

EDITORIAL

The neurodevelopmental basis of sex differences in schizophrenia¹

Male schizophrenics tend to manifest a severe form of the disease, characterized by early onset, poor pre-morbid adjustment, 'typical' and 'negative' symptoms, and poor outcome; they are more likely than their female counterparts to have a history of pre- or peri-natal complications, and to exhibit structural brain abnormalities. The most plausible explanation for these differences is that more male than female schizophrenics have a form of disease due to neurodevelopmental anomaly. This hypothesis also accounts for the excess of males in strictly defined schizophrenic cohorts, and in those who present before 30 years of age. In contrast, many later-onset females diagnosed 'schizophrenic' have more in common, aetiologically, with affective psychosis than schizophrenia. Thus, much of the contemporary confusion about schizophrenia results from the conflation of two separate disorders, one commonest in young males and the other in older females.

There have been many reports in the literature of differences in the characteristic of schizophrenia in males and females. The explanatory hypotheses proposed have mainly been in terms of the different social roles of men and women, though some authors have suggested that antidopaminergic properties of oestrogens may be 'protective' in females. This editorial argues that a neurodevelopmental perspective has greater explanatory power for the male–female differences in schizophrenia.

GENDER DIFFERENCES

Epidemiology

The best replicated gender difference in schizophrenia is the tendency for males to manifest the disease at an earlier age (Lewine, 1981, 1988; Angermeyer & Kuhn, 1988). This finding is robust to the diagnostic system used (Lewine *et al.* 1981; Shimizu *et al.* 1988*a*; Goldstein *et al.* 1989). Furthermore, it is not a result of differences in help-seeking behaviour between male and female schizophrenics or their families, or a consequence of differences in social role-expectation or marital status (Loranger, 1984; Angermeyer, 1985; Lewine, 1988; Riecher *et al.* 1989; Häfner *et al.* 1989).

Loranger (1984) has pointed out that the age distribution curves for schizophrenia are not isomorphic, and that some female patients manifest the disease in adolescence; thus the appearance of the disease is delayed in 'some but not all women'. This is represented in Fig. 1, which shows first admission rates for schizophrenia by sex, for England in 1984. It has usually been accepted that the greater number of late-onset females eventually 'balance out' the early males excess (e.g. Rosenthal, 1970; Dohrenwend & Dohrenwend, 1976; Flor-Henry, 1985; Häfner, 1987). However, some recent data suggest that the overall sex incidence may not be equal. For example, in England the overall first admission rate for schizophrenia (ICD code 295) for 1984 was 6.6 per 100 000 for males, and only 5.1 per 100 000 for females (Government Statistical Office, 1986). Higher rates in males have also been reported by Strömberg (1987) and Häfner *et al.* (1989) in Denmark, Babigian (1975) in the USA, and in most centres participating in the WHO collaborative study (Sartorius *et al.* 1986). Furthermore, the application of stringent diagnostic criteria to cohorts of schizophrenics results in an even greater male preponderance (Lewine *et al.* 1984; Katschnig & Lenz, 1988). This has also been shown in population-based studies. For example, Cooper *et al.* (1987) reported an annual incidence of DSM-III defined schizophrenia in Nottingham of 7 per 100 000 for women, but 17 per 100 000 for men. In Montreal, Nicole *et al.* (1990) reported an annual incidence of DSM-III-R

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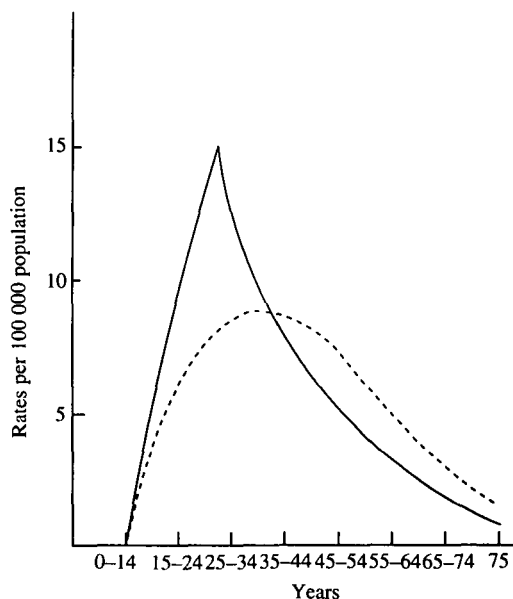


FIG. 1. First admission rates for schizophrenia by sex, for England, 1984 (source: *Statistical Bulletin of Department of Health and Social Security, Government Statistical Office, 1986*). (—, Males; ---, females.)

schizophrenia of 2.5 per 100 000 for women and 6.9 per 100 000 for men; the low rates in this study may be due to calculations being based only on patients admitted to hospital.

