Autism and Schizophrenia are not Due to a Single Genetic Locus

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... schizophrenia is a gigantic jigsaw puzzle, and its etiology defies simplistic explanations
(Gottesman & Shields, 1982, p.xi)

The fitting of genetic models to schizophrenia data is an old sport and as such it is unlikely to be one for which any obvious solution has not yet been tried. If any simple model is likely to be successful then it will need a new twist, and the linking of schizophrenia to lateralisation is potentially inspired. The Annett model should therefore be taken seriously. That said, though, the very fact that it is a single allele model makes it a priori doomed. Lykken, McGue, Tellegen, & Bouchard (1992) have stressed that certain traits can be genetic, highly correlated in monozygotic (MZ) twins, and yet unlikely to show any familial tendency. The genetic signature of these ‘‘emergenetic’’ traits, dependent on the co-occurrence of multiple alleles at several or many loci, is a high correlation in MZ twins and a low correlation in dizygotic (DZ) twins, and they specifically point at schizophrenia as an example. The implication is that schizophrenia will depend on multiple loci. That, however, is a general criticism, and any refutation of the present model must be specific.

The model of schizophrenia and autism presented in Marian Annett’s paper is, as one would expect, ingenious, building on the right shift model which she has presented so forcefully elsewhere. However, it is a mathematical model and the test of it comes in the details of its fit to the available data, and its ability to preduct new and counter-intuitive findings. ‘‘The devil is in the details’’, as it is said.

At the outset two general problems must be emphasised:

1. Most of the predictions in Annett’s paper are nothing to do with lateralisation. Although the model is couched in terms of the right shift (RS) model, it actually uses almost none of the RS model in making its predictions. Few of the data presented or the predictions made are in terms of the lateralisation of individuals with schizophrenia or autism or their relatives. Instead, we are presented with the standard concordance rates between a proband and their relatives. Many genetic models will produce broadly similar figures to these without invoking anything to do with lateralisation. As an example, consider a simple two-allele genetic model with a partially dominant gene, S, in which homozygotes, S/S, and heterozygotes, +S, each have a 70% chance of being schizophrenic. Let the gene frequency of S be .007: Then, about
1% of the population will be schizophrenic, 53% of MZ schizophrenic twin probands will have a schizophrenic co-twin, 53% of the children of two schizophrenic parents will be schizophrenic, and 35% of the children of one schizophrenic parent will be schizophrenic. All these figures are broadly compatible with the evidence presented in the present paper, but laterality has not been invoked at all. If the RS theory of psychosis is therefore to have any empirical utility it has to make specific predictions about the relationship between schizophrenia and laterality, and those are the predictions missing from the present paper.

2. The hypothesis that individuals of extreme handedness are intellectually impaired is not supported well empirically. The paper proceeds as if the hypothesis of a balanced polymorphism with a cognitive advantage for individuals of moderate degree of handedness is a well-established scientific fact. It has been clear for a while that the theory has theoretical problems. Now it is also becoming clear that empirical studies find little support for it. In recent years there have been large-scale studies from Austria (Klicpera & Gasteiger-Klicpera, 1994), Germany (Resch et al., in press), Greece (Natsopoulos, Kiosseoglou, Xeromeritou, & Alevriadou, in press), and New Zealand (Corballis & Palmer, 1996), which have failed to replicate Annett’s findings. At some point that fact will have to be accepted.

Annett’s present extension of the RS model has two very separate components, which attempt to explain the genetics of schizophrenia and of autism. These involve separate sets of assumptions, and it is more than possible that one is correct and the other incorrect. They will therefore be considered separately here. I will start with the model for autism, because it is most straightforwardly shown to be wanting.

The Right Shift Genetic Model for Autism

The right shift (RS) model of autism says that autistics are of genotype $RS^+/RS^+$, of whom a half have the full syndrome with damage to both hemispheres, and the remainder have a partial syndrome with damage to one hemisphere or the other. Either way these individuals have the genotype $RS^+/RS^+$, which means that they must have received an $RS^+$ allele from each parent. There are several implications:

1. The raised incidence of schizophrenia in the parents of autistics. The parents, assuming they are not autistic themselves, which is unlikely, must then be of genotype $RS^+/RS^+$ or $RS^+/RS^-$, the former in about 57% of cases, and the latter in about 43% of cases (in distinction to what is stated in the paper on
p.207, where it is claimed the majority are \( RS^+/RS^- \). Given the RS model of schizophrenia, a half of the \( Rs^+/RS^+ \) parents will then be schizophrenic (i.e. \( 57%/2 = 28.5\% \); that is about 28 times the rate in the general population). That prediction is readily shown to be wrong. Gottesman and Shields (1982) reviewed eight studies looking at the parents of patients with early onset childhood autism (i.e. not childhood schizophrenia) and found a diagnosis of schizophrenia in only about 1.9% of 936 parents. The discrepancy from the predicted value of 28% is damning to the RS theory, the actual value being only one-fifteenth of that predicted.

2. The raised incidence of autism in the siblings of autistics. Under the RS model, because autistics must be of genotype \( RS^+/a^+ \) then the parents will usually both be heterozygotes for \( RS^+ \) and hence one in four siblings of autistics must also be autistic (with perhaps only half having the full syndrome), that is either 25% or 12.5%, according to definition. Although it has, rather dramatically, been said that family data show a ‘50 to 100 times increase in the rate of autism in siblings’ (Rutter, Bailey, Botton, & Le Couteur, 1993), the base-rate is, of course, low at about 1 in 2500, meaning the rate in siblings is from about 2% to 4%. Again this is different from 12.5% by a factor of 3 to 6 times and from 25% by a factor of 6 to 12 times. Trying to claim that 20.4% of siblings have at least one of the symptoms, as the author does on p.205, is not acceptable. These siblings simply do not meet diagnostic criteria for autism in most cases.

