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Schizophrenia as failure of hemispheric dominance for language

T.J. Crow

Schizophrenic illnesses occur with approximately the same incidence in all human populations with a characteristic distribution (slightly earlier in males) of ages of onset. Given that the predisposition (which presumably is genetic) is associated with a procreative disadvantage why do such illnesses persist? Here it is suggested that these conditions are a manifestation of genetic diversity in the evolution of the specifically human characteristic of language, an innovation that has occurred by a process of progressive hemispheric specialization – the establishment of dominance for some critical component of language in one or the other hemisphere. Individuals who develop schizophrenic symptoms show lesser anatomical and functional asymmetries than the population as a whole; such symptoms may reflect 'dominance failure' for language.

Trends Neurosci. (1997) 20, 339–343

IN THE COURSE of a lifetime, approximately 1% of the population will suffer from a 'schizophrenic' illness. These individuals may experience hallucinations (most characteristically voices that provide a running commentary on the individual's actions) or develop delusions (that thoughts are inserted or removed from their head, or that their thoughts and actions are 'controlled' by an outside force). In addition, the ability of sufferers of schizophrenia to express or even experience emotion can be severely blunted, and they may become withdrawn and socially isolated. Such symptoms tend to persist and recur, are associated with an increased (at least 20-fold) risk of suicide, substantial loss of employment capacity and disruption to social and family relationships. What causes such destructive psychological change?

From the World Health Organization Ten Country study of incidence, Jablensky *et al.*[1] concluded: '…schizophrenic illnesses are ubiquitous, appear with similar incidence in different cultures and have clinical features that are more remarkable by their similarity across cultures than by their difference.'

Such constancy suggests that the disorder is independent of the environment. Indeed the search for common environmental precipitants (birth injury, viruses and social stressors) has yielded little hard evidence that they are relevant to the core process[2]. By contrast, a genetic factor gains credence from studies demonstrating increasing risk for psychosis with genetic proximity to an affected individual[3] and a concordance rate of approximately 48% in monozygotic (MZ) twins versus 17% in dizygotic (DZ) pairs[4]. Although less than 100% MZ concordance suggests that factors other than genetic are relevant, careful lifetime histories of discordant MZ pairs have failed to reveal consistent environmental differences between ill and well twins[5]. If the only contribution to aetiology is genetic, discordance in MZ twins requires explanation. One possibility is that random factors, such as those invoked in some theories of neural development[6], play a role.

Two demographic features of the disease process provide clues to the nature of the genetic contribution. Onsets occur from late adolescence through middle adult life, an epoch coinciding with the reproductive phase. In view of the documented decrease in fecundity associated with the disease[7] the question arises[8,9], how can these genes survive in the face of a biological disadvantage? Genes for thalassaemia and sickle cell anaemia persist in spite of associated disadvantages but only in populations in which they provide protection against malaria. Genes predisposing to schizophrenia survive in all populations without a balancing advantage being apparent. The second puzzle is a sex difference in age of onset, with males presenting a mean two to three years earlier than females. This suggests that pathogenesis is determined by some normal anatomical or physiological difference between the sexes. Here I advance a hypothesis to explain the persistence of these genes in the light of the morphological changes in the brain, what is known about the neuropsychological profile in schizophrenia, and the recent evolution of modern *Homo sapiens*.

T.J. Crow is at the Prince of Wales International Centre, University Dept of Psychiatry, Warneford Hospital, Oxford, UK OX3 7JX.

