Correspondence

EDITED BY KIRIAKOS XENITIDIS and COLIN CAMPBELL

Is *DISC1* really a gene predisposing to psychosis?

In their editorial on chromosomal abnormalities and psychosis Muir *et al* (2006) concluded that *DISC1* 'is an important modulator of risk for schizophrenia and severe affective disorder in people without cytogenetic abnormalities and may also influence cognition and brain structure in the general population'. They base their conclusions on work that originated in the finding of a rearrangement between chromosomes 1 and 11 in a single large family with polymorphic psychiatric syndromes (Millar *et al*, 2001). The two genes (*DISC1* and *DISC2*) that they are concerned with were identified at the breakpoint and by linkage analysis were postulated to be relevant to psychiatric disease within that family.

Muir *et al* argue that these findings are relevant to schizophrenia in general. However, the evidence is less compelling than they suggest. Figure 1 presents the findings of the three largest linkage studies to date in relation to the location of *DISC1* on chromosome 1 (the location of another 'candidate gene' *RGS4* is also shown). Each study included over 300 sibling pairs with schizophrenia or schizoaffective disorder and each included markers spaced at 10 cM intervals across the genome. The Lod (log of the odds) score is a measure of linkage – transmission of a disease state with particular genetic markers within families – and values above 3 are generally taken as significant evidence for linkage. In these three studies there is no evidence of linkage at the *DISC1* locus or elsewhere on chromosome 1. The two claims of linkage made in Table 1 of Muir *et al*'s editorial relate to *post hoc* subdivision of one of these populations by diagnosis and to a finding in a separate smaller Finnish study. Given the ubiquity of psychosis across populations, and the relative uniformity of incidence of the core syndrome, and in the face of lack of evidence of linkage in populations of over 1000 sibling pairs (Crow, 2007), it is difficult to see that *DISC1* can have an 'important role in the development of psychosis' as Muir *et al* argue. The evidence has been overinterpreted.

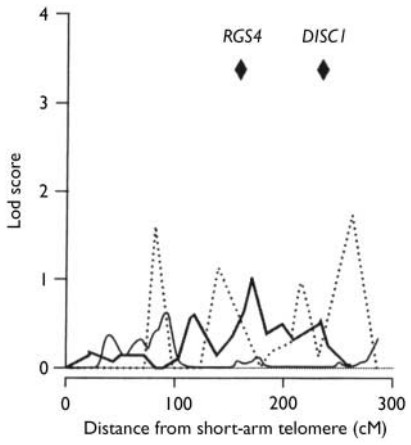

Fig. 1 Linkage studies of *DISC1* in sibling pairs with schizophrenia or schizoaffective disorder. —, DeLisi *et al*, 2002 (382 sibling pairs); ...., Williams *et al*, 2003 (353 sibling pairs); —, Suarez *et al*, 2006 (409 sibling pairs).

Crow, T. J. (2007) How and why genetic linkage has not solved the problem of psychosis: review and hypothesis. *American Journal of Psychiatry*, **164**, 13–21.

DeLisi, L. E., Shaw, S., Crow, T. J., *et al* (2002) A genome-wide scan for linkage to chromosomal regions in 382 sibling pairs with schizophrenia or schizoaffective disorder. *American Journal of Psychiatry*, **159**, 803–812.

Millar, J. K., Christie, S., Anderson, S., *et al* (2001) Genomic structure and location within a linkage hotspot of Disrupted In Schizophrenia 1, a gene disrupted by a translocation segregating with schizophrenia. *Molecular Psychiatry*, **6**, 173–178.

Muir, W. J., Pickard, B. S. & Blackwood, D. H. R. (2006) Chromosomal abnormalities and pscyhosis. *British Journal of Psychiatry*, **188**, 501–503.

Suarez, B. K., Duan, J. B., Sanders, A. R., *et al* (2006) Genomewide linkage scan of 409 European-ancestry and African American families with schizophrenia: suggestive evidence of linkage at 8p23.3-p21.2 and 11p13.1-q14.1 in the combined sample. *American Journal of Human Genetics*, **78**, 315–333.

