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 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.


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 (thoughts that 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of sufferers of schizophrenia to express or even experience emotion can be severely blunted, and they may become withdrawn and socially isolated.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. 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. In contrast, a genetic factor gains credence from studies demonstrating increasing risk for psychosis with genetic proximity to an affected individual and a concordance rate of approximately 48% in monozygotic (MZ) twins versus 17% in dizygotic (DZ) pairs.

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. 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, 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 the question arises, 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.

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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. 11. An important feature is that the variance within the patient group is not increased 12 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 13–14 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 19–22 (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, 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 19–20. Asymmetries of cortical volume or width are also reported as diminished or lost in patients with schizophrenia in their first episode of illness 20–22, a change that is probably more marked in those with an early onset of illness (see Table 1). 23

Although an MRI study of monozygotic twins discordant for schizophrenia 24 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 25, a result consistent with the asymmetry findings of an earlier twin study 26. 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. 27

Ockham’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 28 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 29, 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. 30

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. 31 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

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But see Kalinchy et al for contrary findings.

these functional markers being correlated with the usual left larger than right posterior anatomical asymmetries discussed above46. 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 cognition45. 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. Annett47 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 lateralized48. This could be relevant to schizophrenia. Although there is little evidence of an increase in left handed writers amongst patients with schizophrenia49, 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’50,51. 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 population52. 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 dysfunction53. 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 lost54, a loss that was also present in some test circumstances in the ill twin in a study of discordant MZ pairs55. Paradoxically, there have also been studies demonstrating an exaggerated left hemisphere advantage compared to control subjects (for a review, see Walker and McGuire56) suggesting that the mechanism by which dominance is maintained is labile in schizophrenia. An alternative explanation57 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 other58. Annett 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 lateralization, 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 difficulties⁶⁴, 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 ability⁶⁵. These children therefore have deviations in aspects of symbolic processing that apparently pre-dispose them to later psychoses.

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 schizophrenia⁶⁶ 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 schizophrenia⁶⁷,⁶⁸. 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 schizophrenia⁶⁹, 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 function⁷⁰, 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, correspond¬ing 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 dis¬tinction 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 dis¬order; the relationship of these findings to the evi¬dence for loss of anatomical asymmetries described above is of particular interest. Could these functional deviations reflect a change in inter- or intra-hemi¬sphere connectivity?⁷¹

Consideration of the positive symptoms of schizo¬phrenia (hallucinations, delusions and formal thought disorder) reinforces the conclusion that lan¬guage systems are involved. Hearing spoken voices is the essence of the experience of auditory hallucina¬tions; 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 pre¬eminently a disorder of the organization and direction of language. Delusions can be seen as a pathological change in the way of looking at categories of words. Indeed without language, it is dif¬ficult to imagine that an individual could contemplate the world, develop ideas, (even the most informal and least coherent) 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 Bickerton⁷² has suggested, it is not intelligence but language that is the function that has been selected for in the evolu¬tion of Homo sapiens, and this latter function domi¬nates all aspects (not just word comprehension and production) of human cerebral function. Some nega¬tive 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 lateraliza¬tion 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 differ¬ent between the two sexes, but there are subtle differ¬ences that may be relevant. Verbal fluency shows a mean superiority and develops earlier in females; males have a mean advantage for spatial ability⁷³. Such differences could relate to a mean sex difference in anatomic asymmetry (greater in males) that has been detected in some studies⁷⁴, and could be explained by a genetic influence on the sex chromo¬some⁷⁵. Specifically, a gene that is present in homolo¬gous form on both the X and the Y chromosomes has been proposed⁷⁶ and is supported by observations of an association within families between handedness and sex⁷⁷.

Concluding remarks

Language is the function that separates man from earlier hominid species, and hemispheric specializ¬ation is apparently of value, as evidenced by how much of it has evolved. Anomalies of structural and functional asymmetry have been observed in patients with schizophrenic illness, and this may be 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. 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.

**Selected references**