Pre-morbid characteristics

Many studies have suggested that schizophrenic males exhibit poorer pre-morbid social competence than do females (see Zigler & Levine, 1973; Zigler *et al.* 1977; Klorman *et al.* 1977; Lewine, 1981). Offord & Cross (1969) reviewed such studies and concluded that there was a correlation between 'disturbed' behaviour in childhood and early illness-onset; there was also an association between the latter and minimal brain dysfunction. The evidence from child guidance clinics is that attenders who go on to develop schizophrenia are mostly male, and show a mixture of antisocial and emotional problems in childhood (Garnezy, 1974; Zeitlin, 1986). Males are also over-represented among cohorts of 'schizoid' children (Wolff & Chick, 1980), such children being considered prone to the later development of schizophrenia (see Gunderson & Siever, 1985; Kendler, 1985).

Few studies have included a control group. However, Foerster *et al.* (1991a) compared schizophrenics and affective psychotics, and found that male schizophrenics had exhibited more abnormalities of pre-morbid personality and poorer pre-morbid social adjustment than female schizophrenics and both male and female affective psychotic patients. Importantly, this held true even in early childhood, a finding which precludes the possible confounding effect of earlier onset of psychosis in males.

Similar sex differences have been reported in pre-morbid IQ. Thus, Offord (1974) reported low pre-morbid IQ and poor school performance among male, but not female, schizophrenics. Aylward *et al.* (1984) reviewed the literature and concluded: 'Pre-morbid IQ deficit may be an exclusive, or more pronounced characteristic of schizophrenic males'. This gender difference in pre-morbid IQ was also found in a study of offspring of schizophrenic mothers (Rieder *et al.* 1977); 'soft' neurological signs (clumsiness, incoordination) and hyperactivity were also more prevalent among males in this 'at risk' group (Rieder & Nichols, 1979).

Presentation and outcome

Male schizophrenics are more likely to exhibit 'typical' schizophrenic symptomatology, with a tendency to withdrawal and passivity, while females more often manifest 'atypical' features, including a strong affective component (see Lewine, 1981; Goldstein & Link, 1988). Furthermore, a number of studies have found males more likely to exhibit 'negative' features (Kay *et al.* 1986; Goldstein & Link, 1988; Nasrallah & Wilcox, 1989; Haas *et al.* 1989), though not all have concurred (reviewed by Pogue-Geile & Zubin, 1988).

Few studies have specifically addressed gender differences in neuroleptic response in schizophrenics. However, female schizophrenics appear generally to respond more favourably to neuroleptic medication than do their male counterparts (Goldberg *et al.* 1966; Hogarty *et al.* 1974; Goldstein *et al.* 1978; and reviewed by Seeman, 1986); they also require lower doses of neuroleptics, at least prior to the menopause (Seeman, 1983, 1986).

Angermeyer *et al.* (1989) reviewed 50 studies reporting on gender and hospital treatment of schizophrenics. These studies differed widely in methodology and thus direct comparison was difficult, and findings inconsistent. A number of the studies reported no gender differences in hospital treatment. However, in almost all those studies which did report gender differences, women fared better in terms of rate of rehospitalization, number of admissions, and length of hospital stay. In their own careful study, Angermeyer *et al.* (1989) confirmed these impressions.

Seeman (1986), who reviewed the early-1980s literature concerning gender differences in social outcome of schizophrenics, again encountered difficulties in comparing studies which had employed varying methodology and different diagnostic criteria for schizophrenia. However, she concluded that overall 'schizophrenic women live better than schizophrenic men'. A number of more recent studies (e.g. Shepherd *et al.* 1989; Goldstein *et al.* 1989) concur.

