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The British Journal of Psychiatry 1992 161: 680-685
Access the most recent version at doi:10.1192/bjp.161.5.680

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British Journal of Psychiatry (1992), 161, 680–685

Psychotic Illness in Multiple Sclerosis
A Clinical and Magnetic Resonance Imaging Study

ANTHONY FEINSTEIN, GEORGE du BOULAY and MARIA A. RON

Ten patients with multiple sclerosis (MS) and psychosis were assessed using the Present State Examination, and matched retrospectively with respect to age, disability, duration of symptoms, and disease type with 10 MS patients without psychosis. Both groups underwent MRI of the brain. There was a trend for the psychotic group to have a higher total lesion score, particularly around the periventricular areas. This reached statistical significance in the areas around the temporal horn. In all cases, neurological symptoms preceded the onset of psychosis. The psychotic group also had a later age of onset of psychosis than psychotic patients without brain disease. These results point to an aetiological association between the pathological process of MS and psychosis.

The presence of psychiatric symptoms as part of the clinical picture of multiple sclerosis (MS) has long been recognised. The commonest symptoms reported are those of depressive mood states with psychotic disorders featuring far less frequently. However, the possibility that psychoses occurring in the presence of demonstrable brain disease may throw light on the causation of schizophrenia and manic–depressive disease makes this association particularly interesting (Feinstein & Ron, 1990).

Syndromes resembling schizophrenia in association with MS have been reported in the literature, but appear to be rare (Davison & Bagley, 1969; Mathews, 1979; Awad, 1983). A similar conclusion can be drawn from Johnstone *et al*'s (1987) study of 268 consecutive, first-admission schizophrenic patients investigated for physical disease, none of whom had MS. However, similarities between the course of the two conditions and certain common epidemiological features such as age of onset, unimodal age distribution and geographical clustering led Stevens (1988) to postulate that the two may share an infectious or immunological cause. In a series of 39 published cases collected by Davison & Bagley (1969) both conditions had started simultaneously in a third of cases, while in a further 25% the psychosis began within two years either side of the onset of the neurological symptoms and this temporal link was interpreted as signalling an aetiological connection. More recent studies of psychiatric morbidity in MS (Ron & Logsdail, 1989), while reporting that onset of neurological symptoms came first in most cases, suggested that psychotic symptoms may have been associated with the presence of temporal lobe pathology.

Major depression is, by contrast, common in MS, being reported in a quarter to a half of patients (Minden & Schiffer, 1990), and the frequency of bipolar affective disorder appears to be greater than that in the general population (Schiffer *et al*, 1986; Joffe *et al*, 1987). However, it is unclear how often psychotic symptoms are an integral part of this picture.

We report here a group of MS patients who experienced psychotic symptoms during their neurological illness. The aim of the report is firstly, to analyse the presentation, course and symptoms of these patients and secondly, to attempt a clinico-pathological correlation by studying the size and location of brain lesions detected by magnetic resonance imaging (MRI) in comparison with a matched group of non-psychotic MS patients. It is thereby hoped to clarify the association between MS and psychotic disorders.

Method

A total of 10 patients with definite MS who had experienced psychotic symptoms and had MRI scans had been referred to the psychiatric department of the National Hospital for Neurology and Neurosurgery over the past six years; these constituted the study group. The criteria of Poser *et al* (1983) were used to define clinically definite MS, while the term psychosis implied the presence of delusions and/or hallucinations in the absence of dementia or delirium. This allowed the inclusion of patients with both schizophrenia and affective psychosis. Levels of physical disability were rated from case notes using the Expanded Disability Status Scale (EDSS; Kurtzke, 1983). Nine of these patients had been encountered in the course of two other studies looking at psychiatric morbidity in MS (Ron & Logsdail, 1989) and psychosis in patients with demonstrable brain disease (Feinstein & Ron, 1990), and a further patient not previously reported has also been included.

