The XY Gene Hypothesis of Psychosis: Origins and Current Status

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Sex differences in psychosis and their interaction with laterality (systematic departures from 50:50 left-right symmetry across the antero-posterior neural axis) are reviewed in the context of the X-Y gene hypothesis. Aspects of laterality (handedness/cerebral asymmetry/the torque) predict (1) verbal and non-verbal ability in childhood and across adult life and (2) anatomical, physiological, and linguistic variation relating to psychosis. Neuropsychological and MRI evidence from individuals with sex chromosome aneuploidies indicates that laterality is associated with an X-Y homologous gene pair. Within each mammalian species the complement of such X-Y gene pairs reflects their potential to account for taxon-specific sexual dimorphisms. As a consequence of the mechanism of meiotic suppression of unpaired chromosomes <MSUC> such X-Y gene pairs generate epigenetic variation around a species defining motif that is carried to the zygote with potential to initiate embryonic gene expression in XX or XY format. The Protocadherin11XY (PCDH11XY) gene pair in Xq21.3/Yp11.2 in probable coordination with a gene or genes within PAR2 (the second pseudo-autosomal region) is the prime candidate in relation to cerebral asymmetry and psychosis in Homo sapiens. The lately-described pattern of sequence variation associated with psychosis on the autosomes may reflect a component of the human genome's adjustment to selective pressures generated by the sexually dimorphic mate recognition system.

INTRODUCTION

The genetic basis of psychosis is unsolved. Whereas heritability calculated from family and twin studies is in the range of 80–90%, linkage and genome wide association studies have so far been unsuccessful in identifying major sequence variation. Here an account is given of the origins and current status of an hypothesis that, contrary to assumptions in the current literature, predicts that variation relating to psychosis is associated with changes on the X and Y chromosomes [Crow, 1988; DeLisi and Crow, 1989], and is epigenetic in nature.

ORIGINS OF THE HYPOTHESIS

Sex interacts with psychosis in three ways:

1. onsets of schizophrenia are earlier (by a mean of 3–4 years) and outcome is worse in males [Penrose, 1991]; later onsets for example, of schizoaffective and affective illness show an increase in females with a clear excess among late-onset paraphrenic psychoses.
2. among hospitalized populations of patients with psychosis there is over-representation of individuals with sex chromosome aneuploidies [DeLisi et al., 1994b] see footnote 1.

[1]Mors et al. [2000] examined the relationship between aneuploidies of the sex chromosomes and an ICD8 diagnosis of schizophrenia or bipolar disorder in the Danish population and found no excess amongst XXX or XXY syndromes. They did however uncover an excess of such cases in the XYY syndrome and a deficit in Turner's (XO) syndrome, consistent with influences of the Y and X chromosomes. They excluded mosaicisms of the X chromosome that have been reported associated with schizophrenia [Kunugi et al., 1999; Koc et al., 2010]. Recent series [DeLisi et al., 2005; Van Rijn et al., 2006, 2009] confirm that XXY individuals score high on schizotypy, and some experience psychotic symptoms.

3. within families individuals with schizophrenic or affective psychosis tend to be of the same sex ("same-sex concordance" [Rosenthal, 1962; Penrose, 1991]).

Father to son transmission, incompatible with an X chromosomal locus, is sometimes observed. A gene present in homologous form on both X and Y chromosomes can be transmitted from a father to a son on the Y chromosome, as well as to a daughter on the X. To the extent that such transmission occurs on both X and Y, a trend towards concordance by sex (para 3 above) will be observed [Crow et al., 1989c].

FORMULATIONS OF THE HYPOTHESIS

Three classes of XY homologous gene can be distinguished [Affara et al., 1996]:

1. within the 3.5 Mb pseudo-autosomal region 1 (PAR1) at the short arm telomeres of the X and Y chromosomes a single obligatory recombination occurs in each male meiosis, and strict homology between genes on the X and Y is maintained.

2. within the 0.4 Mb pseudo-autosomal region 2 (PAR2) at the long arm telomeres recombination occurs much less frequently, perhaps once in 20–40 meioses [Freije et al., 1992]. As in PAR1 homology between X and Y sequences is maintained.

3. within the sex-specific parts of the X and Y recombination does not take place, and sequence divergence between the X and Y forms occurs, and is exposed to sex-specific selective pressures. Some XY homologies are relics of the origin of the sex chromosomes from an autosomal pair [Ohno, 1967]; others have arisen as duplications from the X to the Y-chromosome at irregular intervals in mammalian evolution (Fig. 1).

A degree of concordance by sex within families may be expected with each of these locations, and has been reported in schizophrenia, schizo-affective and bipolar disorder [Rosenthal, 1962; Penrose, 1991; Crow, 1994b].

