Sexual selection, Machiavellian intelligence, and the origins of psychosis

T J Crow

Summary

According to Darwin's theory of sexual selection some features that differentiate the two sexes evolve by a process of "male competition" and "female choice". The sex difference in age of onset of psychotic illness in man may relate to a sexual dimorphism in cerebral organisation (the male brain being more lateralised or asymmetrical than the female brain), a difference consistent with a role for sexual selection in the evolution of the human brain. Differing criteria (reflected in a cross-culturally stable difference in mean age at marriage) in males and females for selecting personality characteristics in a mate may generate diversity in the balance of growth between the hemispheres, and this could maintain the high and relatively constant rates of psychosis in human populations.

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Introduction

In 1871 in *The Descent of Man and Selection in Relation to Sex*,[1] Darwin made explicit his view that had only been hinted at twelve years earlier, in the *Origin of Species* ("Light will be thrown on the origin of man and his history")—namely, that man and the apes shared an ancestor. According to his accompanying theory of sexual selection, some features (eg, deers' antlers, the peacock's tail) that distinguish the two sexes within a species can be accounted for by a process of selection ("male competition" and "female choice") acting on members of one or the other sex. The two arguments of *The Descent* were related: many characteristics of man, expecially the size of his brain and his capacity for speech, had evolved in this way. ". . . Sexual selection has apparently acted on both the male and female side, causing the two sexes of man to differ in body and mind . . . [and] has indirectly influenced the progressive development of various bodily structures and of certain mental qualities. Courage, pugnacity, perseverance, strength and size of body . . . have all been indirectly gained by one sex or the other, through the influence of love or jealousy, through the appreciation of the beautiful in sound, colour or form, and through the exertion of a choice . . .".

Psychoses (disorders in which aberrations of perception and thought are prominent) are found in all human societies with a lifetime prevalence of 2–3%. They are associated with a substantial decrease in fertility, the effect being greater in schizophrenic illnesses (in which psychotic symptoms are prominent and mood incongruent) than in affective disorders (in which psychotic symptoms and mood disturbance are more closely matched). Twin and adoption studies support a genetic contribution.[2,3] Near uniform incidence in diverse human populations,[4] and the observations that adoption away from a family with psychosis does not reduce risk, that early separation of monozygotic twins does not reduce concordance rates,[3] and that onset in siblings is at the same age and not the same time,[5] all suggest an origin that is predominantly genetic.

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Age of onset and fertility in psychosis

Age of onset is puzzling. Typical psychoses are unusual before puberty but increase to a peak in the mid and late twenties and remain high throughout reproductive life.

In Penrose's Ontario survey,[6] including admissions for both manic-depressive and schizophrenic psychoses, onsets before the age of 15 are rare but rise more rapidly in males than in females (figure 1A), a sex difference that is perhaps the best documented but least explained epidemiological characteristic of schizophrenia. If the rarer childhood-onset illnesses are included, the sex ratio (M/M + F) in schizophrenic-type psychoses decreases in an approximately linear manner from 4 to 59 years[2] (figure 1B).

Penrose[6] noted another sex difference: the "relative rarity of schizophrenia in male parents is an important feature that permeates the whole survey . . . schizophrenic