Summary

It is clear that males are prone to a more severe form of schizophrenia than are females; age of onset is earlier, relapses more frequent and more severe, and response to neuroleptic medication less favourable. Male schizophrenics are more likely to show poor pre-morbid competence and low IQ, and are less well adjusted, socially and occupationally, than their female counterparts. In terms of the illness itself, males are more prone to 'typical' schizophrenic symptomatology, with a tendency to be withdrawn and passive, while females exhibit more affective features. Furthermore, some studies suggest that there is an overall excess of males among schizophrenics; what is certainly true is that there is an excess of males among those schizophrenics with a severe form of illness, as defined by restrictive operational criteria (see Lewine, 1988).

EXPLANATORY THEORIES

In seeking to explain why males are prone to a more severe form of schizophrenia, previous authors have implicated, *inter alia*: (i) more severe role-stresses in males (see Rosenthal, 1962; Farina *et al.* 1963; Lewine, 1981; Seeman, 1985; Al-Issa, 1985); (ii) social protective factors in females, for example less active courting behaviour, and less career-stress (Seeman, 1985); (iii) biological factors, specifically a 'triggering' effect of androgens in the male (see Loranger, 1984; Al-Issa, 1985), or a 'protective' effect of oestrogens in the female (see Seeman, 1985; De Lisi *et al.* 1989). However, as Lewine (1988) has pointed out, such hypotheses do not seek to explain the primary cause of schizophrenia, but rather to account for the earlier manifestation in males, given that schizophrenia will occur. We suggest that a neurodevelopmental perspective not only provides a causal explanation for the early-onset, severe schizophrenia to which males are more prone, but also takes into account recent evidence regarding the structural brain abnormalities found in some schizophrenics.

Structural brain abnormalities

Non-invasive investigations of the brain in schizophrenia have been widely undertaken. The consensus of computerized tomographic (CT) studies is that schizophrenics tend to have increased ventricle-brain ratios (VBR) compared with normals (reviewed by Shelton & Weinberger, 1986). Such changes are non-progressive, present at the onset of illness, and are associated with poor pre-morbid function (Pearlson *et al.* 1985; Nasrallah *et al.* 1986; Turner *et al.* 1986). More recently, magnetic resonance imaging (MRI) studies have shown smaller temporal lobe structures in schizophrenics (Johnstone *et al.* 1989a; Suddath *et al.* 1990). Post-mortem studies of the brains of schizophrenics show abnormalities in the hippocampal region (Bogerts *et al.* 1985; Brown *et al.* 1986; Jakob & Beckmann, 1986). No gliosis accompanies these lesions, suggesting that they originate *in utero* or in early infancy, possibly through genetically-mediated arrest of cell migration or pre- or peri-natal environmental insult (Jakob & Beckmann, 1986; Lewis, 1989; Gill *et al.* 1989). The exact clinical significance of such lesions is unclear, but Randall (1983) and subsequently Weinberger (1987) have proposed that a fixed brain lesion, incurred at an early age, might manifest itself through an interaction with 'normal brain maturational events that occur much later'.

Numerous studies have demonstrated that a history of pre- and peri-natal hazards (collectively termed obstetric complications) is more common in schizophrenics than in normal subjects and in other psychiatric patients; this has been shown both in retrospective studies which rely on maternal interviews, and in those fewer studies which have examined contemporaneous birth records (Murray & Lewis, 1987; McNeil, 1988; Lewis *et al.* 1988; O'Callaghan *et al.* 1988, 1990). Thus, there is little doubt that obstetric complications are associated with later schizophrenia; whether these (detectable) obstetric events are of aetiological importance in themselves, or whether they are themselves a consequence of earlier (undetected) events, is unclear. What is undisputed is that schizophrenics with a history of obstetric complications present earlier than those without such a history (De Lisi *et al.* 1987; O'Callaghan *et al.* 1988; Owen *et al.* 1988); and a number of studies have shown that such patients are more likely to exhibit ventricular enlargement (Lewis & Murray, 1987; Murray *et al.* 1988; Lewis *et al.* 1988; Pearlson *et al.* 1989), though not all have concurred (Nimgoankar *et al.* 1988).