The hypothesis that a gene for psychosis is located within PAR1 [Crow, 1988; Crow et al., 1989c] was investigated by linkage. Although positives [Collinge et al., 1991; d'Amato et al., 1992, 1994; Gorwood et al., 1992] were reported, these were not consistent
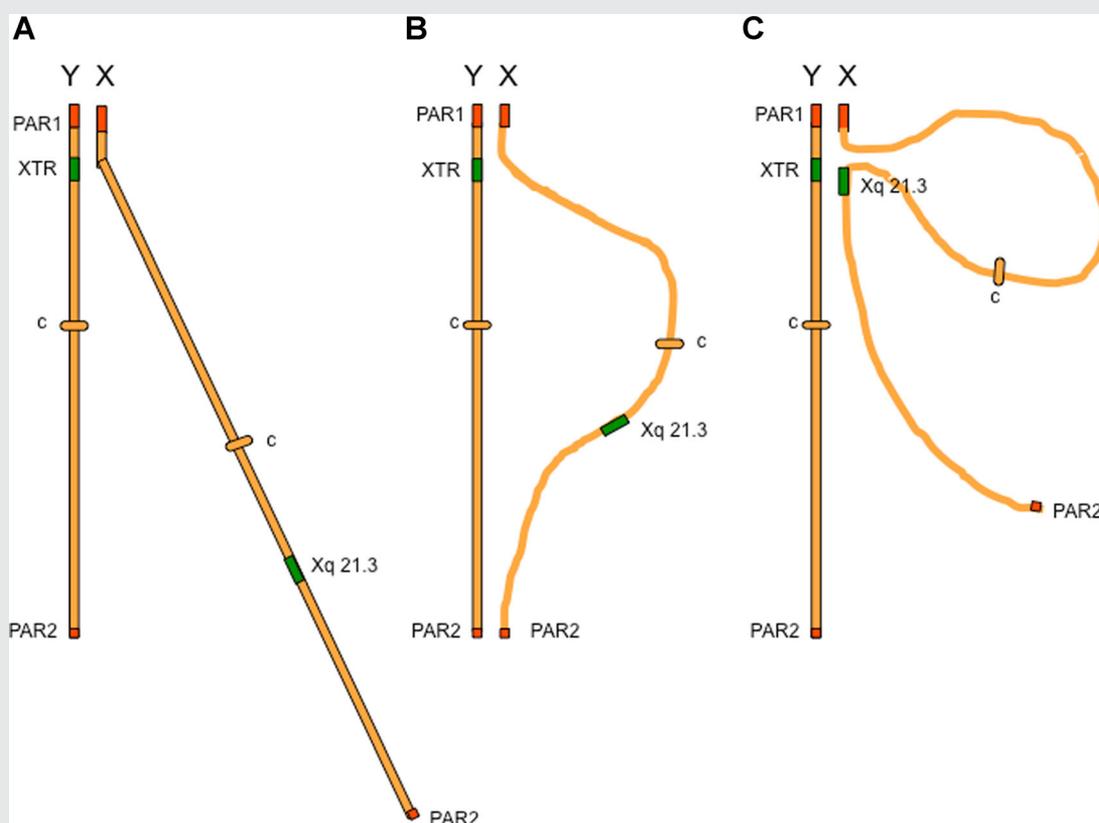
FIG. 1. Pairing of XY homologous areas in male meiosis. A: Within PAR1 pairing is complete and extends beyond the PAR1 boundary down Xp; a single recombination within PAR1 is obligatory in each male meiosis, (B) within PAR2 recombination occurs in approximately 1 in 40 meioses, and pairing is assumed to be similarly irregular, and (C) the frequency of pairing within the Xq21.3/Yp11.2 region of homology is unknown, but may be assumed to have been facilitated by the paracentric inversion in Yp that orientated the X and Y sequences in the same direction. Recombination does not take place within the Xq21.3/Yp11.2 region of homology. Regions that do not pair are subject to *meiotic suppression of unpaired chromosomes*. Abbreviations—PAR1, pseudoautosomal region 1; PAR2, pseudoautosomal region 2 and Xq21.3, the 3.5 Mb block that was duplicated from the X to the Y 6 years ago to give the "X transposed region" (XTR) in Yp11.2 region (the Y chromosome short-arm).

across locations and studies [Asherson et al., 1992; Wang et al., 1993; Barr et al., 1994; Crow et al., 1994]. An unusual case of an XX male with schizophrenia [Nanko, 1981] was found to have one breakpoint within PAR1 and the second within the Yp11.2 homologous region [Ross et al., 2001]; the significance remains unclear. Thus while linkage to PAR1 has been ruled out some questions regarding this region (class 1 above) remain.

A genetic influence of the sex-chromosomes has also been considered in relation to PAR2 (class 2) in bipolar disorder [Hawi et al., 1999; Saito et al., 2000; Muffer et al., 2002], in a cohort at high risk for schizophrenia [Goldstein et al., 2011], and as an explanation for the effect of paternal age [Perrin et al., 2010].