A control group of MS patients who had not experienced a psychotic illness was used for comparison. Attempts were made to match each subject individually with a control in terms of age (±5 years), sex, EDSS (±1.0) and duration of MS (±3 years). In one case the age matching was seven years apart and in another the difference in duration of

illness was six years. Controls were drawn from a large group of patients taking part in a study of MRI abnormalities in MS at the same hospital. Although cognitive assessment was not part of this study, no gross cognitive impairment had been clinically observed in any of the psychotic group, and it had been noted in only one of the control subjects.

In the psychotic group, mental state was assessed retrospectively using a symptom check-list (SCL) derived from the Present State Examination (Wing *et al*, 1974). From the SCL computerised CATEGO, subclasses, classes, and diagnoses were generated. Of these, the subclasses were preferred as they give the most information concerning the phenomenology of the disorder, e.g. 'nuclear schizophrenia' implying the presence of Schneiderian first-rank symptoms.

Subjects and controls underwent contiguous, multislice axial MRI of the brain (Picker superconducting system) using a group standard transverse imaging plane (MacManus *et al*, 1989). All scanning protocols included T_2 weighted images that optimised lesion detection. Thus a spin echo $(SE)_{2000/60}$ was used with a field of view of 30 cm. The number of excitations was 2, the matrix 128×256 pixels and the phase-encoding gradient horizontal. Patients and controls had been scanned over a period of six years, during which time changes to the MRI scanner and software upgrades ensured that better images were obtained. Thus, soon after installation the strength of the magnet was increased from 0.25 to 0.5 tesla, and slice thickness reduced from 10 mm to 5 mm. Despite these changes, the imaging protocols and slice thickness were the same in all patient and control groups. It was not, however, possible in one case to match the images for strength of magnetic field. The EDSS and MRI were performed when the patients were psychotic in eight cases. In the remaining two cases, MRI was undertaken one and three years after the psychotic episode with a normal mental state at the time.

Subjects were compared with controls with respect to site and extent of lesions. MRI analysis was undertaken by a neuroradiologist (G du B) blind to psychiatric diagnosis. In assessing the MRI, a system used in previous studies at the National Hospital (Ormerod *et al*, 1987) was followed. The size and presence of lesions were recorded in the following periventricular areas: body of the ventricles; frontal, temporal and occipital horns; trigone; and third and fourth ventricle. These seven areas provided a periventricular score. A further eight areas of brain parenchyma were also examined, namely internal capsule; basal ganglia; frontal, parietal, temporal and occipital lobes; brain stem; and cerebellum. The lobes of the cerebrum were defined as including not only cortex, but also underlying white matter. Planes separating lobes are projected from their cortical boundaries to the foramen of Munro or the lateral ventricular trigone, as appropriate. The largest lesion in each particular area was scored using a four-point scale (0–3) according to the greatest diameter measured (0 = 1 mm, 1 = 2–5mm, 2 = 6–10 mm, 3 = > 10 mm). A total lesion score was obtained by adding scores from all areas assessed. The percentage of the total lesion score in each particular area was obtained by dividing the score for each area by the total lesion score and multiplying by 100. This was termed the 'percentage score'.

Data were analysed using the Statistical Package for the Social Sciences (SPSS; Norusis, 1989). Non-parametric statistics were used because of the ordinal system of rating the MR images. Comparisons between patient and control groups with respect to total lesion score were undertaken using *t*-tests.

Results

Despite the demographic differences between two of the patients and their controls, the overall group matching was very close (Table 1). The psychotic group was equally divided into either relapsing-remitting (RR) or chronic-progressive (CP) MS while the control groups had 6 CP and 4 RR patients. Eight patients from each group had been treated with steroids since the onset of MS, but in only a single subject had steroids been given before the onset of psychosis.