3. The raised incidence of schizophrenia in the siblings of autistics. In the non-autistic siblings of an autistic, two-thirds will be heterozygotes carrying an \( RS^+/a^+ \) allele, with roughly 57% being \( RS^+/RS^+ \) and 43% being \( RS^+/RS^- \). Half of the \( RS^+/RS^+ \) siblings will be schizophrenic under the RS model, so that \(.66 \times .57 \times .5 = 19\% \) of siblings of autistics will be schizophrenic. Gottesman and Shields (1982) also review eight studies looking at the incidence of schizophrenia in siblings of probands with early onset childhood autism and find an incidence of about 1.7% of 743 cases. Again, the value is seriously discrepant from the prediction by a factor of about 11 times.

It would be tempting to continue to explore the problems of the model of autism, perhaps looking at the large sex difference in the presentation of autism, or asking about precisely how handedness is distributed in autistics, but that would seem to be unnecessary. The present model fails on a very straightforward and clear prediction of the theory concerning the co-morbidity of autism and schizophrenia, one which Annett mentions (p.207), but then ignores. Under the RS theory individuals with either condition should have a raised incidence of relatives with the other condition. That possibility has long been considered in research on schizophrenia and, as Gottesman and Shields (1982, p.159) put it:
The vast majority of early-onset childhood psychoses are not genetically related to adult schizophrenia.’’ Annett also recognises that herself on p.197: ‘’schizophrenia and autism are not related in families more often than expected for base-rates in the population.’’ Schizophrenia and autism are therefore extremely unlikely to be the result of a single common genetic process.

The Right Shift Genetic Model for Schizophrenia

The key to understanding the right shift model of schizophrenia is that all schizophrenics, in the model as presented, must be of genotype $RS^{+a}/RS^{+}$. Because they have an $RS^{+a}$ allele that can only have come from one of their parents, and hence the condition will show relatively strong familiarity. More problematic for the theory is that $RS^{+a}/RS^{-}$ individuals do not become schizophrenic. Schizophrenics must therefore carry an $RS^{+}$ allele and an $RS^{+a}$ allele, which both must have come from somewhere. Those facts produce several predictions that are testable in principle.

1. Relatives of schizophrenics are more likely than controls to be left-handed. Because schizophrenics are of genotype $RS^{+a}/RS^{+}$ it is tempting at first sight to conclude that their relatives must be more likely than controls to be right-handed, as they must of necessity carry $RS^{+}$ alleles. However, more detailed scrutiny shows that this effect is easily overridden by the $RS^{+a}$ alleles, and my calculations suggest that the nonschizophrenic parents of schizophrenics should be left-handed in about 15% of cases, an odds ratio of 1.5 times greater than the population incidence; and the nonschizophrenic siblings of schizophrenics should be left-handed in about 35% of cases, an odds ratio of 4.6 times the population incidence. The only study of which I am aware that has looked at the incidence of left-handedness in the relatives of schizophrenics is the Roscommon Family Study. In an as yet unpublished manuscript (Karkowski, Walsh, & Kendler, 1996), it was found that the first degree relatives of schizophrenics were slightly more likely to be left-handed, by a factor of 1.35 times, although the 95% confidence interval was wide (0.76–2.50). That interval is compatible with the incidence in parents but is not compatible with the calculated incidence in siblings. Clearly further data are needed on what is a straightforward prediction.

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1 It should be noted, however, that if the genetic theory of autism is wrong then there is the difficulty of what happens to individuals with the $RS^{-a}/RS^{+a}$ genotype. The most reasonable hypothesis is that half of them, those with a deficit to both hemispheres, are also schizophrenic. Even if that is so, $RS^{+a}/RS^{+a}$ schizophrenics will only represent about 1.7% of all schizophrenics. The arguments will therefore be little changed, and I will present the rest of the section on the basis, as does Annett, that only $RS^{+a}/RS^{+a}$ genotypes become schizophrenic.
2. In monozygotic (MZ) twins, discordant for schizophrenia, the nonschizophrenic twin should be more likely to be right-handed and should be more strongly right-handed. Under the model, all schizophrenics are of the $RS^+/RS^+$ genotype. If they have a monozygotic twin then there is a 50% chance that that co-twin will be discordant for schizophrenia. In that case the nonschizophrenic twin must of course also be of the $RS^+a/RS^+$ genotype but they should be strongly right-handed on standard tests of dexterity, as compared with the general population, with only about 1% being left-handed. In the study of Boklage (1977), 5/12 (42%) of nonschizophrenic co-twins of monozygotic twins with schizophrenia were left-handed, a proportion very different from the predicted 1% ($P < 10^{-9}$, exact binomial test).

In conclusion, the right shift model of schizophrenia and autism is a clever piece of theorising, and it puts into the fore the problem that there is almost certainly some relation of both schizophrenia and autism with atypical laterisation. However, the detailed predictions of the present model suggest that this particular formulation is not the answer to assembling the pieces of this enigmatic jigsaw.

REFERENCES