Because recombination ensures strict identity between X and Y sequences, a pseudo-autosomal gene pair will not explain a sex difference (although gene expression within PAR2 can now be seen as subject to further complexity on account of the presence of a "hot-spot" of recombination [Sarbajna et al., 2012]). However within a region of sex-specific homology (class 3 above), such a difference can be explained by divergence over evolutionary time of the gene copies on the two chromosomes.

HUMAN SEXUAL DIMORPHISM FOR COGNITIVE ABILITY

In many studies females are found to have a modest advantage with respect to verbal ability, and males with respect to spatial ability [Maccoby and Jacklin, 1975; McGlone, 1980; Halpern, 2000; Kimura, 2000]. These differences have been attributed to lateralization, females lateralizing earlier, and being less likely to be left-handed than males [Crow et al., 1998]. McGlone [1980] in her account of sex differences in human brain asymmetry quotes Crichton-Browne [1879]: "It would appear that the tendency to symmetry in the two halves of the cerebrum is stronger in women than in men." How this difference came about is perhaps the central problem in human evolution.

A gene for cerebral dominance in the XY homologous class was predicted from the neuropsychology of individuals with sex chromosome aneuploidies [Crow, 1989; Crow, 1994a]. Individuals who lack an X chromosome (Turner syndrome) read early and relatively well but have deficits in spatial ability; individuals with an extra X (XXY or XXX syndromes [Netley, 1986, 1998]), as also those with an extra Y (XYY syndrome [Geerts et al., 2003; Bryant et al., 2012]), have delays in the acquisition of words but normal spatial abilities. Anomalies of anatomical asymmetry—diminished anteriorly, and exaggerated posteriorly—consistent with the location of a gene for cerebral laterality on the X and Y chromosomes were observed in an MRI study in XXY and XO syndromes, respectively [Rezaie et al., 2009].

In a survey of 15,000 families for handedness, the outward manifestation of cerebral dominance, same sex concordance was detected [Corballis et al., 1996] consistent with XY linkage.

Degrees of lateralization predict verbal and non-verbal ability according to an M-shaped curve, with deficits at the extremes of left- and right-handedness, and at the point of ambidexterity; thus those who are moderately right or left-handed have an advantage relative to those who are at the extremes or in the middle of the scale.

This finding, originally reported in 11 year olds in the UK National Child Development cohort [Crow et al., 1998], has been replicated across adult life in the population of 1/4 million in the BBC Internet survey [Peters et al., 2006], and in children in the ALSPAC cohort [Gregg et al., 2008]. Thus laterality as a heritable index behaviorally assessed predicts human ability in a way that no molecularly identified gene has been shown to do [for the failure of microarray studies to predict dyslexia see Plomin and Davis, 2009].

SEARCH FOR LINKAGE TO HANDEDNESS AND PSYCHOSIS ON THE X CHROMOSOME

This background justified a search for linkage for both psychosis and handedness to the X chromosome. Markers at approximately 10 cM intervals along the 200 cM extent of the chromosome failed to detect linkage [DeLisi et al., 1994a]. A study that combined samples of families with psychosis with a series of 180 left-handed pairs of brothers [Laval et al., 1998] revealed a modest peak (Lod score 1.8) for psychosis overlapping with a stronger peak (Lod score 2.8 at DXS990 see also Francks et al., 2002) for handedness in the Xq21.3 region of the long arm. The location is significant in that it includes a block (in class 3 above) duplicated onto the Y chromosome approximately 6 million years ago (i.e., close in time to the chimpanzee-hominid lineage separation); the duplicated block (referred to as the "X-transposed region" or XTR on the Y [Ross et al., 2005]) together with the sequences of origin in Xq21.3 therefore constitutes a hominin-specific region of homology. However a systematic approach to the X in 301 families [DeLisi et al., 2000] and a targeted study of the marker DXYS156 within the Xq21.3 block again failed to detect evidence of linkage to psychosis [Nicholson et al., 2002].

Thus a body of work converged on the conclusions that (1) there are sex differences in psychosis, (2) laterality, the major determinant of human cognitive ability, is located on the X and Y chromosomes, and (3) genetic linkage on the X chromosome to psychosis is absent, and to handedness is at best weak (although modest support for Xq21.3 was reported in a revised linkage analysis [Francks et al., 2002]). In the absence of strong linkage signals elsewhere it was concluded "the possibility that the genetic predisposition" (to schizophrenia and schizo-affective disorder) "is contributed by epigenetic modifications rather than variations in the nucleotide sequence has to be considered" [DeLisi et al., 2000]. This conclusion can now be evaluated in the context of the relative failure of systematic search for linkage [Crow, 2007] and the unpredicted and puzzling findings [Collins et al., 2012; Lee et al., 2012] of whole genome association studies.