Table 1
Demographic characteristics of MS patients with and without psychosis (mean (s.d.) where applicable)

	Psychotic group ($n = 10$)	Control group ($n = 10$)
Age: years	39.6 (10.8)	37.9 (8.9)
Sex	5M : 5F	5M : 5F
Duration: years	10.0 (7.1)	10.6 (4.2)
EDSS	4.9 (2.3)	4.6 (2.1)

Psychiatric features

The mean age of onset of psychosis was 36.6 years (range 26–52). Using the SCL four subjects obtained a CATEGO subclass of mania, two of nuclear schizophrenia, two of schizoaffective psychoses and one each of paranoid disorder and psychotic depression. The schizoaffective and paranoid patients were incorporated into the schizophrenic rubric which assumes primacy in a hierarchical classification system. Thus two broad categories of schizophrenia and affective psychosis each with five subjects were obtained. There were no differences between the schizophrenic and affective subgroups with respect to any demographic variables, duration of MS symptoms or age of onset of the psychosis. They did however differ in physical disability – the affective subgroup had a significantly higher EDSS (means 6.4 v. 3.5, $Z = 2.1$, $P < 0.04$).

The mean duration of neurological symptoms before the onset of psychosis was 8.5 years (range 0–19). In all cases neurological symptoms preceded psychosis, but in one case the diagnosis of MS was made at the time of the onset of psychosis. Steroids were possibly implicated in the aetiology of one manic episode. Six patients were neurologically stable at the time of the psychosis while four were in exacerbation.

A breakdown of the frequency of individual psychotic symptoms is shown in Table 2. The commonest were persecutory delusions (70%) followed by less well defined symptoms designated by the PSE as 'non-specific evidence of psychosis' (60%). This included heightened or changed perception, 'minor' hallucinations (music, voices calling a

Table 2
Commonest symptoms and signs (PSE) in the psychotic group ($n = 10$)

Symptom	%
Lack of insight	100
Persecutory delusions	70
Non-specific evidence of psychosis	60
Irritability	60
Agitation	50
Anxiety	40
Sexual delusions	30
Passivity phenomena	30
Delusions of reference	20
Grandiose delusions	20
Second-person auditory hallucinations	20
Visual hallucinations	20
Thought disorder	20
Third-person auditory hallucinations	10
Thought broadcast	10

Table 3
Mean (s.d.) MRI lesion scores in psychotic and control patients

	Psychotic patients	Control patients
Total lesion score	32.6 (13.6)	27.4 (13.8)
Periventricular score	19.3 (8.1)	14.0 (6.6)
Temporal (bilateral)	8.6 (4.3)	6.9 (4.4)
Temperoparietal (bilateral)	12.1 (6.2)	9.4 (5.6)
Temporal horn R	1.8 (0.9)	1.0 (0.8)
Temporal horn L	1.7 (0.8)	1.0 (0.8)
Trigone R	2.2 (1.2)	1.7 (0.8)
Trigone L	2.3 (0.9)	1.5 (0.9)
IIIrd ventricle	0.7 (0.5)	0.3 (0.5)
Temporal lobe R	0.2 (0.6)	0.6 (0.9)
Temporal lobe L	0.4 (0.8)	1.1 (1.5)
Temporal horn + trigone R	4.0 (2.1)	2.7 (1.6)
Temporal horn + trigone L	4.0 (1.6)	2.5 (1.4)

No differences were found for frontal lobes/horns, occipital lobes/horns, parietal lobes, internal capsule, basal ganglia, IVth ventricle, and cerebellum.

name), suspicion, perplexity, etc. Passivity phenomena and sexual/fantastic delusions were experienced by 30%, while 20% had thought disorder, second-person auditory hallucinations, delusions of reference or grandiose delusions. All psychotic patients showed lack of insight.

Six of the ten psychotic patients had only one episode of psychosis, while three had two episodes and one had three. The median duration of psychosis was five weeks (range 1 to 72 weeks). Eight of these patients required psychiatric in-patient treatment and the remaining two were treated as out-patients. Neuroleptic medication was used in eight subjects. In nine patients the psychosis remitted, but in one, a chronic, paranoid course ensued.

Two of the psychotic group had a positive psychiatric history before the onset of neurological symptoms, diagnosed as a phobic and antisocial personality disorder respectively, while one control had been treated for a premorbid major depressive illness. Two control subjects had been treated for depressive disorders following the onset of demyelination. A positive family history was present in one subject with a depressive psychosis and another with 'nuclear schizophrenia' who both had a relative with a major depressive disorder. It was not possible to obtain this information from the case notes of the controls.

