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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 'impoverishment of those feelings and strivings 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 (3×2) 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 (Craddock & 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

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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 'schizotype' 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 unworldly prophet is then looked after not by adoring acolytes but by psychiatric nurses.

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Selton & Cantor-Graae (2005) proposed that long-term experiences of social defeat may sensitise 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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