Brain abnormalities in schizophrenic males

In schizophrenic populations, males are more likely to have a history of obstetric complications than are females (Pearlson *et al.* 1985; Wilcox & Nasrallah, 1987; Owen *et al.* 1988; Foerster *et al.* 1991b). This is consonant with the fact that structural brain anomalies have been reported more commonly in male than female schizophrenics (see Table 1). For example, Andreasen *et al.* (1989) showed that male schizophrenics had significantly larger ventricles than normal males, but no such difference could be found between female schizophrenics and normal females. Similarly, Bogerts *et al.* (1990a), in a MRI study of first-episode schizophrenics, found smaller hippocampal volume on the left side only in male patients. Moreover, neuropathological abnormalities also appear to be more common in male schizophrenics. For example, Bogerts *et al.* (1990b) found hippocampal volume to be significantly reduced in male, but not female, schizophrenics. Many of these studies have small sample-sizes, and the results need replication in studies specifically designed to assess gender differences; however, the available studies point in a consistent direction.

There has been considerable controversy over the clinical correlates of structural brain abnormalities in schizophrenia. However, the characteristics most frequently associated with increased ventricular size have been cognitive impairment, poor pre-morbid adjustment, more negative symptomatology, poor clinical outcome, poor employment record, and poor response to neuroleptics (for references, see Crow, 1985; Pearlson *et al.* 1989). We have already noted that each of these is more typical of male than female schizophrenics. Furthermore, Haas *et al.* (1989) have delineated male patients as being particularly likely to exhibit negative symptoms, poor pre-morbid adjustment, and poor cognition in association with increased ventricular size. Similarly, Goldstein

Table 1. Gender differences in structural brain anomalies in schizophrenic samples

Studies	No.	Measure	Findings
CT scan studies			
Reveley (1988)	35 M 16 F	VBR	Increased VBR in 16 M and 3 F.
Vita <i>et al.</i> (1988)	74 M 50 F	Cortical atrophy	Atrophy in 30 M and 11 F.
Pearlson <i>et al.</i> (1989)	33 M	VBR	VBR > 2 s.d. in 9 M and 5 F.
	57 F	Brain slice area	Absence of expected relationship between height and brain size in males only.
Haas <i>et al.</i> (1989)	25 M 25 F	VBR	Males showed increased VBR in association with poor pre-morbid competence, negative symptoms and cognitive deficits.
Andreassen <i>et al.</i> (1989)	65 M	VBR	> 2 s.d.: M + F = 6%; M alone = 19%
	43 F		> 1 s.d.: M + F = 28%; M alone = 43%
Harvey <i>et al.</i> (1990)	24 M	VBR	M: 7.3; F: 5.9
	13 F	LVA	M: 11.6; F: 8.5
MRI studies			
Andreassen <i>et al.</i> (1986)	28 M 10 F	Frontal cerebral and cranial area	All measures smaller and disproportionate to height in males only.
Lewine <i>et al.</i> (1989)	28 M + F	Various structures	Higher rate of anomalies in males (28%) v. females (0%).
Johnstone <i>et al.</i> (1989a)	15 M 6 F	Temporal horn area	Greater in males
Bogerts <i>et al.</i> (1990a)	22 M	Various structures	Smaller left hippocampus in males only.
	12 F		

VBR = Ventricular brain ratio; LVA = Left ventricle area; s.d. = standard deviation; M = male, F = female.

et al. (1990), using latent class analysis, found males to be more prone to a form of disease characterized by deficit symptoms, poor pre-morbid adjustment, winter birth (suggestive of environmental insult), and low familial risk for schizophrenia.

An excess of mild dysmorphic features, suggestive of abnormal foetal development, has been described in schizophrenic populations (Guy *et al.* 1983; Green *et al.* 1989). Green *et al.* (1989) found that males with poor pre-morbid functioning were particularly likely to exhibit dysmorphic features, while Waddington *et al.* (1990) reported an association between such anomalies and male sex, cognitive dysfunction, and obstetric complications.

Cerebral laterality

Left temporal lobe dysfunction appears to be of particular importance in schizophrenia; electroencephalographic (Flor-Henry, 1985), auditory evoked potential (Morstyn *et al.* 1983), and neurochemical (Reynolds, 1983) investigations have attested to this. Moreover, CT (Reveley *et al.* 1987), MRI (Johnstone *et al.* 1989a; Bogerts *et al.* 1990b; Suddath *et al.* 1990), and neuropathological (Brown *et al.* 1986; Crow *et al.* 1989) studies have revealed structural anomalies of the left temporal lobe in some schizophrenics.