MRI abnormalities

Comparisons between the MRI scans of the psychotic and control groups are shown in Table 3. The psychotic group had a greater total lesion and a total periventricular lesion score, but these were not statistically significant. Trends emerged for a higher lesion score in the psychotic group in the areas surrounding the temporal horns bilaterally ($P<0.06$ (right), $P<0.07$ (left)). A similar result was also obtained in the left trigone ($P<0.07$) and area surrounding the third ventricle ($P<0.08$). Combining the left temporal horn and adjacent left trigone area scores gave a statistically significant difference between the psychotic and control groups ($P<0.04$).

A clearer picture of the difference in distribution of lesion scores between the psychotic and control MS patients is demonstrated by observing what percentage of the total lesion score was present in each particular area. In the controls, the total lesion score was distributed equally between periventricular and other brain areas while in the psychotic patients the periventricular lesion score contributed more than 60% to the total lesion score. This difference was not, however, statistically significant. The most marked differences were present around the temporal horns where the 'percentage score' in the psychotic patients was almost double that of the control group (Fig. 1). Thus, not only did the psychotic patients have a greater lesion score but lesions were differentially distributed in periventricular areas and in particular around the temporal horns of the lateral ventricles.

The various brain areas were also analysed to determine whether the presence or absence of lesions, rather than their size, was the crucial factor, but no differences were found between the two groups.

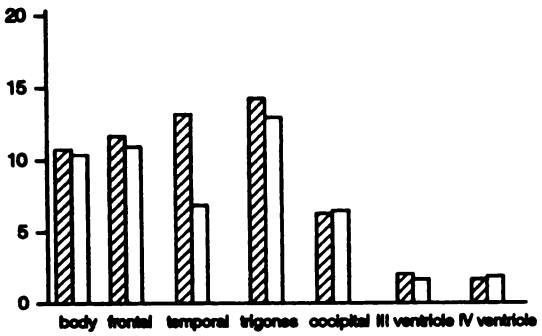

Fig. 1 Percentage lesion score distribution in periventricular areas for patients (▨) and controls (□).

There were no differences between the schizophrenic and affective psychosis subgroups in relation to any of the MRI parameters examined. In the psychotic group, lesion scores between the right and left hemispheres did not differ significantly. In addition, there were no significant correlations between individual psychotic symptoms and site of MRI lesions.

Discussion

The results from a MRI study comparing 10 psychotic MS patients with 10 matched controls with a normal mental state are reported. While there have been other MRI studies of psychiatric abnormalities in MS, this is the first report of a sample comprising only psychotic patients. There was a trend for the psychotic group to have a higher total lesion score which was due to higher scores in periventricular areas, in particular around the temporal horns of the lateral ventricles. The presence or absence of lesions in a particular site was not sufficient to discriminate between patient and control groups, and lesion score was the critical variable in this regard.

Some limitations of MRI need to be considered in interpreting these results. The anterior parts of the temporal lobes are more subject to artefact on MR images, namely carotid artery and pulsation of cerebrospinal fluid, than other regions of the cerebrum. Although no motion-suppression MR sequences were employed, the greatest care was exercised in distinguishing lesion from artefact and the blinded observation of subjects and controls throughout should be reassuring. The frequency of artefact in the temporal lobe region could also be influenced by more generalised factors such as arterial pulse pressure (du Boulay *et al*, 1972), the dimensions of the cerebral sulci, and by the mechanical compliance of the brain tissue, all of which might differ from normal in schizophrenia without multiple sclerosis. Theoretically, this could help explain our findings if the coincidence of psychosis and multiple sclerosis in our patients was by chance and not causally related. The observer (G du B) was, however, aware of these difficulties and exercised special care in excluding from the lesion count in the temporal region all abnormal signals that it seemed possible to interpret as artefacts.