The paradox that laterality has an influence on cognitive ability and psychosis that depends on sex, but that sex linkage cannot be detected, requires that the role of laterality be re-considered. Is it central to pathophysiology, and what is the nature of the interaction with sex?

The evidence is first summarized that the dimension of laterality is pervasive to pathogenesis, and then its interaction with sex is examined. It is argued that there is greater coherence of evidence on incidence and clinical characteristics relating to sex linkage and to

the ontogeny and phylogeny of the capacity for language, than is associated with alternative concepts, for example, the concepts that genetic predisposition is due either to "common polygenes" or "multiple rare variant" genes located on the autosomes, or a combination of such genetic effects in the absence of an influence from the X and Y chromosomes.

LATERALITY DEVIATIONS IN PSYCHOSIS

Since the report of Flor-Henry [1969] that when psychosis occurs in association with temporal lobe epilepsy and the lesion is on the left side, the form of psychosis is schizophrenia-like, and when on the right side it is affective, there has been interest in lateralization in psychosis. Earlier origins of the concept of lateralization and its influence on neurology and psychiatry in the nineteenth century have been traced by Harrington [1987].

Principal findings are summarized in Tables I–X.

An implication of the finding that features are lateralized is that they may be, as Broca [1877] first proposed species-specific. That is to say in Homo sapiens, they are language-related. This claim raises empirical questions concerning the nature of human/non-human primate differences [Crow, 2004a; Rogers, 2004], and introduces a challenge to formulate a saltational account of the speciation process [Crow, 2005]. These issues are addressed in the section below on Speciation in the Hominin lineage.

Gur [1977] first reported that a population of 200 patients with schizophrenia was less strongly right-handed on a laterality index than a control population of similar size, inferring dysfunction in the left hemisphere (Table I). Two meta-analyses [Sommer et al., 2001; Dragovic and Hammond, 2005] support a shift away from strong right-handedness. An excess of ambidexterity preceding the onset of psychosis by >15 years in the UK National Child Development cohort [Crow et al., 1996] indicates that individuals predisposed to psychosis are lateralizing less, or more slowly than the general population. Sex-matching [Gur, 1977] establishes these deviations are independent of the sex difference in handedness in

the normal population, a point raised by Deep-Soboslay et al. [2010].

Ventricular enlargement. First reliably documented with computerized tomography [Johnstone et al., 1976] was found in a radiographic postmortem study proportionally greatest in the left temporal horn [Crow et al., 1989a]. Subsequent MRI studies have found symptoms selectively related to enlargement of the left temporal and occipital horns [Table II and see also Narr et al., 2001].

Loss of torque. Losses of the cerebral torque (greater width of the right frontal and left occipital lobes relative to their contra-lateral counterparts) in patients with schizophrenia compared to normal controls have been reported in CT scan and MRI studies, sometimes in relation to early onset (Table II). Volume assessments of the hemispheres in four coronal sections along the antero-posterior axis [Bilder et al., 1994] revealed a torque systematically reduced in patients with schizophrenia, individuals with mood disorders showing reductions intermediate between those of patients with schizophrenia and controls [Bilder et al., 1999]. Comparable reductions in torque were not obtained in gray and white matter assessed perpendicular to the mid-line plane (although three patients and no controls failed to show the predicted deviation either anteriorly or posteriorly) [Barrick et al., 2005]. The nature of the torque therefore remains obscure. It has been suggested it reflects "ballooning" (thinning and broadening—a surface area change) of the cortex on one side relative to the other [Harasty et al., 2003] but there are alternative interpretations (see, e.g., the following para and Table VI on gyrification below).

Decrease in lobar volume asymmetries. Selective decrease in volume in the left temporal and right frontal regions in patients with schizophrenia [Turetsky et al., 1995] and a reduction in left temporal lobe gray matter, and absence of normal left-greater-than-right asymmetry of the temporal pole gray volume [Kasai et al., 2003b] are consistent with the concept of Gratiolet and Leuret [1839] that the left frontal lobe, and right occipito-parieto-temporal regions gyrify earlier than their contralateral counterparts. Apparent volume losses in right frontal and left temporal

	TABLE I. Deviations in Handeness and Relative Handskill in Schizophrenia		
Study	**Variable**	**Finding**	**Interpretation**
Gur [1977]	Laterality index (200 SCHZ pts vs. 200 HC)	Patients less strongly lateralized: controlled for sex	"Dysfunction in left hemisphere" in SCHZ
Crow [1996]	Writing hand at age 7 and relative handskill at 11 years in UK National Child Development cohort	Excess of ambidexterity ($P < 0.0003$ age 7; $P < 0.01$ age 11) in individuals who developed schizophrenia by age 28 years	"Hemispheric indecision" predicts psychosis (weakly)
Sommer et al. [2001]	Meta-analysis of 19 studies of handedness in schizophrenia	Increase of left- and mixed-handedness (OR 1.61 (95% CI 1.4–1.81)) vs. HC (OR 1.54 (CI 1.28–1.84)) vs. other psychiatric pts	
Dragovic and Hammond [2005]	Meta-analysis of 40 studies	Increase in non-right- (OR 1.58 (95% CI 1.22, 2.04)), mixed- <OR 1.77 (CI 1.29, 2.45)> and notably left-handedness (OR 1.82 (1.55, 2.13)) separately assessed, confirmed	

HC, healthy controls; SCHZ, patients with a diagnosis of schizophrenia; OR, odds ratio; CI, confidence interval.