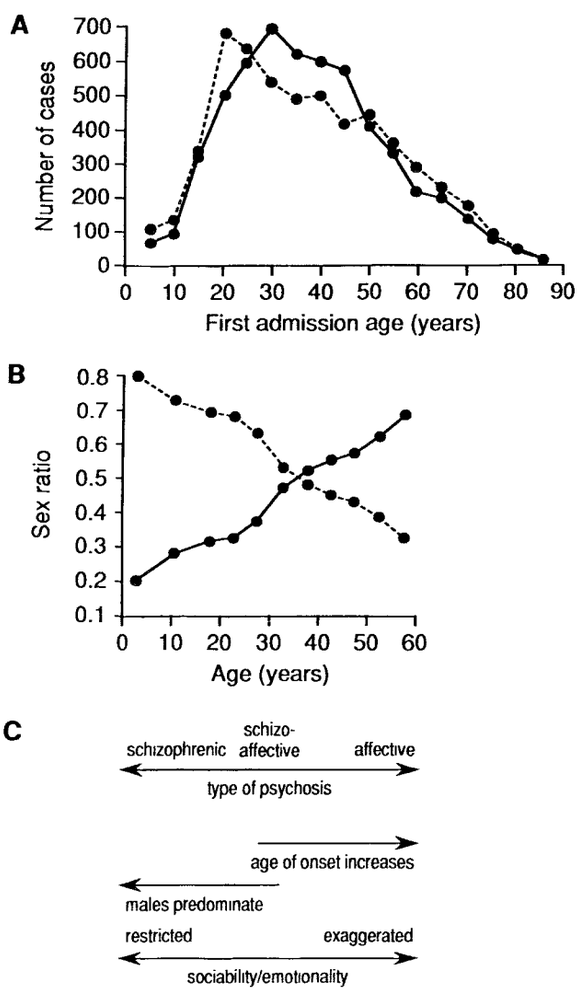

Figure 1: **Relation between age, sex, and onset of psychosis**

A, age at first hospital admission for all psychoses in Penrose's Ontario survey[6] (dashed line, males; continuous line, females).
B, sex ratio for schizophrenic type of psychoses at different ages (adapted from Rosenthal:[2] dashes, % male; continuous line, % female).
C, the continuum notion of psychosis, illustrating the relation between form of illness, age of onset, and range of sociability/emotionality in the normal population.

diagnosis is altogether rarer in parents than in offspring, but male schizophrenic parents are especially uncommon". The explanation is that the fertility of patients with schizophrenic-type psychoses is decreased, and it is decreased three times more in males than in females. Penrose also concluded that "given that the psychotic relative of a schizophrenic patient is not schizophrenic, he is more likely to be diagnosed manic-depressive than anything else . . . schizophrenia and affective psychosis are not very distinct entities and groups of closely related familial cases frequently include both diagnoses." Categorical distinctions (such as might be expected if there were aetiologically separate diseases) between different forms of psychotic illness are not supported either by phenomenological or family studies.[7] Many symptoms are present in both schizophrenic and affective psychoses, and schizo-affective disorders are common. It is more likely that psychoses originate in a continuum of genetic variation than in disease-specific genes (figure 1C).

Such variation might, as Kretschmer[8] has suggested, be related to differences in personality structure in the normal population. Often schizophrenic illnesses are associated with restricted affective expression, which leads to social isolation, whereas the core feature of manic-depression is an exaggeration of affect. The form of the illness also relates to age of onset, this being generally later in affective than in schizophrenic illnesses.[6] Schizophrenic psychoses are more commonly preceded by personality deviations, sometimes extending back into childhood (notably in males). In some way age at onset of psychosis and the emergence of personality characteristics in early adult life are interdependent—the continuum of psychosis shadows the development of normal individuality.

Brain size and asymmetry

By considering the entire spectrum of illness, and by taking a lifetime perspective, we may begin to see the survival value of the gene. But whereas Kretschmer and the notion expressed in figure 1C suggest a variation in personality and affect, the continuum also relates to intelligence, a variable that may have a more fundamental importance. Schizophrenic illnesses are sometimes preceded by a degree of intellectual deficit,[9] and may have an outcome in dementia.[10] Such findings should provoke us to look at studies of brain morphology in schizophrenia in a new light. A mean increase in the size of the cerebral ventricles is reported with no evidence of bimodality in the distribution within the patient group.[11] Variance within the patient population is not increased.[12] Therefore ventricular enlargement is characteristic of schizophrenia (and also, perhaps, of psychosis) as a whole, and not of a particular subgroup.

Why are the ventricles bigger? Ventricular enlargement implies that the ventricles get bigger as a result of tissue loss, as in the case of Alzheimer-type dementia. But perhaps the ventricles do not get bigger, but simply do not get smaller. The ventricles fill up during development and if there is an arrest or delay of this process, then this could explain why the ventricles of psychotic patients are larger than those of other individuals.

