrum concept of manic–depressive illness. A test of the Kraepelinian dichotomy would thus be better served by the use of patients with affective disorders rather than bipolar I disorder (with psychotic symptoms) as the comparator group.

The non-significant differences in grey matter between patients with bipolar I disorder and healthy volunteers could be a result of sampling bias. Recruitment of patients from voluntary support groups might have resulted in inclusion of those with less-severe illness. In addition, depression, anxiety, medical disorders (e.g. hypertension, diabetes mellitus) and seizures, which can give rise to structural abnormalities on magnetic resonance imaging, were not excluded in the ‘healthy volunteers’. The mean IQ and ethnicity of patient groups and the healthy volunteers were not given. These variables are important as they may contribute to differences in brain structure among groups (Thase, 2000). Similarly, the use of spoiled gradient recall echo sequence instead of inversion recovery sequence might have led to type 2 errors in comparisons of white matter volumes between patients with schizophrenia and those with bipolar I disorder (Karson & Renshaw, 2000).

The statistical analysis used the analysis of covariance (ANCOVA) model for differences between each patient group and the healthy volunteer group and differences between the two patient groups. Risk of type 1 errors would have been lower in a single ANCOVA (3 x 2) model.

Finally, it would be interesting to know whether ‘normalisation’ using the International Consortium for Brain Mapping data-set instead of the Talairach space would have made a difference to the results and whether some of the results were confirmed by the ‘region of interest’ methodology, which is known to be more accurate.


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Authors’ reply: Drs Sharan and Bharadwaj object to our representation of Kraepelin’s manic–depressive illness with DSM–IV psychotic bipolar I disorder because Kraepelin used the term to refer to a broader spectrum of affective disorders. By this logic our inclusion of patients fulfilling modern diagnostic criteria for schizophrenia rather than dementia praecox should be equally unacceptable to them. However, the Kraepelinian dichotomy continued to stimulate controversy over the past century precisely because the evolution of diagnostic criteria for these syndromes consistently failed to fully separate the disorders on clinical and neurobiological grounds. Thus ‘the Kraepelinian dichotomy’ has come to refer to the distinction between schizophrenia and bipolar disorder (Cradock & Owen, 2005). Furthermore, there is considerable morphometric heterogeneity between bipolar disorder and major depressive disorder (Strakowski et al, 2002), which underlines the need for more homogeneous rather than broader-spectrum affective disorder patient groups for magnetic resonance imaging studies.

Their hypothesis that our failure to identify grey matter abnormalities in bipolar disorder may result from recruiting patients with less-severe illness and a group of healthy volunteers with conditions associated with structural abnormalities is difficult to reconcile with our success in identifying white matter abnormalities in the same patients and typical grey matter deficits in patients with schizophrenia, who were recruited in a similar manner.

Moreover, there is no reason why healthy volunteers would have higher rates of the conditions suggested than the patient groups. Ethnicity is given in the cited associated paper (McDonald et al, 2004). Although type 2 errors are frequently possible, the magnetic resonance sequences used are common for computational morphometry studies and successfully detected differences in patients and healthy volunteers. The ICBM152 template was indeed used, as is standard with the SPM99 (Statistical Parametric Mapping 99) package, to create the customised template. We accept that the risk of type 1 errors would be lower with a single screening analysis of covariance but we hypothesised changes in a voxelwise comparison between each patient group and the control group and thus reported these results.

Although results from computational morphometry have been interpreted
variously as volume change, shape change or a result of other processes altering voxel intensity, we dispute the simplistic assertion that region of interest methodologies are ‘more accurate’ – such methodologies have their own difficulties, in particular with interrater reliability and the optimal parcellation boundaries chosen for structures, and the two methodologies are perhaps better viewed as complementary. Region of interest analyses of a similar sample demonstrated that volume deficits of the hippocampus and amygdala characterise schizophrenia but not bipolar disorder (Marshall et al, 2004; McDonald et al, 2006). This is consistent with our computational morphometry study – and with Kraepelin’s seminal dichotomy.


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Social defeat and schizophrenia

Selton & Cantor-Graae (2005) relate schizophrenia to social defeat. Given Darwin’s theory of intrasexual selection, social defeat is inevitable for a proportion of any population, and it is not unlikely that we are seeing this unselected or deselected portion in the psychiatric clinic. The response to social defeat is variable. In chimpanzees there is conditional reconciliation, in which the defeated animal engages in affiliative behaviour with the one who has defeated him (Aureli et al, 2002). The hugging and kissing ritual relieves post-conflict anxiety (indicated by scratching and other self-directed acts), so that in the chimpanzee world the sun goes down on no one’s wrath. In partially migratory species of birds, such as the robin, the defeated birds who have no territories migrate, and if they return in the spring they may find that the winners have succumbed to the cold. In partially hibernating species the defeated animals hibernate. In general, in territorial species defeated animals disperse, whereas in group-living species they stay in the group in a subordinate role.