 0166 - 2236/97/$17.00 PII: S0166-2236(97)01071-0

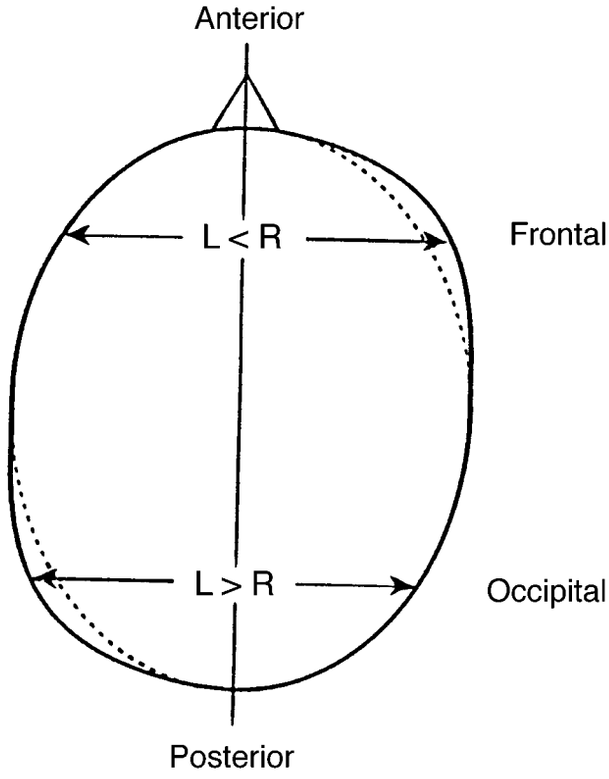

Fig. 1. ***Width asymmetries in the human brain.*** Adapted from Calvert and Crow[22].

The evidence of morphology

Amongst the plethora of morphological deviations reported in schizophrenic patients, three changes appear relatively consistent, and may be related. The most robust and well replicated is a degree of ventricular enlargement, reported in the first CT scan investigation by Johnstone *et al.*[10]. An important feature is that the variance within the patient group is not increased[11] and neither is there evidence of bimodality. The mean increase in ventricular space is therefore characteristic of schizophrenic patients in general, not of a sub-group. This suggests there is a single pathological process, that is, one disorder not many. Although ventricular enlargement is consistent with a number of different pathologies, the finding acquires greater significance when considered in conjunction with the following two morphological changes.

Brain size, and perhaps more importantly cortical mass, appears to be decreased. This reduction has been detected both in post-mortem studies[12–14] and in magnetic resonance imaging investigations[15,16]. In that the change is unrelated to the presence of gliosis[17] it presumably reflects an anomaly of development. Whether hemispheric or ventricular volume changes with the course of illness remains an issue of considerable interest and importance[18].

More specific and informative than changes in ventricular or cortical size are reports of reductions or absence of cerebral asymmetry[19–21] (Fig. 1). One of the first asymmetries to be recognized was the greater length of the Sylvian fissure on the left side of the brain[23]. This difference reflects the increased extent in most individuals of the planum temporale (or Wernicke's area) in the left hemisphere[24], an asymmetry that is probably the most salient manifestation of a single genetically-determined asymmetry in the human brain. Post-mortem studies of hospitalized patients with schizophrenia found that this asymmetry was reduced[25,26]. Asymmetries of cortical volume or width are also reported as diminished or lost in patients with schizophrenia in their first episode of illness[21,27], a change that is probably more marked in those with an early onset of illness (see Table 1)[28].

Although an MRI study of monozygotic twins discordant for schizophrenia[39] was reported as showing no difference between the twins in asymmetry of the Sylvian fissure, measures of the posterior fissure revealed a lesser asymmetry in the ill twin and a greater asymmetry in the well twin than those seen in controls[40]; a result consistent with the asymmetry findings of an earlier twin study[29]. Given the genetic predisposition therefore, whether or not one twin develops the disease may depend upon those random factors that normally enter into the development of the nervous system[6].

Occam's principle requires a unitary explanation for the three morphological changes, that is, ventricular enlargement, modest reduction in cortical mass and loss of asymmetry. I suggested[20] that the enlargement in ventricular space and reduction in cortical mass are a secondary consequence of the failure to develop cortical asymmetry – as the cortex increases in size and becomes more infolded the ventricles get smaller. Ontogeny follows phylogeny. If the rapid increase in brain:body weight ratio in man relative to other primate species occurred on the basis of progressive separation of function of the hemispheres[41], then an arrest of the key process of lateralization (reflected as failure to develop asymmetry) could be associated with a restriction in cortical mass and an increase in ventricular size. All three changes therefore can be considered developmental in origin. Although one might wonder whether such changes, for example loss of asymmetry, result from an insult at a critical stage of foetal development, studies of the pregnancies of mothers whose children become schizophrenic reveal no evidence of systematic disturbance[42].

An anatomical hypothesis of pathogenesis requires a functional correlate. What are the implications of these changes for cognitive performance; what mechanisms are involved in the generation of psychotic symptoms?