Other morphological studies (computed tomography,[13,14] magnetic resonance imaging,[15] and necropsy[16-18]) yield evidence of a decrease in brain size, which could reflect an overall reduction in cortical grey matter.[15] One interpretation is that ventricular enlargement

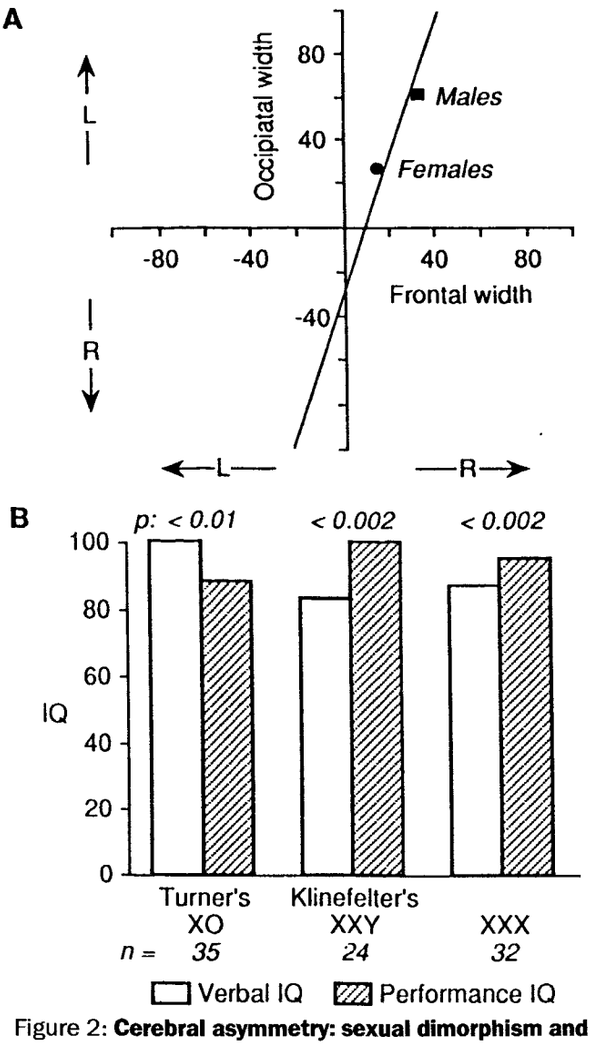

Figure 2: **Cerebral asymmetry: sexual dimorphism and genetic origin**

A, asymmetries in the normal human brain (redrawn from a computed tomographic scan study[27]); occipital and frontal asymmetry are strongly correlated, as represented by the regression line, indicating that there is a single major asymmetry. The asymmetry is greater in males.
B, neuropsychological findings in patients with sex chromosome aneuploidies.[30,31]

is an index of arrest, or early terminaton, of cerebral cortical development.

A clue to the meaning of these brain changes comes from their distribution between the two sides of the brain.[19] Enlargement is more noticeable in the temporal lobes than elsewhere in the ventricular system; in necropsy examinations and magnetic resonance imaging studies, the changes are greater on the left side.[20] There is also a corresponding reduction in substance of the temporal lobe which is greater on the left than on the right; two imaging studies of monozygotic twins discordant for schizophrenia have shown a relative tissue reduction in the ill twin in the occipito-temporal region on the left. This region includes the planum temporale (which approximates to Wernicke's area for speech reception), the structure that carries the greatest asymmetry in the human brain and forms the floor of the posterior part of the lateral (Sylvian) sulcus. In two post-mortem studies,[21,22] the normal asymmetry of length of the sulcus (left longer than right) was found to be lost in schizophrenia.

These findings in schizophrenia suggest that brain development and asymmetry have arrested at an earlier age than in other subjects. The planum temporale may be the last structure to complete its development: as a consequence of its arrest (by its local connections) the size of the temporal lobe on the left side is reduced and the temporal horn

increased, and (by its bilateral connections) the volume of cortex is reduced and the ventricle-to-brain ratio increased.