Williams, N. M., Norton, N., Williams, H., *et al* (2003) A systematic genomewide linkage study in 353 sib pairs with schizophrenia. *American Journal of Human Genetics*, **73**, 1355–1367.

T. J. Crow SANE Prince of Wales Centre, Warneford Hospital, Oxford OX3 7JX, UK. Email: tim.crow@psych.ox.ac.uk

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Authors' reply: Professor Crow takes issue with our view that *DISC1* is important to schizophrenia in general and is not restricted to the initial family in which disruption of this gene was reported. His argument is based on a selected set of sib-pair studies whose results do not support linkage anywhere on chromosome 1. This finding was unsurprising in view of the lack of power of such studies in the presence of genetic heterogeneity in schizophrenia susceptibility, which was not mentioned by Professor Crow. We and a large number of other workers in the field consider that such locus heterogeneity is highly likely and have shown that the sib-pair strategy has limited power to detect a locus that contributes less than 20% of the variance (Macgregor *et al*, 2002). Where heterogeneity is expected then linkage analysis, especially of extended multiplex pedigrees, and gene candidacy identified though the investigation of psychosis-associated karyotype anomalies are appropriate research strategies. Where there is *a priori* evidence from cytogenetic and linkage studies (such as the Finnish studies mentioned in the editorial) then the case–control association approach provides a useful resource to delineate potential population haplotype distortions that may indicate underlying functional mutations.

We would therefore disagree strongly with Crow in his statement that we have 'overinterpreted' the importance of *DISC1* and commend an excellent review of schizophrenia neurobiology which emphasises heterogeneity (Ross *et al*, 2006). Although our theoretical framework differs from that of Bleuler (1950), we feel that the recent genetics and neurological discoveries are in agreement with his position that there is indeed a 'group of schizophrenias'.

Bleuler, E. (1950) *Dementia Praecox or the Group of Schizophrenias* (trans. J. Zinkin). International Universities Press.

Macgregor, S., Visscher, P. M., Knott, S., *et al* (2002) Is schizophrenia linked to chromosome 1q? *Science*, **298**, 2277.

Ross, C. A., Margolis, R. L., Reading, S. A. J., *et al* (2006) Neurobiology of schizophrenia. *Neuron*, **52**, 139–153.

W. J. Muir Division of Psychiatry, University of Edinburgh, Kennedy Tower, Royal Edinburgh Hospital, Morningside Park, Edinburgh EH10 5HF, UK. Email: walter.muir@ed.ac.uk

B. S. Pickard Medical Genetics Section, University of Edinburgh, Edinburgh, UK

D. H. Blackwood Division of Psychiatry, School of Molecular and Clinical Medicine, University of Edinburgh, Edinburgh, UK

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Hippocampal and amygdala volume reductions in first-episode schizophrenia

Steen *et al* (2006) performed a systematic review and meta-analysis of cross-sectional and longitudinal magnetic resonance imaging (MRI) studies of brain volumes in patients with first-episode psychosis and healthy controls. Despite some methodological differences, the findings were in line with a recent meta-analysis performed by our group (Vita *et al*, 2006).

A significant decrease in hippocampal but not amygdala volumes was found in patients at illness onset in both reviews. Another relevant paper reporting amygdala and hippocampal volumes in a large sample of patients with first-episode schizophrenia was published after these two meta-analyses (Velakoulis *et al*, 2006). Thus we considered it worthwhile to conduct a new set of meta-analyses including these MRI data.

The results of the new meta-analyses for hippocampus (7 studies, 290 patients, 355 controls) and amygdala (5 studies, 218 patients, 175 controls) confirmed our previous findings. Even with the inclusion of the study of Velakoulis *et al* (2006), the composite effect sizes for the hippocampus remained significant (d=0.357, 95% CI 0.208–0.541 for the right hippocampus and 0.574, 95% CI 0.405–0.742 for the left hippocampus) whereas those for the amygdala were not (d=−0.046, 95% CI −0.247 to 0.154 for the right amygdala and 0.025, 95% CI −0.175 to 0.226 for the left amygdala).