Functional asymmetries

Traditional neuropsychological approaches have proved uninformative[43]. Patients with schizophrenia do not typically present with focal cognitive abnormalities against a general background of intact performance. Typically the picture is of a general intellectual deficit, although whether, and at what stage, there is deterioration remains controversial. The nature of the disturbance is such that it must be devastating enough to disrupt almost every aspect of cognition in episodes of illness and yet subtle enough to sustain these abilities in periods of remission. What capability is sufficiently protean, and variable between individuals, that its dysfunction could account for this range of symptoms?

A clue to the solution (that it is cerebral dominance for language) is provided by the asymmetrical morphological changes. In the normal population, some 80–90% of individuals are right handed with corresponding left hemisphere dominance for language,

TABLE 1. Anomalies of cerebral asymmetry in schizophrenia

Asymmetry assessed	Method	Findings	Refs
Para-hippocampal gyrus width	Post-mortem	Loss of asymmetry in patients with schizophrenia relative to affective disorder. (ANOVA side × diagnosis interaction $P<0.02$)	12
Overall hemispheric 'density' in discordant MZ twins	CT scan	'Density' diminished on the left in ill *vs* well twin	29
Components of the lateral ventricle	Post-mortem	Left temporal horn increased in area in schizophrenic patients *vs* controls. (ANOVA side × diagnosis interaction $P<0.005$)	19
Sagittal suture	CT scan	More symmetrical in R handed patients with schizophrenia *vs* controls	30
Occipital width	CT scan	Width asymmetry diminished in early *vs* late onset patients with schizophrenia, and *vs* controls	28
Temporal lobe area	MRI	Reduced on left in patients with schizophrenia *vs* controls	31
Lateral ventricular enlargement		Greater increases on the left side, particularly of the temporal horn	32
Temporal lobe grey matter in MZ twins	MRI	Diminished on left but not on right in ill *vs* well twin	33
Sylvian fissure length	Post-mortem	Asymmetry lost in patients with schizophrenia *vs* controls	25,26
Cortical volumes on coronal sections in first episode cases	MRI	'Yakovlevian torque' (right frontal to left occipital preponderance) reduced in patients *vs* controls	21
Planum temporale area	MRI	Asymmetries diminished in patients with schizophrenia[a]	34
Planum temporale volume and antero-posterior length	Post-mortem	Asymmetries of volume and A-P length lost in patients with schizophrenia *vs* controls	35
Planum temporale area	MRI	Reversal of asymmetry in patients with schizophrenia[a]	36
Cortical widths in first episode cases	MRI	Frontal and occipital asymmetries reduced in patients *vs* controls	27
Neuronal density correlations in hippocampus	Post-mortem	Inter-hemispheric correlations greater in patients with schizophrenia *vs* controls	37

But see Kulynych *et al.*[38] for contrary findings.

these functional markers being correlated with the usual left larger than right posterior anatomical asymmetries discussed above[44]. If the loss of these anatomical asymmetries in schizophrenic patients is associated with an equal decrement in functional specialization, then one can envisage that a breakdown at this level of processing would have damaging (but not disastrous) consequences for many areas of cognition[45]. The function that from studies of neurological patients appears to be the most lateralized, that has evolved most recently and develops over the longest time course in ontogeny, is language. Language it seems depends upon a fine balance of specialization and cooperation between the hemispheres. Is this balance also associated with variation between individuals?

Handedness, a manifestation of cerebral dominance, is closely correlated with anatomical asymmetry and language lateralization. Annett[46] proposed that the variation for handedness present in all studied populations reflects a balanced polymorphism, that is, differing degrees of handedness are associated with differences in cognitive ability. This conjecture is supported by observations on the National Child Development cohort: individuals closer to the point of equal hand skill are disadvantaged relative to those who are more clearly lateralized[47]. This could be relevant to schizophrenia. Although there is little evidence of an increase in left handed writers amongst patients with schizophrenia[48], the recent literature provides support for an atypical leftward shift in the handedness distribution; populations of patients with schizophrenia are characterized by a more variable and less completely lateralized pattern of manual preference, that is, an increase in mixed or 'ambiguous handedness'[49]. The latter subtype is defined as a failure to manifest a consistent hand preference within, rather than across, tasks, a phenotype reported as present in 19.4% of patients with schizophrenia by comparison with 2–3% of the normal population[50]. The correlate of this phenomenon may be failure or delay in allocating specific cognitive functions to each hemisphere.