Machiavellian intelligence

Brain size increased rapidly in primate evolution. What then is the exceptional problem to which the large brain of the primate, with man as the most egregious example, is the response? Machiavellian intelligence[23] is the notion that the environmental challenge is not physical, but is social, arising from con-specifics. Members of the same species are both potential aids and threats to survival. The individual must learn whether and when to collaborate or to compete. The primate brain has developed an "awareness of awareness", an ability to conceive other individuals as having aims and desires that are similar, but often in conflict with its own, and to use this awareness to its advantage. The brain is a device for gaining an advantage over a con-specific while concealing the fact that a loss has been incurred.

The specifically human contribution is the evolution of language, as Darwin[1] appreciated: "The large size of the brain in man, in comparison with that of the lower animals ... may be attributed in chief part ... to the early use of some simple form of language". Almost certainly this development was made possible by the progressive independence of function of the two hemispheres, and this change occurred under social selection that favoured intraspecific communication: "Bilateralisation of function arose in response to specifically human pressures, occurring in a socially organised species, the members of which were mutually interdependent".[24]

The brain changes in schizophrenia (with an asymmetrical and a generalised component) reveal the evolutionary affinities of psychotic disorder.[25] Asymmetry (as indicated by its selective loss, especially in the temporal lobe) is central to the disease process, demonstrating that the genetic variation associated with psychosis is aligned along a path followed by the recent evolution of the human brain.

Cerebral sexual dimorphism

In 1879 Crichton-Browne[26] wrote that "the tendency to symmetry in the two halves of the cerebrum is stronger in women than in men". That the normal asymmetries do indeed show a sexual dimorphism, with wide variation but a mean greater in the male than the female (reference 27 and figure 2A) provides a clue to their origin, and a possible explanation for the sex differences in psychosis (as well as that in the pattern of intelligence[28]).

The genetics of handedness (the salient manifestation of cerebral asymmetry) can be explained by postulating that there is a single gene[29]—the "right shift factor" or "cerebral-dominance gene"—that is transmitted in an autosomal dominant manner and which biases the left hemisphere (and the right hand) to be dominant. In the absence of this gene, hemispheric dominance is randomly determined. A clue to the chromosomal location of the gene comes from studies of the psychological impairments associated with sex-chromosome aneuploidies (figure 2B). Patients with Turner's syndrome (XO) have performance deficits relative to their verbal intelligence quotients (IQs) (which are normal) consistent with a right hemisphere impairment.[30] Patients with an extra X chromosome—Klinefelter's syndrome and triple X syndrome[31]—have verbal deficits or delays, but are normal with respect to performance IQ, a pattern that suggests left hemisphere arrest. In hormonal and gender terms, Klinefelter's