TABLE II. Anomalies of Asymmetrical Structure of the Ventricles and Lobar Volumes in Psychosis

	Method	Finding	Comment
Asymmetries of the ventricles			
Crow et al. [1989a]	Lateral X-rays of radio-opaque filled ventricles of formalin-fixed post-mortem hemispheres	Percentage enlargement greatest in temporal horn and selective to the left side	"Schizophrenia as an anomaly of development of cerebral asymmetry— … a proposal concerning the genetic-basis of the disease"
Degreef et al. [1992], Kawasaki et al. [1993], and Yotsutsuji et al. [2003]	MRI: ventricular shape analysis	Left temporal horn enlargement—selectively correlated with indices of clinical severity [Degreef et al., 1992]; with positive symptoms [Kawasaki et al., 1993]; greater than right (M > F) [Yotsutsuji et al., 2003]	?Arrest of development of left temporal pole
Cerebral torque			
Crow et al. [1989b] and Falkai et al. [1995b]	CT scan: hemisphere width measures	Loss in early onset cases [Crow et al., 1989b]; overall loss of anterior and posterior asymmetries [Falkai et al., 1995b]	
Bilder et al. [1994]	MRI: coronal section volumes	Loss of torque in schizophrenia [Bilder et al., 1994]; mood disorder pts intermediate between pts with schizophrenia and controls [Bilder et al., 1999]	Consistent with a continuum concept of SCHZ and BP
DeLisi et al. [1997] and Maher et al. [1998]	MRI: hemisphere width measures	Loss of posterior and occipital asymmetries [DeLisi et al., 1997]; loss of torque in early onset cases [Maher et al., 1998]	
Chance et al. [2005]	Post-mortem MRI serial coronal sections	Maximum coronal hemisphere area: Left anterior to right in HC; Left posterior to right in SCHZ ($P < 0.01$)	Shift of "centre of gravity" caudad in left hemisphere
Decrease in lobar volume asymmetries			
Turetsky et al. [1995]	MRI: lobar volumes	Selective decrease in volume in left temporal and right frontal regions correlated with negative symptoms, and duration of illness respectively	Consistent with the torque
Kasai et al. [2003b]	MRI: gray matter volume	Reduction in left temporal lobe; absence of normal left-greater-than-right asymmetry of the temporal pole in SCHZ and BP	?Arrest of development of left temporal pole

HC, healthy controls; SCHZ, patients with schizophrenia; BP, bipolar disorder.

lobes together with relative loss of late-developing gray matter in the temporal pole on the left side could result from asynchrony of gyrification. Such a change is consistent with the post-mortem observation of Chance et al. [2005] that the maximum coronal area of the left hemisphere in psychosis is caudal to that for the right, while the reverse is the case in unaffected controls.

Loss or reversal of planum temporale asymmetry (Table III), summarized in meta-analyses [Shapleske et al., 1999; Sommer et al., 2001] of the MRI literature, was found also in two post-mortem studies [Falkai et al., 1995a; Chance et al., 2008]. However in three systematic MRI investigations [Kulynych et al., 1995; Shapleske et al., 2001; Meisenzahl et al., 2002] asymmetry was present equally in patients as in healthy controls.

Demarcation of the planum temporale depends on delineation of segment HB (from Heschl's gyrus to the bifurcation) of the Sylvian fissure, complicated by variable extension beyond the bifurcation into descending and ascending rami [Ide et al., 1996]. The latter may sometimes slope forwards, these arrangements being sexually dimorphic [see also Kulynych et al., 1994], and thereby constituting a potential source of difference in findings between studies. The definition of planum temporale asymmetry and its relevance to psychosis remain uncertain.

In a meta-analysis of VBM studies [Honea et al., 2005] while the superior temporal gyrus was frequently implicated in schizophrenia, this was as often on the right as the left. For asymmetry two structures stood out—the anterior cingulate gyrus on the right, and the medial temporal lobe (and adjacent parahippocampal gyrus) on the left [Crow et al., 2013]. Thus change in neocortex may be secondary to asymmetries in limbic cortex. Review of meta-analyses of structural MRI studies concluded that the structures most consistently affected were the insula (more often in schizophrenia including the left as well as the right, and in bipolar disorder more often confined to the right), the anterior cingulate gyrus (more to the right in schizophrenia and to the left in bipolar disorder), and the left para-hippocampal gyrus, amygdala and uncus in schizophrenia [Crow et al., 2013] (see also section on Genetic High Risk studies below).