The frequency of persecutory delusions and relative preservation of affective responses in our sample confirms these features as the hallmark of psychosis associated with coarse evidence of brain disease (Slater & Bard, 1963; Davison & Bagley, 1969; Feinstein & Ron, 1990). However, there was also a broad degree of symptom overlap between our sample and those patients reported in the International Pilot Study of Schizophrenia (World Health Organization, 1973) thus emphasising that on an individual basis patients with and without coarse brain disease are indistinguishable. Phenomenological reports of mania (Peselow *et al*, 1981), rapidly cycling bipolar disorder (Kellner *et al*, 1984), paranoid psychosis (Drake, 1984) and schizophrenia (Schmalzbach, 1954; Parker, 1956) in association with MS confirm this.

The late age of onset of psychosis in our sample contrasts with the findings of studies of patients without brain disease. Thus, the World Health Organization's (1973) study of schizophrenia reported a mean age of onset of 28 years as opposed to 36 years in our sample and Winokur *et al* (1969) reported a median of 25 years for the onset of mania. This age difference argues in favour of a specific causal link between the presence of MS pathology and psychosis, which could not be explained as a result of steroid therapy in nine of our patients.

It is notoriously difficult to determine the precise onset of demyelination and that may obscure the relationship between duration of neurological symptoms and onset of psychosis. Moreover, MRI has shown the frequency of widespread 'silent' lesions of unknown age at the time of the first clinical manifestation and the association between size of lesions and clinical status is often poor (Thompson *et al*, 1990). Our finding of psychosis occurring after MS symptoms had been present, often for many years, may have been subject to a referral bias as the sample was selected from a neurological hospital. Nevertheless, it is likely that this pattern is the rule as no MS cases were detected among first-episode schizophrenic patients studied by Johnstone *et al* (1987). Discrepancies with Davison & Bagley's (1969) data may be due to shortcomings of their series which was made up of heterogeneous, published case reports. Our finding, together with the late onset of psychosis, argues for the role of long-standing as well as strategically placed MS lesions in the pathogenesis of psychosis.

What evidence exists regarding the relationship between MRI and psychiatric abnormalities in MS tends to support our findings of an association between psychosis and temporal, periventricular pathology. Thus, Reischies *et al* (1988) have reported a relationship between periventricular involvement and psychopathology although it is unclear what percentage of their patients were psychotic. In a study that comes closest to our own, Honer *et al* (1987) undertook MRI comparisons between eight MS patients with and without psychiatric disorders, matched across relevant parameters, three of whom were psychotic. No differences were found with respect to total lesion area, although the psychiatric group had a greater lesion area in the temporal lobes.

The importance of temporal lobe pathology in schizophrenia has been demonstrated in a number of studies. Crow *et al* (1989) found enlargement in the left temporal horn at post-mortem while MRI evidence of reduction in temporal lobe (Suddath *et al*, 1989) and in particular hippocampal volume (Suddath *et al*, 1990) is the most sensitive *in-vivo* evidence to date implicating these areas. Similar findings in patients with schizophrenia secondary to brain disease have been reported by some (Slater & Beard, 1963; Davison & Bagley, 1969), although our earlier study (Feinstein & Ron, 1990), which included heterogeneous pathologies, failed to do so. In the present study, however, the uniformity of the sample allowed us to draw more specific conclusions about clinico-pathological correlates.

The fact that only ten cases were available for study over a six-year period in a tertiary setting illustrates the rarity of psychosis in MS. A possible explanation may be that although periventricular pathology is important in the pathogenesis of psychosis, it is an age-linked phenomenon and related to brain development – hence the recognition of perinatal complications affecting similar anatomical areas as a significant risk factor in schizophrenia (Reveley *et al*, 1982).

The situation concerning anatomical correlates of affective psychosis has not been researched so thoroughly. Results from computerised tomography studies are equivocal and only a single MRI study has focused on structural brain abnormalities of patients with bipolar affective disorders (Swayze *et al*, 1990). Here, ventricular enlargement was less than in schizophrenic patients and confined to males. Our results point to pathological changes in temporal periventricular areas as a non-specific marker for psychosis and suggest that in these patients other factors may be relevant in determining the type of psychosis. The fact that our affective patients were significantly more disabled than their schizophrenic counterparts despite similar brain involvement on MRI, suggests that greater physical disability, caused by spinal cord involvement and independent of brain pathology, may have acted as an important aetiological factor in this group.