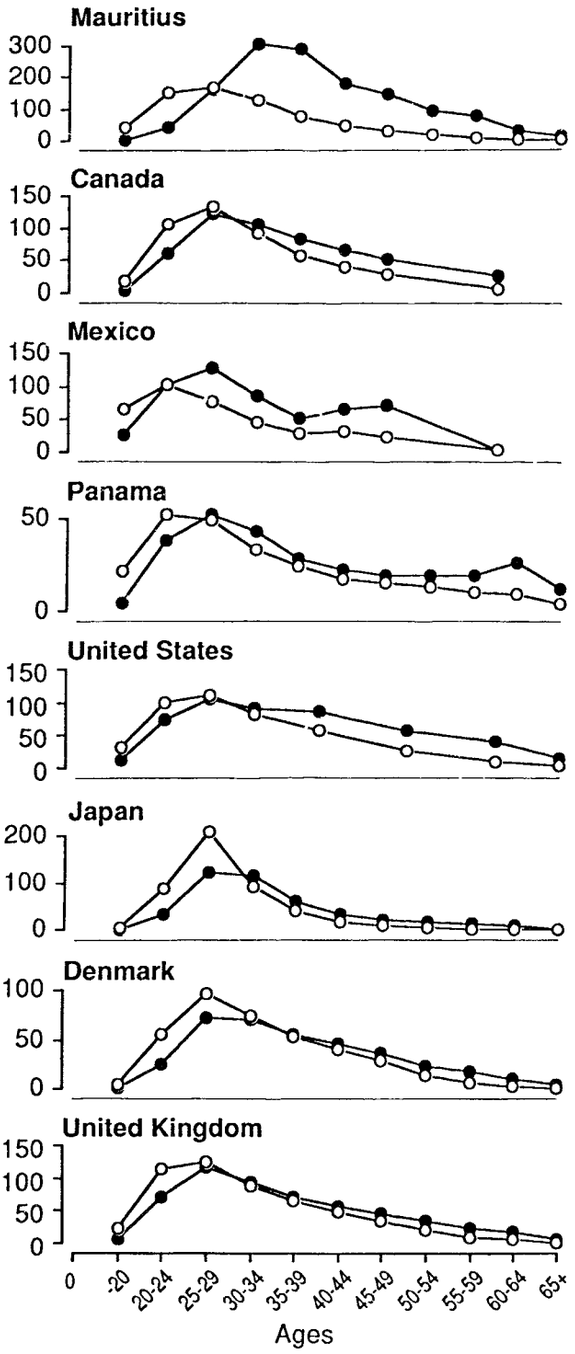

Figure 3: **Marriage rates for age of groom and age of bride.**
Abstracted from the United Nations Demographic Yearbook[34] (females, open circles; males, filled circles).

subjects are male and triple X individuals are female. Therefore the impairments are unrelated to gonadal function. They are consistent with the possibility that there is a gene on the X chromosome which influences the relative development of the two hemispheres. But the performance deficits in Turner's syndrome are absent in normal males. Thus, if there is a gene that influences hemispheric development on the X chromosome it must have a counterpart on the Y.

Several X-Y homologous genes are known.[32] Characteristically, these genes are not subject to X inactivation and, because outside the pseudoautosomal region the chromosomes do not recombine, there are sequence differences between X and Y copies. Such a difference could account for a sexual dimorphism—eg, as present in the case of cerebral asymmetry,[27] age of onset of psychosis,[6] and the pattern of distribution of intellectual abilities.[28] Because the Y copy of an X-Y homologous gene is linked to the sex-determining factor (SRY), associated variants will (while otherwise mimicking an autosomal

pattern of transmission) tend to affect individuals of the same sex within families. For both schizophrenic and affective psychoses there is evidence of concordance by sex of affected siblings.[7]

Mate preference and age of marriage

Do males and females select for different personality traits? Buss[33] studied the rankings of those characteristics that men and women state that they seek in a mate. For 11 of the first 13 (eg, kindness and understanding, intelligence) the rankings of the two sexes are similar but for two there is a highly significant difference. Males rate physical attractiveness higher than women and women rate earning capacity higher than men.

A possible explanation is that men select for youth which they (or their genes) hope will be correlated with fecundity; women select for established success which they hope will ensure support through the pregnancy and beyond. This difference is translated into a highly cross-culturally stable difference in age at procreation—men are consistently a mean 3 or more years older than women at marriage (ref 34, and figure 3) and, presumably, at the time of the births of their children.

One may assume that the sexes differ in a corresponding manner in their selection of personality characteristics—males perhaps selecting for the livelier emotional expression associated with youth and sociability, and females for the more restricted affective expression that goes with ambition and success. A selective pressure between the sexes, generated by their differing interests, could be relevant to the evolution of mechanisms for recognising and responding to increasingly complex verbal and non-verbal signals, and for developing empathy and predicting personality. Intelligence in man may have evolved as a consequence of inter-sexual selection, in which the interests of the two sexes are partly shared and partly in competition. It has been suggested[35] that the increase in brain size in man has occurred by a process of neoteny—the prolongation of fetal development by a relative delay in sexual maturity. Such delay could be the result of an evolutionary debate between the sexes—males selecting for an earlier and females for a later age of maturity—with both sexes attempting to maximise the social competence of their offspring. With a degree of paternal investment in child care and a pattern of mating fluctuating around monogamy (consistent with a modest sexual dimorphism for body size), detection of infidelity and prevention of desertion could both have played a part. The prime mover in the evolution of Machiaevellian intelligence, according to this idea, was selection of social characteristics by the mechanism of mate choice.