This prediction is strengthened by the demonstration that mixed handedness is indeed associated with the abnormal development of language processes (for example, in dyslexia and autism). In addition, a recent study has revealed that the mixed or ambiguous handedness subtype in schizophrenic patients is significantly related to severity of formal thought disorder and to language dysfunction[51]. Furthermore, studies of language lateralization in schizophrenic patients using divided visual field and dichotic listening paradigms suggest that the usual left hemisphere advantage for linguistic processing is lost[52], a loss that was also present in some test circumstances in the ill twin in a study of discordant MZ pairs[53]. Paradoxically, there have also been studies demonstrating an exaggerated left hemisphere advantage compared to control subjects (for a review, see Walker and McGuire[54]) suggesting that the mechanism by which dominance is maintained is labile in schizophrenia. An alternative explanation[46] is that the critical variable is whether speech output and input are controlled from the same side of the brain. In mixed handers, there is a greater likelihood that determination of handedness, ear advantage and speech are independent of each other[55]. Annett[46] suggests that

when speech output and input systems are located in opposite hemispheres the acquisition of language is delayed. The inconsistent asymmetries in individuals with schizophrenia could be a secondary consequence of random allocation of manual dominance, speech input and output systems, a possibility that deserves to be systematically assessed.

If schizophrenia indeed is associated with atypical patterns of laterality, then we might expect to find evidence of delayed acquisition of certain aspects of linguistic processing. In the cohort of individuals (the UK National Child Development Survey) born in a single week in March 1958, those, who by the age of 28 years were found to have developed schizophrenic illnesses, had reading difficulties[56], were more likely to have been described by their mothers as ambidextrous at age 7 and on a test of hand skill were less strongly right hand dominant at the age of 11 (Ref. 57). In addition, retrospective analyses on the entire sample show that individuals who were mixed handed at age 11 years were also performing worse on a test of reading ability[47]. These children therefore have deviations in aspects of symbolic processing that apparently predispose them to later psychosis.

Whilst findings of atypical patterns of cerebral dominance are a pointer to the nature of the dysfunction, the critical question is what relationship do these indices have with the symptoms of schizophrenia? Clearly there exist left and mixed handers who show no sign of any schizophrenic symptom whatsoever. What is it that precipitates an individual into psychosis?

Is language the key?

A modest delay in reading in children who later develop schizophrenia[56] is an insufficient explanation of the onset of unusual perceptual experiences in early adulthood, since children with dyslexias of greater severity do not develop psychotic symptoms. Additional impairments, for example in syntax, semantics, cohesion and use of metaphors, are found in the language of at least some patients with schizophrenia[58–61]. Thus a subtle failure of lateralization of language that becomes manifest at a critical and late stage of development, may be the primary dysfunction in schizophrenia[62], but exactly what aspect of language it is that distinguishes individuals who develop psychotic illness from those who have linguistic problems and delays at an earlier age, requires urgent research.

Recent PET studies consistent with a primary disturbance in the regions that subserve language function[63], have pinpointed a difference between schizophrenic patients and control subjects in their ability to inhibit activation in the superior temporal gyrus during verb generation tasks. This region, corresponding to Wernicke's area, is usually activated by listening to spoken language, but appears to be inhibited during self-generated speech. Such inhibition may represent a critical feedback process which permits the distinction of self-generated from externally elicited speech signals. In patients suffering from schizophrenia, no such inhibition was recorded during the PET scanning procedure. This suggests that self-monitoring of speech signals is a key component of the disorder; the relationship of these findings to the evidence for loss of anatomical asymmetries described above is of particular interest. Could these functional deviations reflect a change in inter- or intra-hemispheric connectivity?

Consideration of the positive symptoms of schizophrenia (hallucinations, delusions and formal thought disorder) reinforces the conclusion that language systems are involved. Hearing spoken voices is the essence of the experience of auditory hallucinations; hearing musical or non-linguistic sounds is a less central feature of psychotic experience. Thought disorder itself, the evidence for which comes only from observation of a disorder of speech, is preeminently a disorder of the organization and direction of language. Delusions can be seen as a pathological change in the symbolic value, that is the 'meaning', of categories of words. Indeed without language, it is difficult to imagine that an individual could contemplate the world, develop ideas, delusional or otherwise, or the capacity for rational thought. Furthermore, it may be precisely because other species lack the systems specifically involved in language that we have had limited success in modelling the disorder in animals.