The brain is, to an extent, capable of 'compensating' for early unilateral brain damage. Thus, a lesion in the left hemisphere tends to result in right-hemisphere dominance and 'pathological left-handedness' (Satz, 1972). Clinically, this is evidenced by high rates of non-right-handedness in individuals who were 'at risk' of obstetric hazard. For example, O'Callaghan *et al.* (1987) and Ross *et al.* (1987) showed a correlation between very low birth weight and non-right-handedness. The latter group also showed that non-right-handers had lower IQ and more language delays. In a group

of schizophrenic patients, Seeman (1985) reported an association between left-handedness and lengthy maternal labour, suggestive of birth injury.

Although attempts to assess cerebral laterality in schizophrenics have met with limited success (see Nasrallah *et al.* 1981; Merrin, 1984), left-handedness and crossed dominance have been associated with early onset of illness (Piran *et al.* 1982); inferior social competence (Merrin, 1984); more negative symptomatology (Andreasen *et al.* 1982); and increased VBR and poor performance on neuropsychological tests (Katsanis & Iacono, 1989). Lewine *et al.* (1989) found a correlation between clinical anomalies, reversed visual field preference, and MRI abnormalities in male schizophrenics. All this suggests that 'pathological' left-sided hand and eye preference may be associated with developmental insult and a severe form of disease to which males are more prone.

MALE SUSCEPTIBILITY TO NEURODEVELOPMENTAL DISORDERS

The main neurodevelopmental disorders are all more common in males than in females. Table 2 shows that estimates of the male:female ratio in such conditions range from 1.6:1 for severe mental retardation through 2.5:1 for autism to 3.75:1 for Asperger's Syndrome. This compares with a ratio of 2.3:1 among schizophrenics presenting before 25 years quoted by Rosenthal (1970), and 2.1:1 for first admissions for schizophrenia between ages 20 and 24 years in England in 1984 (Government Statistical Office, 1986).

Table 2. Sex ratio in developmental disorders

Disorder	Authors	Male:female ratio
Dyslexia	Rutter & Tizard, 1970	3.3:1
Autism	Bryson <i>et al.</i> 1988	2.5:1
Stuttering	Andrews & Harris, 1964	2.4:1
Asperger's Syndrome	Wing, 1981	3.75:1
Severe mental retardation	Broman <i>et al.</i> 1987	1.6:1

Goodman (1990) has reviewed the characteristics of neurodevelopmental disorders. In addition to boys being more vulnerable, he points out that such disorders (a) are over-represented among individuals with brain abnormalities; (b) show an association with pre- and peri-natal complications; and (c) have increased rates of left-handedness. It will not have escaped the reader that these have all been said of early-onset schizophrenia.

Why are males more prone to neurodevelopmental impairment? Geschwind & Galaburda (1985) claim that males are more prone to obstetric hazards, but the evidence is flimsy. Certainly, males are more susceptible to both the short- (Yu *et al.* 1986) and long-term (Hadders-Algra *et al.* 1986) consequences of such hazards. For example, low birth weight males are more likely than their female equivalents to (a) develop intra- and peri-ventricular haemorrhage (Amato *et al.* 1987), and (b) experience long-term adverse neurological deficit (Rantakallio & von Wendt, 1985); in rats at least, males are more likely to have behavioural/learning problems after perinatal insult (Grimm & Freider, 1985).

The pace of cerebral development is slower in males than females (Taylor, 1969; Seeman, 1989). Thus, the male brain may be susceptible to environmental adversity for a longer period than the more rapidly-maturing female brain (Seeman, 1989). Also, in rats (see Diamond, 1989) and probably humans (e.g. Thatcher *et al.* 1987), males and females show different patterns of cerebral development. Geschwind & Galaburda (1985) have suggested that pre-natal testosterone may interfere with the proliferative processes involved in left hemisphere development, leaving the male more prone to developmental disorders affecting left hemisphere functions (see Chi *et al.* 1977; Goodman, 1990).

Differences in cerebral organization between the sexes could also play a part in determining the gender differences in frequency of neurodevelopmental disorders. Specifically, males exhibit more lateralization of cerebral function than do females (McGlone, 1980). Such laterality differences affect not only the cortex, but also, in rats at least, the hippocampal-dentate complex (Diamond, 1989). It has been suggested that the male brain may consequently be less able to 'compensate' for those unilateral lesions considered important in the pathogenesis of schizophrenia (Seeman, 1982; Al-Issa, 1985).