Form and timing of psychotic symptoms

Such selection could account for the sex-related aspects of psychotic illness. A preference of females for personality characteristics that are manifest at a later age (and with lesser emotional display) could permit the survival of genes in their sons that are expressed in terms of early onset psychosis with restricted affect; selection by males for the more pronounced emotional display that is characteristic of an earlier stage of development reduces the likelihood of an early onset illness in their daughters but increases the likelihood that such an illness will include an exaggerated range of emotional expression.

How does this relate to cerebral asymmetry? It may be a question of the rate or length of time of development of the two hemispheres. Perhaps the imbalance in the hemispheres starts earlier or continues longer in males, the difference between the sexes being a consequence of sexual selection acting on an X-Y homologous gene as outlined above. Allelic variation in the X and Y copies is predicted to be associated with personality variation, the range of variation being generated and maintained in the population by mechanisms favouring diversity (eg, frequency-dependent selection), and the extremities accounting for the phenotypic variation in personality and cognitive function which we recognise as psychotic.

Lewine has previously noted[36] that the sex difference in age of onset of psychosis is similar in magnitude to the difference between the sexes in age of puberty (ie, 2–3 years) but in the opposite direction—namely, being earlier in males. According to my hypothesis, it is not puberty itself that is important but the age of mate selection. The age difference corresponds to that in puberty but the effect, being on the other sex, accounts for the observed difference in onset of psychosis.

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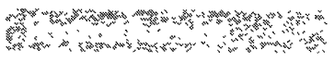

Wolfram syndrome: a mitochondrial-mediated disorder?

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Summary

Mitochondrial DNA mutations cause several human diseases, (eg, Leber's hereditary optic neuropathy). Wolfram syndrome (characterised by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness) also has, in some cases, a mitochondrial origin. The disease, often familial, has been well documented as an autosomal recessive disorder, and most of the clinical phenotypes are consistent with an ATP supply defect that is often seen in mitochondrial-mediated disorders. We propose a dual genome defect model for Wolfram syndrome in which nuclear genetic defects or mitochondrial genetic defects can independently lead to the disease. This model suggests that besides a mitochondrial gene defect alone, a nuclear gene defect, which interferes with the normal function of mitochondria (probably with a normal mitochondrial genome), can also be the underlying explanation for the pleiotropic features of Wolfram syndrome. This hypothesis explains how an autosomal recessive disorder can result in mitochondrial dysfunction, and has a general application in the identification of candidate genes for the various important phenotypes (eg, deafness and diabetes mellitus) seen in mitochondrial disorders.

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Mitochondria and mitochondrial genetics

The essential components of a functional mitochondrion are five multi-enzyme complexes of more than 60 subunits situated in its inner membrane, which together make up the respiratory chain and phosphorylating systems. Each complex consists of 4 to 25 polypeptide subunits—25 in complex I, 4 or 5 in complex II, 9 or 10 in complex III, 13 in complex IV, and 12 or 14 in complex V. Distinct from other cell organelles, mitochondria have their own autonomously replicating genome. The human mitochondrial genome (which has 16 569 base pairs arranged in a circular fashion) encodes 12S and 16S ribosomal RNAs, 22 tRNAs, and 13 of the subunits of the mitochondrial multi-enzyme complexes. The remaining subunits are encoded by nuclear DNA.

The mitochondrial genome has several distinctive and interesting genetic characteristics. In human beings, the mitochondrial DNA (mtDNA) is transmitted exclusively through the maternal line—ie, females, but not males, transmit their mtDNA to all their offspring. Unlike nuclear DNA, which is diploid, mitochondria have multiple copies (hundreds to thousands) per cell. The mutation rate of mtDNA is 7–10 times higher than that of nuclear DNA. The mitochondrial genome and nuclear genome interact with each other in various ways, such as encoding the subunits for the same enzyme complex of the respiratory chain. To function properly a cell (apart from the erythrocyte) should have both a normal nuclear genome and a normal mitochondrial genome. Dysfunction of either one could be deleterious to the cell and lead to abnormality. In man, certain organs and tissues (eg, the brain and nervous system, muscle, kidney, and pancreatic islets) are highly dependent on the energy produced by mitochondrial oxidation. As a consequence, these tissues are more vulnerable to mitochondrial defects. Thus, in almost all the mitochondrial diseases identified so far, one or more of