I think that defeated humans have the alternative defeat strategies of either dispersing or staying in the group. The ‘schizotypy’ appears to be a dispersal phenotype, modified from the usual mammalian dispersal phenotype because of the uniquely cohesive structure of human groups, which are held together by common belief systems. When a person with this phenotype is defeated, they develop a new belief system, recruit followers and take them off to a new location (Stevens & Price, 2000). This appetitive behaviour may well require stimulation of the dopamine reward system, as was found in defeated mice, which being territorial disperse when defeated. However, when defeated the depression-prone human stays in the group in a subordinate role. He may be happily reconciled to this subordination or he may use the depressive strategy of ‘deceiving downwards’ in which he develops the cognition that he is not such a useful member of the group as he thought he was (Hartung, 1987). This depressive strategy may involve some downregulation in the hippocampus, as occurs in defeated rats, which are group-living animals (McEwen, 2005).

In general, we think people with the schizotypal phenotype become depressed when dispersal is blocked whereas those who are prone to depression become depressed when reconciliation is blocked. People with the schizotypal phenotype and depression also have their new belief system, which in the absence of followers is likely to be labelled delusion, and the unworlthy prophet is then looked after not by adoring acolytes but by psychiatric nurses.


Selton & Cantor-Graae (2005) proposed that long-term experiences of social defeat may sensitize the mesolimbic dopamine system, increasing the risk for schizophrenia. Regrettably they continued the tradition of ignoring the distal evolutionary perspective. An underemphasised observation is that although neurological illnesses have lifetime prevalence rates in the order of thousands, prevalence rates for psychiatric illness often lie between 1% (as for schizophrenia) and about 20%. When considering highly disabling conditions such as schizophrenia, depression or anxiety, one must consider the survival implications. Over evolutionary time if there were not some adaptive advantage these genes would have been eliminated. The suggestion that these conditions are products of modern culture is untenable, as they are found in all cultures and have been observed back in time as far as history permits. Furthermore, animals certainly have depression and anxiety.

Selton & Cantor-Graae could have referred to the book by Stevens & Price (2000) on the evolutionary adaptiveness of social subordination and schizophrenia. They proposed that schizotypal individuals at times of social crises may come to the fore and lead individuals with similar genes in new directions. Similarly, work by Gilbert (1992) and Sloman (2000) on depression and defeat warrant consideration.

Evolutionary perspectives often suggest obvious but new directions for gene–environment research. For example, I have proposed a model of post-traumatic stress disorder (PTSD) based on mammalian defences (Cantor, 2005). An understanding of these suggests that looking for genes for the entity PTSD is misguided. The six mammalian defences operate under different selection regimes, therefore greater evolution of one will be associated with a

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decreased need for others. The tortoise, although not a mammal, provides the perfect example: its extraordinary defensive shell reduces the need to flee or fight to virtually zero.

Furthermore, the possibility arises that future gene therapies may have serious untoward consequences (Watson & Andrews, 2002). The genes associated with social defeat may encourage a battered wife to yield to her brutal husband, albeit at the price of chronic depression. Should her relevant genes be deleted by future gene therapy, potential consequences include being killed as a result of not yielding, killing her abuser in retaliation or at least a heightened state of domestic abuse. The potential for such untoward consequences must be considered.

**Schizophrenia, cancer and imprinting: early nutritional influences**

We read with interest the important findings of Goldacre et al. (2005) on the association between schizophrenia and cancer morbidity. Compared with the general population, they found a reduced rate of cancer of the colon in the schizophrenia cohort (adjusted rate ratio 0.72, 95% CI 0.50–1.01) with a trend towards significance ($P = 0.06$). Rates of rectal cancer were significantly reduced in people with schizophrenia (rate ratio 0.57, 95% CI 0.33–0.93, $P = 0.03$). In their discussion, they emphasised the reduced rate of skin cancer in the schizophrenia cohort (rate ratio 0.56, 95% CI 0.36–0.83, $P = 0.004$).

Recent studies suggest that abnormal insulin-like growth factor-2 (IGF-2) imprinting is aetiological in the development of colorectal cancer (Jirtle, 2004). Genomic imprinting occurs following epigenetic modification of the germ line, which results in parent-of-origin dependent, monoallelic gene expression in somatic cells. Epigenetic changes in the genome are stable but reversible alterations in a CpG dinucleotide or histones, for example through changes in methylation. The genome of colonic epithelium from patients with colorectal cancer is hypomethylated compared with normal colonic epithelia (Feinberg & Vogelstein, 1983). Hypomethylation results in the loss of IGF-2 imprinting. We proposed abnormal imprinting (deletion of paternally expressed IGF-2) as a possible mechanism associated with schizophrenia risk (Abel, 2004). Early nutritional influences (pre-natal/maternal) may stimulate changes in cytosine methylation to which imprinted genes such as IGF-2 seem susceptible. Early nutrition may influence susceptibility not only to adult obesity, diabetes and cardiovascular disease (Waterland & Jirtle, 2004) but also to schizophrenia. This suggests that early nutritional interventions aimed at preventing chronic disease are an exciting possibility in schizophrenia. This view is supported by Dutch and more recent Chinese data which indicated that rates of schizophrenia doubled following prenatal exposure to famine (St Clair et al., 2005).