As in previous reports (Honer *et al*, 1987) we failed to find a laterality effect in association with a schizophrenic or affective psychosis. This may have been due to the use of the CATEGO classification which includes all patients with first-rank symptoms under a 'nuclear schizophrenia' grouping, even if up to 20% of manic patients may exhibit these symptoms (Carpenter *et al*, 1973). However, the lack of correlation between lesion side and individual psychotic symptoms argues against this. MRI evidence of a generalised brain abnormality in schizophrenia (Harvey *et al*, 1992) could also explain our failure to find a laterality effect.

The homogeneous composition of our sample suggests the hypothesis that psychosis in MS is not a chance occurrence, but rather a consequence of the disease process. Future research may be advanced by the use of functional imaging which could reveal the final path linking structural brain abnormalities with psychosis.

Acknowledgements

Dr Feinstein is supported by a grant from the Wellcome Trust. The authors thank the Multiple Sclerosis Society of Great Britain and Northern Ireland for access to the MRI scan, Mr Dave MacManus for help with the MR images and Dr Alan Thompson for assistance in matching patients with controls and supplying Kurtzke ratings.

References

AWAD, A. G. (1983) Schizophrenia and multiple sclerosis. *Journal of Nervous and Mental Disease*, **171**, 323–324.

CARPENTER, W. T., STRAUSS, J. S. & MULEH, S. (1973) Are there pathognomonic symptoms of schizophrenia? An empiric investigation of Schneider's first rank symptoms. *Archives of General Psychiatry*, **28**, 847–852.

CROW, T. J., BALL, J., BLOOM, S. R., *et al* (1989) Schizophrenia as an anomaly of development of cerebral asymmetry: a postmortem study and a proposal concerning the genetic basis of the disease. *Archives of General Psychiatry*, **46**, 1145–1150.

DAVISON, K. & BAGLEY, C. R. (1969) Schizophrenia-like psychoses associated with organic disorder of the central nervous system: a review of the literature. In *Current Problems in Neuropsychiatry* (ed. R. N. Harrington), pp. 113–184. Ashford, Kent: Headley.

DRAKE, M. E. (1984) Acute paranoid psychosis in multiple sclerosis. *Psychosomatics*, **25**, 60–65.

DU BOULAY, G. H., O'CONNELL, J. E. A., CURRIE, J., *et al* (1972) Further investigations on pulsatile movements in the cerebrospinal fluid pathways. *Acta Radiologica (Diagnosis)*, **13**, 496–523.

FEINSTEIN, A. & RON, M. A. (1990) Psychosis associated with demonstrable brain disease. *Psychological Medicine*, **20**, 793–803.

HARVEY, I., DU BOULAY, G. E., WICKS, D., *et al* (1992) Reduction in cortical volume in schizophrenia on magnetic resonance imaging (in press).

HONER, W. G., HURWITZ, T., LI, D. K. B., *et al* (1987) Temporal lobe involvement in multiple sclerosis patients with psychiatric disorders. *Archives of Neurology*, **44**, 187–190.

JOFFE, R. T., LIPPERT, G. P., GRAY, T. A., *et al* (1987) Mood disorder and multiple sclerosis. *Archives of Neurology*, **44**, 376–378.

JOHNSTONE, E. C., MACMILLAN, J. F. & CROW, T. J. (1987) The occurrence of organic disease of possible aetiological significance in a population of 268 cases of first episode schizophrenia. *Psychological Medicine*, **17**, 371–379.

KELLNER, C. H., DAVENPORT, Y., POST, R. M., *et al* (1984) Rapidly cycling bipolar disorder and multiple sclerosis. *American Journal of Psychiatry*, **141**, 112–113.

KURTZKE, J. F. (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status (EDSS). *Neurology (Cleveland)*, **33**, 1444–1452.

MACMANUS, D. G., KERMODE, A. G. & TOFTS, P. S. (1989) A repositioning technique for cerebral magnetic imaging of patients with multiple sclerosis. In *Book of Abstracts, Society of Magnetic Resonance Imaging in Medicine*, **2**, 617 (abstract). Berkeley, CA: Society of Magnetic Resonance Imaging in Medicine.