Parietal lobe asymmetries. Lyttelton et al. [2009] found greater (18%) surface area asymmetry in the inferior parietal region than in the planum temporale (8%) in normal individuals; reductions of asymmetry to the left in patients with schizophrenia are reported (Table III).

Sylvian fissure. Anomalies of asymmetry of the Sylvian fissure have been identified, some associated with sex differences (Table IV).

Morphology in discordant MZ twins. Suddath et al. [1990] presented data indicating that the affected twin differed from the unaffected asymmetrically with respect to anterior temporal lobe volume and length of the posterior segment of the Sylvian fissure [Crow, 1995, 1999]. Borgwardt et al. [2010] found lateralized differences between ill and well twins for the medial frontal gyrus on the left, and anterior cingulate and post-central gyri on the right, the finding of a deficit in the anterior cingulate to the right appearing also in a number of meta-analyses of singletons with schizophrenia [Crow et al., 2013]. Csernansky et al. [2008] found loss of asymmetry of the posterior Sylvian fissure, and the parietal operculum, and in a DTI study of white matter tracts there was

relatively discrete increase in rightward asymmetry of the external capsule and decrease in leftward asymmetry of the posterior limb of the internal capsule [Miyata et al., 2012]. The findings suggest asymmetrical change in the Sylvian fissure and underlying insula.

In a series of studies the paracingulate sulcus (PCS), a variable feature of the medial frontal surface that demarcates the boundary between paralimbic and neocortex, has been found to be generally longer in the left than the right hemisphere. In schizophrenia the asymmetry is diminished or lost in five studies, and in one study in normal subjects was found correlated with verbal fluency (Table V). In two studies there are indications of a difference between the sexes in the time course and lateralization of this developmental anomaly. Relative normality of PCS length in a high-risk group and first episode cases in one study together with prominent change in patients with longer durations of illness is compatible with a deviation that progresses with the illness.

Cortical gyrification. Increases in cortical folding in the right superior frontal cortex observed in three studies (in two of these in male but not female patients) contrast with possible reductions on the left. A side by diagnosis interaction (reversal of normal L > R asymmetry) was observed by Palaniyappan et al. [2011] in a predominantly male population.

Cortical complexity. On a measure of voxel count along the gray matter-CSF boundary [Wiegand et al., 2005] left-greater-than-right asymmetry of pre-frontal cortex in normal controls was reduced in schizophrenia. In normal subjects it appears that there is an increase in gyrification and complexity of the cerebral cortex aligned along a diagonal from left frontal to right occipital as envisaged by Pierre Gratiolet. A possibility to be considered is that the angle that this trajectory makes with the antero-posterior axis is variable between individuals and has particular values in relation to psychiatric states.

Broca's and Wernicke's areas. Studies of functional connectivity (assessed in a visual lexical decision task with a seed located in Broca's area) and structural asymmetry with MRI, are in agreement for example, in showing a leftward deviation in normal subjects and a skew toward the right frontally [Li et al., 2007; Kawasaki et al., 2008] in schizophrenia. Similarly reduction in leftward asymmetry in the planum temporale in patients relative to control subjects [Kawasaki et al., 2008] parallels loss of connectivity of Wernicke's area (see also the study of Bhojraj et al. [2009] in the section below on High Genetic Risk). In adolescent onset patients hypergyrification of Broca's area on the left and an adjacent area of the anterior insula was observed together with hypogyr-ification of an area corresponding to Wernicke's area but in the right hemisphere, together with an adjacent area of posterior insula [Palaniyappan et al., 2013]. In healthy controls of the same age gyrification was right lateralized in Broca's area. At 2-year follow-up gyrification decreased in patients, in correlation with impaired category fluency [Crow et al., 2012], but increased in controls.

Lateralization of speech production. In 12 right-handed monozygotic (MZ) twin pairs discordant for schizophrenia fMRI activations in a verbal fluency task were similar to controls in the left hemisphere but were significantly higher in the right hemisphere in both ill and well twins [Sommer et al., 2004] compared to healthy controls. In a second study [Spaniel et al., 2007] (in four pairs of right handed MZ twins with at least one twin suffering from