**Post-traumatic stress disorder after life events**

In their interesting article Mol et al. (2005), who conclude that life events might cause as many post-traumatic stress disorder (PTSD) symptoms as do traumatic events. The design and conclusions of the study raise some doubts.

Our first concern relates to the assumption that a particular symptom or disorder may be diagnosed in the absence of the fundamental nature or essence of the disorder. The authors claim to identify PTSD in the absence of (a) a traumatic event and (b) a response involving intense fear, helplessness or horror. Both these criteria are diagnostic A criteria of the DSM-IV and essential features of PTSD. Diagnosing PTSD with disregard for a traumatic event is like diagnosing a major depressive disorder in the absence of depressed mood.

Our assumption regarding the broad use of the PTSD diagnosis is strengthened by the instrument used for assessing PTSD symptoms, which has high sensitivity but lacks specificity (Carlson, 1997). In addition, it is questionable whether a self-report scale can assess the clinical relevance of symptoms. Our concern is corroborated by the results in Table 4. The only item on which the life events group scored higher than the traumatic events group was the non-specific symptom of ‘having trouble concentrating’, whereas the traumatic events group scored higher on ‘trauma-specific items’ such as amnesia and hyperarousal.
Another concern is the selection of traumatic events. Accidents, sudden death of a loved one and witnessing violence are categorised as traumatic events but gave relatively low PTSD scores. In our opinion, such events may evoke a range of reactions such as guilt, anger, sadness, anxiety and apathy. Again, if criterion A2 – a response involving intense fear, helplessness or horror – has not been assessed, it is questionable whether these experiences were really traumatic.

The conclusion that life events can generate as many PTSD symptoms as traumatic events is unjustified. At most it could be concluded that some of the PTSD items might not be specific to trauma but are more general stress-related symptoms.

Authors' reply: Drs de Bruijn & Denys are concerned about identification of PTSD in the absence of the A1 and A2 criteria of the DSM–IV. However, we did not diagnose PTSD but we looked at PTSD symptomatology to the worst event experienced by participants (including traumatic and non-traumatic events). We did not include the A1 criterion because we wanted to investigate whether the 17 symptoms that are thought to typically occur in those who have experienced a traumatic event, as defined by DSM–IV, are indeed specific for that type of event or occur as frequently following non-traumatic events. In order to study this we inevitably chose events that did not fulfil the A1 criterion (otherwise we would not have had a control group of events). Regarding the A2 criterion, it would be interesting to study respondents’ subjective appraisal of the event in terms of fear, helplessness and horror. This would clarify whether the A2 criterion is also as specific for traumas as it is often argued and how it is related to the 17 B criteria of the DSM–IV. We would not be surprised if non-traumatic major events could also evoke the emotions of fear, helplessness and horror.

Drs de Bruijn & Denys were also concerned about the somewhat low specificity of the self-report scale we used to measure PTSD symptoms (the Post-traumatic Stress Symptom Scale – Self-Report version; Foa et al, 1993). However, it is conceivable that our results are owing to the lack of specificity of PTSD symptoms in general for diagnosing PTSD, as was demonstrated in a recent study by Gold et al (2005).

Concerning the results in Table 4: the traumatic events groups did score higher on several items (3 out of 17) but these differences were not significant, indicating that no specific items were more strongly related to traumatic events than to life events.

In summary, our main conclusion that life events can generate as many PTSD symptoms as traumatic events is upheld.

Declaration of interest

The Achmea Foundation for Victim Support in Society paid the salary of S.S.L.M. but had no influence on the methodology or analyses of the study.


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Psychiatric comorbidity and chronic fatigue syndrome

Prins et al (2005) assessed psychiatric comorbidity in chronic fatigue syndrome (CFS) using the Structured Clinical Interview for DSM–III–R. Comorbidity was remarkably low compared with similar investigations, and in particular the apparent absence of current post-traumatic stress disorder (PTSD) was striking. The authors speculated that the low comorbidity rates might result mainly from a lack of ‘psychiatric bias’ of the examiners. They also found that psychiatric comorbidity did not predict the outcome of cognitive–behavioural therapy.