If language is the focus of the disturbance, can this account for the global and non-specific nature of the cognitive impairments and for non-verbal features such as the negative symptoms? Maybe, as Bickerton[64] has suggested, it is not intelligence but language that is the function that has been selected for in the evolution of *Homo sapiens*, and this latter function dominates all aspects (not just word comprehension and production) of human cerebral function. Some negative symptoms, for example, poverty of speech, can readily be understood as failures of verbal fluency but others (for example, affective flattening) can be seen as a loss of the meaning of significant symbols, that is, a semantic failure. According to this view lateralization of the human brain is its most specific feature, and all those areas of 'heteromodal' association cortex that have evolved in man have done so on the basis of lateralization of components of language mechanisms to one hemisphere or the other; in other words, all these areas are a part of the 'language system'.

How might the sex difference in age of onset be explained? Syntactic competence is not notably different between the two sexes, but there are subtle differences that may be relevant. Verbal fluency shows a mean superiority and develops earlier in females; males have a mean advantage for spatial ability[65]. Such differences could relate to a mean sex difference in anatomic asymmetry (greater in males) that has been detected in some studies[66], and could be explained by a genetic influence on the sex chromosomes[8]. Specifically, a gene that is present in homologous form on both the X and the Y chromosomes has been proposed[8] and is supported by observations of an association within families between handedness and sex[67].

Concluding remarks

Language is the function that separates man from earlier hominid species, and hemispheric specialization is apparently the mechanism by which language has evolved. Anomalies of structural and functional asymmetry have been observed in patients with schizophrenic illnesses and these can be interpreted as a failure, or delay in, establishing dominance for speech in one hemisphere. Some schizophrenic symptoms (particularly the positive ones) can be understood as

deviations in the interpretation and organization of speech. In a number of studies, failures in linguistic processing have been demonstrated at the levels of semantic, syntactic and discourse structure. Schizophrenia, a condition which apparently occurs in all societies with approximately the same incidence, may best be understood as an anomaly of the function which is most characteristically human – language.

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Acknowledgements
I am grateful to S.D. Iversen and G. Calvert for their helpful advice and suggestions in the preparation of this paper.

LETTERS TO THE EDITOR

How should brain nuclei be delineated? They don't need to be!

Gahr[1] reviewed three common methods to delineate brain areas in tissue sections: the cytoarchitectural, the connectional and cytochemical delineation. He focussed on the HVC (higher vocal center) nucleus of songbirds. He showed that the cytoarchitectural, cytochemical and projection properties of the same HVC brain area change independently both during development and in adulthood, and concluded that a combination of the three delineation methods may give new insights into neural plasticity and the dynamics of brain parcelation in general.

Insight into neural plasticity, however, does not depend on delineation of brain areas, but on estimation of total neuron numbers and glial cells. Total cell numbers of any brain nucleus with circumscript boundaries can be easily determined by multiplying the mean neuronal density with the volume of the nucleus[2–6]. The nucleus volume can be estimated by Cavalieri's principle[7]: multiply the sum of the cross-sectional areas of equidistant sections throughout the whole extent of the nucleus with the intersection distance. When more than ten sections are investigated and more than 100 cells are sampled the coefficient of error of the volume is less than 5%, which is negligible to the coefficient of variation of the group mean[8,9]. Unfortunately, in Gahr's review[1] no statement on total neuron number or total volume of the HVC nucleus has (or could have?) been made.

Delineation of brain structures with indistinct boundaries, however, such as the human basal nucleus of Meynert is impossible and, consequently, so is the volume, but total neuron numbers can still be estimated in normal controls and in disease[10] by using a systematic sampling design also known as the fractionator[2,3,6,11]. Again, the coefficient of error of the estimate is below 5% (Refs 10,11).

Techniques such as Cavalieri's principle and the fractionator form part of a set of tools for obtaining quantitative information about three-dimensional structures, based