TABLE III. Anomalies of Asymmetry Within Temporal and Parietal Lobes

Area and authors	Method	Findings	Comment
Loss/reversal of PT asymmetry			
Rossi et al. [1992, 1994], Petty et al. [1995], Barta et al. [1997], Kwon et al. [1999], and Kawasaki et al. [2008]	MRI volume and surface area measures	Losses of area asymmetry [Rossi et al., 1992]; correlated with [Rossi et al., 1994] thought disorder, or reversals of area [Petty et al., 1995; Barta et al., 1997] and volume asymmetry [Kwon et al., 1999], correlated with persecution/suspicion, VBM reduced [Kawasaki et al., 2008] asymmetries	
Falkai et al. [1995a] and Chance et al. [2008]	Post-mortem	Surface area asymmetry reduced due to decrease on left ($P < 0.01$ [Chance et al., 2008]); area correlated with minicolumn spacing	
Shapleske et al. [1999] and Sommer et al. [2001]	Meta-analyses of MRI	Asymmetry "much reduced" due to larger right PT [Shapleske et al., 1999]; reduced (effect size 0.18 [Sommer et al., 2001])	But see Shapleske et al. [2001] below
Kulynych et al. [1995], Shapleske et al. [2001], and Meisenzahl et al. [2002]	MRI	Negative findings: surface morphometry [Kulynych et al., 1995]; surface area and volume [Shapleske et al., 2001]; volume [Meisenzahl et al., 2002]	These studies rule out any simple anatomical hypothesis regarding PT asymmetry
MEG source localization			
Reite et al. [2003]	MEG	M50 current dipole location: SCHZ pts left anterior to right; HC right anterior to left	?Arrest of development of left temporal lobe
Amygdala-hippocampus			
Qiu et al. [2009]	MRI	Amygdala hippocampus expansion-deformation: anterior (R > L); posterior (R < L) in HC; R > L exaggerated in medial hippocampus, R < L exaggerated in lateral hippocampus and amygdala in SCHZ and siblings	Shape changes in hippocampus and amygdala along AP and LR axes
Left temporal change with time			
Takahashi et al. [2007], Kasai et al. [2003a], and Takahashi et al. [2009]	MRI in first episodes	DUP inversely related to Left PT volume [Takahashi et al., 2007]; decreases in GM volume in left STG at follow-up [Kasai et al., 2003a]. GM reduction in PT ($P < 0.001$), rostral STG ($P = 0.006$), and caudal STG ($P = 0.009$) in FEP patients >UHRNP on the left	In the Melbourne high-risk study [Takahashi et al.] L−R % volume change scores for superior temporal gyrus between initial and follow-up assessments were: healthy controls 0; ultra-high risk non-psychotic −0.6; ultra high-risk psychotic 1.1; and ultra-high risk schizophrenia 2.1
Loss of parietal lobe asymmetries			
Niznikiewicz et al. [2000]; Frederikse et al. [2000]	MRI lobule volumes	Inferior parietal L > R volume asymmetry reversed [Niznikiewicz et al., 2000]; reversal selective to males Frederikse et al. [2000]	Note [Lyttelton et al., 2009]: found surface asymmetries parietal ≫ temporal in HC

DUP, duration of untreated psychosis; GM, gray matter; HC, healthy controls; PT, planum temporale; STG, superior temporal gyrus; SCHZ, schizophrenia.

TABLE IV. Anomalies of Asymmetry of the Sylvian Fissure

Study	Method	Principal findings
Falkai et al. [1992]	Post-mortem	SF reduced length on left (−16%, $P < 0.0001$) vs. HC; right SF unchanged. L/R ratio reduced more in male (−24%, $P < 0.001$) than female patients (−16%, $P < 0.03$)
Crow et al. [1992]	Post-mortem	Loss of Sylvian fissure asymmetry in schizophrenia—in Runwell two series of brains
Aso et al. [2001]	MRI	Right SF volume correlates with duration of illness
DeLisi et al. [1994c] and Hoff et al. [1994]	MRI first episode cases	Loss of R > L asymmetry of anterior segment; trend to loss of L > R asymmetry of posterior segment in female pts [DeLisi et al., 1994c]; atypical asymmetry associated with better cognition in schizophreniform pts
Suddath et al. [1990]	MRI of discordant MZ twin pairs	Review [Crow, 1999] concluded that the ill twin differs from the well twin with respect to asymmetry of anterior temporal lobe volume and posterior Sylvian fissure length; see commentaries by Weinberger et al. [1991] and Crow et al. [1991]
Csernansky et al. [2008]	MRI	Sulcal depth in the two hemispheres more symmetrical in schizophrenia than HC; loss of asymmetry (R > L) of inclination of posterior SF; loss of depth of sulci in R parietal operculum (R > L)
Miyata et al. [2012]	DTI and TBSS	Rightward asymmetry of external capsule and leftward asymmetry of posterior limb of internal capsule reduced in SCHZ vs. HC

SF, Sylvian fissure; HC, healthy controls. DTI, diffusion tensor imaging; TBSS, tract based spatial statistics.