MATHEWS, W. B. (1979) Multiple sclerosis presenting with acute, remitting psychiatric symptoms. *Journal of Neurology, Neurosurgery and Psychiatry*, **42**, 859–863.

MINDEN, S. L. & SCHIFFER, R. B. (1990) Affective disorders in multiple sclerosis. *Archives of Neurology*, **47**, 98–104.

NORUSIS, M. J. (1989) *SPSS/PC+ TM for the IBM PC/XT/AT*. SPSS: Chicago.

ORMEROD, I. E. C., MILLER, D. H., MCDONALD, W. I., *et al* (1987) The role of NMR imaging in the assessment of multiple sclerosis and isolated neurological lesions. *Brain*, **110**, 1579–1616.

PARKER, N. (1956) Disseminated sclerosis presenting as schizophrenia. *Medical Journal of Australia*, **1**, 405–407.

PESELOW, E. D., DEUTSCH, S. I., FIEVE, R. R., *et al* (1981) Coexistent manic symptoms and multiple sclerosis. *Psychosomatics*, **22**, 824–825.

POSER, C. M., PATY, D. W., SCHEINBERG, L., *et al* (1983) New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology*, **13**, 227–231.

REISCHIES, F. M., BAUM, K., BRAU, H., *et al* (1988) Cerebral magnetic resonance imaging findings in multiple sclerosis. Relation to disturbance of affect, drive and cognition. *Archives of Neurology*, **45**, 1114–1116.

REVELEY, A. M., REVELEY, M. A., CLIFFORD, C. A., *et al* (1982) Cerebral ventricular size in twins discordant for schizophrenia. *Lancet*, *i*, 540–541.

RON, M. A. & LOGSDAIL, S. J. (1989) Psychiatric morbidity in multiple sclerosis: a clinical and MRI study. *Psychological Medicine*, **19**, 887–895.

SCHIFFER, R. B., WINEMAN, N. M. & WEITKAMP, L. R. (1986) Association between bipolar affective disorder and multiple sclerosis. *American Journal of Psychiatry*, **143**, 94–95.

SCHMALZBACH, O. (1954) Disseminated sclerosis in schizophrenia. *Medical Journal of Australia*, **1**, 451–452.

SLATER, E. & BEARD, A. W. (1963) The schizophrenia-like psychoses of epilepsy. *British Journal of Psychiatry*, **109**, 95–150.

STEVENS, J. R. (1988) Schizophrenia and multiple sclerosis. *Schizophrenia Bulletin*, **14**, 231–241.

SUDDATH, R. L., CASANOVA, M. F., GOLDBERG, T. E., *et al* (1989) Temporal lobe pathology in schizophrenia: a quantitative magnetic resonance imaging study. *American Journal of Psychiatry*, **146**, 464–472.

———, CHRISTISON, G. W., TORREY, E. F., *et al* (1990) Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *New England Journal of Medicine*, **322**, 789–794.

SWAYZE II, V. W., ANDREASEN, N. C., ALLIGER, R. J., *et al* (1990) Structural brain abnormalities in bipolar affective disorder: ventricular enlargement and focal signal hyperintensities. *Archives of General Psychiatry*, **47**, 1054–1059.

THOMPSON, A. J., KERMODE, A. G., MACMANUS, D. G., *et al* (1990) Patterns of disease activity in multiple sclerosis: clinical and magnetic resonance imaging study. *British Medical Journal*, **300**, 631–634.

WING, J. K., COOPER, J. E. & SARTORIUS, N. (1974) *The Measurement and Classification of Psychiatric Symptoms. An Instruction Manual for the Present State Examination and CATEGO Program*. Cambridge: Cambridge University Press.

WINOKUR, G. W., CLAYTON, P. J. & REICH, T. (1969) *Manic Depressive Illness*. St Louis: C.V. Mosby Co.

WORLD HEALTH ORGANIZATION (1973) *The International Pilot Study of Schizophrenia*. Geneva: WHO.

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