A CONFLATION OF TWO DISEASES?

Family studies (Bellodi *et al.* 1986; Goldstein *et al.* 1989) have found that the morbid risk of schizophrenia in relatives of male schizophrenics is lower than that in relatives of female probands. Concordance rates for schizophrenia in monozygotic twins also appear lower in males than in females (Rosenthal, 1962; Kringsen, 1987). These data raise the possibility that schizophrenia in males is less heritable than in females.

One might go on to postulate that the overall preponderance of males in strictly-defined schizophrenic samples is due to a higher proportion of males having an illness in which early environmental influences have played a significant pathogenic role. Such reasoning could explain the excess of males among those schizophrenics who present early and exhibit pre-morbid dysfunction, negative features, and structural brain abnormality. It would not, however, explain the excess of women among those individuals who present after 30 and who are characterized by good pre-morbid functioning, positive rather than negative symptoms, more affective features, and better outcome.

Female preponderance in later onset schizophrenia

Later-onset patients are less likely to have a family history of schizophrenia (Kay & Roth, 1961; Harris & Jeste, 1988; Shimizu *et al.* 1988*b*) or to have a history of obstetric complications (Reischies, 1989; Foerster *et al.* 1991*b*). Furthermore, they are less likely to have been intellectually or occupationally compromised. For example, Johnstone *et al.* (1989*b*), who dichotomized their 101 schizophrenic patients into those with early and late onset, noted that the latter group had performed better pre-morbidly in both academic and occupational spheres; they also had fewer negative symptoms and cognitive deficits. Noreik & Odegaard (1966) analysed the incidence of mental illness in those who had graduated successfully from Norwegian high schools; males had a lower- and females a higher-than-expected rate of schizophrenia. Thus, among those individuals with adequate pre-morbid IQ and at least average academic capability, females are more at risk of later developing a psychosis conventionally diagnosed as 'schizophrenia'.

Stringent diagnostic criteria for schizophrenia, particularly those that discount patients with prominent affective symptomatology, exclude more women than men (Lewine *et al.* 1984; Katschnig & Lenz, 1988). Furthermore, females are over-represented among cohorts of psychotic patients labelled 'atypical', 'schizoaffective', or 'cycloid': these groups contain patients with schizophreniform symptomatology, but a relatively benign longitudinal course (Tsuang *et al.* 1976; Cutting *et al.* 1978; Kendell, 1988; Levitt & Tsuang, 1988). Together, these data beg the question of whether some females diagnosed as schizophrenic may suffer a different type of illness from that characteristic of males, or even whether many later-onset female 'schizophrenics' might actually be suffering from affective psychosis (Pope & Lipinsky, 1978).

Family studies have shown an increased morbid risk of affective disorder in the relatives of schizophrenics with 'atypical' or schizoaffective features and good outcome (McCabe *et al.* 1971; Pope & Lipinsky, 1978; Kendler & Hays, 1983; De Lisi *et al.* 1987; Kendler & Tsuang, 1988). These patients are also less likely to show ventricular enlargement on CT scan (Owen *et al.* 1989). The most parsimonious explanation for this, and for the better outcome in women, is that many cases of so-called later-onset schizophrenia in women have more in common, aetiologically, with affective

psychosis than schizophrenia. It is, of course, well known that affective psychosis is more common in women than men (Boyd & Weissman, 1981; Robins *et al.* 1984; Surtees & Sashidharan, 1986).

CONCLUSION

Thus, we suggest that much of the contemporary confusion in schizophrenia is due to the conflation of two separate disorders. Kraepelin (1986) originally described dementia praecox as a severe chronic illness predominantly affecting young males. Almost a century later, it is becoming clear that Kraepelinian schizophrenia is indeed more common in young males, contingent upon their greater susceptibility to neurodevelopmental disorder. In contrast, the 'atypical' later-onset schizophrenia-like illnesses are commoner in women; the greater frequency of affective symptoms in such patients, their better outcome, and the higher risk of affective disorder in their relatives, suggests that they are aetiologically related to the affective psychoses.

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We are grateful to Drs R. Goodman, E. O'Callaghan, A. Riecher, S. Lewis, and E. Hare for their helpful comments, and to the Psychiatry Research Trust and the Leverhulme Trust for financial support.

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