These results, in line with those of Steen *et al* (2006), support the hypothesis of different patterns of involvement of temporolimbic structures over the course of schizophrenia, with the hippocampus affected earlier than the amygdala. In our opinion, these findings have important implications for future neurobiological studies of schizophrenia and emphasise the importance of longitudinal studies to address the issue of different times of occurrence and progression of brain abnormalities in people with first-episode schizophrenia.

Steen, R. G., Mull, C., McClure, R. M., *et al* (2006) Brain volume in first-episode schizophrenia. Systematic review and meta-analysis of magnetic resonance imaging studies. *British Journal of Psychiatry*, **188**, 510–518.

Velakoulis, D., Wood, S. J., Wong, M. T., *et al* (2006) Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. *Archives of General Psychiatry*, **63**, 139–149.

Vita, A., De Peri, L., Silenzi, C., *et al* (2006) Brain morphology in first-episode schizophrenia. A meta-analysis of quantitative magnetic resonance imaging studies. *Schizophrenia Research*, **82**, 75–88.

A. Vita Psychiatric Unit, University of Brescia, Brescia, Italy

L. de Peri University of Milan, Via Francesco Sforza n. 35, Milan 20122, Italy. Email: luca_de_peri@libero.it

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Effectiveness of cognitive–behavioural intervention by mental health nurses in schizophrenia

Turkington *et al* (2006) report on outcomes of an effectiveness trial of brief cognitive–behavioural therapy (CBT) by mental health nurses in schizophrenia. Unfortunately there are flaws in the methodology, which casts major doubts on the validity of the study (Quitkin *et al*, 2000). First, although the authors claim to have a control group, it seems that patients in the control group did not have a placebo-like intervention; for example, the nurses could have spent the same amount of time with the patients without providing the CBT intervention. What is more surprising is that the study was powered to give a 90% chance of detecting only a 25% level difference in overall symptoms at the 0.01 level of significance. A 25% difference between a treatment and non-intervention group can easily be accounted for by a placebo effect. It is well known that the placebo response rate is usually around 30% in psychiatric trials. For over 50 years the inclusion of a placebo control group has been the standard for determining the efficacy of an intervention. Without an adequate comparison group and without adequate comparison conditions, it is impossible to differentiate any specific effects from other 'non-specific' factors, including chance variation, regression to the mean, healthcare provider attention, treatment credibility and rationale, persuasion, patient expectancy effects, researcher allegiance effects, effort justification, spontaneous remission, demand characteristics, etc. (Lohr *et al*, 1999).

Given the lack of a true control group this study would be called nothing but an open-label trial. Open-label trials require at least a 50% level difference in overall symptoms between baseline and post-intervention response; moreover they do not require huge numbers of patients to show a tendency towards improvement.

Lohr, J. M., Lilienfeld, S. O., Tolin, D. R., *et al* (1999) Eye movement desensitization and reprocessing: an analysis of specific versus nonspecific treatment factors. *Journal of Anxiety Disorders*, **13**, 185–207.

Quitkin, F. M., Rabkin, J. G., Gerald, J., *et al* (2000) Validity of clinical trials of antidepressants. *American Journal of Psychiatry*, **157**, 327–337.

Turkington, D., Kingdon, D., Rathod, S., *et al* (2006) Outcomes of an effectiveness trial of cognitive–behavioural intervention by mental health nurses in schizophrenia. *British Journal of Psychiatry*, **189**, 36–40.

F. Alam Avondale Unit, Royal Preston Hospital, Sharoe Green Lane, Preston PR2 9HT, UK. Email: docftalam@aol.com

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Authors' reply: We believe that Dr Alam has misunderstood the difference between efficacy and effectiveness research. The national guidelines on the clinical management of schizophrenia (National Institute for Clinical Excellence, 2002) confirmed CBT to be an evidence-based treatment for persistent symptoms of schizophrenia. However, that decision was based almost entirely on efficacy trials where CBT was given by expert therapists to highly selected samples of people with schizophrenia without comorbidities and using an active comparator such as befriending or supportive counselling (e.g. Sensky *et al*, 2000). Expert therapists and uncomplicated patients are