Without doubt, diagnosing comorbid depression and anxiety disorders in CFS is useful because both are highly treatable emotional reactions to the illness. The relevance of somatoform disorders (such as somatisation disorder) for CFS is more doubtful, given their inherently dualistic character (Mayou et al, 2005). Most importantly, the very low lifetime incidence of PTSD reported by Prins et al (2005) emphasises the value of descriptive psychiatric diagnoses in CFS. In my experience many patients with CFS report victimisation during childhood and/or adult life, and this has been confirmed by a controlled questionnaire-based study (Van Houdenhove et al, 2001). However, most victimised patients have ‘sub-threshold’ symptoms that do not meet diagnostic criteria of clinical PTSD. It is important to listen carefully to the patient’s life history (Van Houdenhove, 2002) in order to shed light on any aetiological role of traumatic experiences in CFS and the resulting personality disturbances that may negatively influence treatment.

In summary, psychiatric evaluation of patients with CFS should not be limited to establishing a diagnosis of psychiatric comorbidity but should first involve narrative strategies (Greenhalgh & Hurwitz, 1998).


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Authors’ reply: It is of course impossible to disagree with Dr Van Houdenhove’s statement that it is important to listen to the patient’s life history. We have been doing this for many years. Therefore, the reason that he finds PTSD in so many of his patients with CFS and we do not is not our lack of listening. From previous presentations by this group from Belgium we know that they recruit patients with CFS with higher psychopathology scores than we do in our centre and than is usually found in other CFS cohorts. Hence it is understandable that they find higher rates of psychiatric comorbidity. To date there are no controlled studies indicating that a history of abuse is a characteristic of many patients with CFS.

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Not all women fancy single-sex wards

Mezey et al (2005) discuss staff and patient perceptions of the safety of women in mixed-sex and single-sex medium secure units. In their conclusion, the authors ask ‘how much choice women should be allowed to exert over the type of setting [single-sex or mixed-sex wards] where they receive treatment’. On the basis of our own survey we can provide tentative answers to the related question of whether they want a choice, and, if so, what they would choose.

As part of a much larger study (in preparation), we conducted a survey of 50 inpatients (31 women) who were admitted to four mixed-sex acute psychiatric wards. We explored their ward milieu preferences: single-sex vs mixed-sex wards. The mean age of the sample was 39.5 years (s.d. = 13.49) and the common diagnostic categories were schizophrenia (45%) and affective disorders (20%). Although 24 patients (48%) stated that they would like a choice in the type of ward they were admitted to, only 16 (32%) preferred single-sex wards to mixed-sex wards. A gender-wise analysis further showed that of the 16 who preferred single-sex wards, only 4 (25%) were women. The remainder of the female sample (27 out of 31) preferred mixed-sex wards. Of course, the reasons given for this choice were varied and complex.

Hence, our findings do not support the widely held belief that women often prefer single-sex wards. In view of the small sample size of our study, more work needs to be done on this subject before definitive conclusions are drawn.


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Psychiatric hospitals operate at three levels (Stokes, 1994) – ‘what we say we do’, ‘what we really believe we are doing’ and ‘what is actually going on’. Most are unconscious of this third level. Mezey et al (2005) rightly remind us that the further development of single-sex secure units for women may not be justified on the grounds of safety alone, but such a narrow focus has never been the principal driving force for developing gender-sensitive and single-sex secure units, which has massive ramifications for the wider hospital organisation.

Ramsay et al (2001) broadly described the issues relating to women and psychiatry and Kennedy (2001) argued for a proper focus on the needs of male patients. Both perspectives reinforce the need for gender-informed practice. While developing different services for male and female forensic patients, it is worth considering that one tenet of feminism is that no person should be discriminated against on the grounds of gender. Although men and women are not the same, Adshead (2004) argues that, in terms of human needs and human rights, male and female patients are more alike than they are different and that differences should not be the basis for abusive or discriminatory practice.

Although not emphasised sufficiently in the literature, particular issues are commonly encountered by both male and female in-patient forensic populations. These include the emotional and behavioural impact of bringing together a number of patients who have high levels of comorbidity, personality disorder and complex post-traumatic stress syndromes (Bercu, 2001). However, models of care for male patients (the majority population in mixed forensic units) fail to address the relational and other specific needs of women, their marginalisation and the impact of their experience of victimisation. Gender-informed forensic services therefore need to be equipped and enabled to provide appropriate levels of care and interventions, in suitable accommodation, for individuals with severe, complex clinical presentations and who present significant risks to themselves and others.

Our position is that gender adequately differentiates between men’s and women’s needs but that in the absence of more sophisticated frameworks, their needs are such that, for the foreseeable future, service planning must be based on the assumption that women forensic patients are sufficiently different from their male counterparts that their needs should be provided for separately.

Declaration of interest

None. This is not a representative view of Nottinghamshire Healthcare NHS Trust, Nottingham City Primary Care Trust or The University of Manchester.


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