Correspondence

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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between unaffected twins from the discordant monozygotic twin pairs and the four control monozygotic twin pairs (unpublished data).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 (twins) patients with schizophrenia compared with healthy (twins) 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 referring to 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 sub-group of offenders with schizophrenia. This sub-group 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 sub-group 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.

**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 11/100 000 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).

In our paper (Helgason et al., 2004) 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 as 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.

**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.

**Fig. 1 Observed suicide rates in Iceland per 100 000 by gender.**
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 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 Robertson 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 ill 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 (Tyrer, 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 recognisable 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

Lancet, 18 February 1905, 445.

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Corrigendum

Retrospective analysis of risk factors in patients with treatment-emergent diabetes during clinical trials of antipsychotic medications. *BJP*, 184 (suppl. 47), s94-s101. 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.
Combating editorial racism
S. Ramaiah
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