TABLE V. Deviations of Asymmetry in the Para-Cingulate Sulcus

Study	Design	Measure	Findings	Comments
Yucel et al. [2002]	55 SCHZ patients and 75 HCs all male and right handed	PCS absent, present or prominent	LH vs. RH: HCs 84% vs. 63% SCHZ 57% vs. 57%	Loss of PCS asymmetry in SCHZ
Le Provost et al. [2003]	40 SCHZ patients and 100 HCs all male and right handed	PCS present, prominent or absent	LH vs. RH: HCs 66% vs. 27% SCHZ 45% vs. 43% i	Loss of PCS asymmetry in SCHZ
Koo et al. [2008]	39 FESZ, 41 FEAFF and 40 HCs high-spatial-resolution MRI, with follow-up scans in 50% of subjects	ROIs of CG and PCS	FESZ loss of asymmetry of PCS, smaller left subgenual, left and right rostro-dorsal, and right posterior CG compared with HCs and progressed; FEAFF showed right and left subgenual loss of CG and progressed	FESZ show possible loss of lateralization of CG across AP axis
Rametti et al. [2010]	23 Treatment-resistant SCHZ patients and 23 HCs	Volume and depth of ACS and PCS	Smaller volume of left ACS in SCHZ patients compared with HC. Female patients also had an increase of right PCS compared to female controls	hemisphere × sex × diagnosis interaction
Clark et al. [2010]	38 adolescent SCHZ patients & 35 HCs with 65% follow-up	PCS length and symmetry	PCS asymmetry at intake correlated with verbal fluency in HCs not in patients; at follow-up had increased in HCs but decreased in patients.	trend to diagnosis × sex × side × time interaction
Meredith et al. [2012]	High genetic risk (HGR) (n = 146), FESZ (n = 34) and healthy controls (n = 36)	PCS absent, present or prominent	PCS in LH HCs 86% HGR 79% FESZ 94% in RH HCs 72% GHR 63% FESZ 69%	No significant differences in PCS structure in HGR and FESZ groups compared to HCs

ACS, anterior cingulate sulcus; AP, antero-posterior; CG, cingulate gyrus; FESZ, first episode schizophrenia; FEAFF, first episode affective disorder; HGR, high genetic risk; HCs, healthy controls; LH, RH, left, right hemisphere; PCS, paracingulate sulcus; ROI, region of interest; SCHZ, schizophrenia.

TABLE VI. Asymmetries of Cortical Gyrification in Psychosis and Those at High Risk

Area and authors	Method	Principal findings	Comments
Cortical morphology Vogeley et al. [2000], Narr et al. [2004], Harris et al. [2004], Falkai et al. [2007] and Sallet et al. [2003]	MRI gyrification Indices	Mean increase in gyrification in right prefrontal region in males. Narr et al [2004] found significant increases in cortical folding in the right superior frontal cortex [Harris et al., 2004], in male but not female patients [Narr et al., 2004]; bilateral increase in SCHZ [Falkai et al., 2007] decrease on left [Sallet et al., 2003].	Finding of an increase on the right together with a decrease on the left is consistent with the concept of failure of hemispheric lateralization
Harris et al. [2007]	MRI high risk study	Increased gyrification of right PFC predicts transition to psychosis	
Wiegand et al. [2005]	MRI gyral surface complexity along the gray matter-CSF boundary	Left-greater-than-right asymmetry of pre-frontal cortex: HC > BP > SCHIZ	Consistent with a continuum concept
Schultz et al. [2010]	MRI entorhinal cortical shape and area	Left but not right entorhinal cortical surface area and folding correlated with positive symptoms	Entorhinal cortex is close to temporal horn and pole.
Palaniyappan et al. [2013]	MRI adolescent onset SCHZ patients and age-matched HC	Hypergyria of Broca's area on L and hypogyria of "Wernicke's area" on R with adjacent areas of insula	Two year follow-up: gyrification increased in HC, decreased in SCHZ patients and predicts impaired category fluency
Mental retardation Bonnici et al., [2007]	MRI of psychotic and retarded populations	Gyrification index: HC > SCHZ+ comorbid group > retarded group	
DLPFC Cullen et al. [2006]	Post-mortem: cell density, size and shape in area 9 of DLPFC	Asymmetries of each index reduced or reversed	

BP, bipolar; SCHZ, schizophrenia; HC, healthy controls; DLPFC, dorso-lateral pre-frontal cortex.

schizophrenia and four healthy MZ twin pairs) activation of the right homologue of Broca's area increased with familial loading.

Discrimination of speech. In an fMRI study of activations by stories presented in a familiar versus an unfamiliar language, lateralization to the left middle temporal, angular, and inferior frontal gyri was decreased in patients [Dollfus et al., 2005], and the decrease was stable over time [Razafimandimby et al., 2007].

In a review of functional brain imaging in relation to language in individuals with, and those at genetic risk of schizophrenia Li et al. [2009] concluded that the normal pattern of left hemisphere dominance for language is significantly disturbed. In eight out of fifteen studies in their Table I disturbance on the left reflected loss of asymmetry between the hemispheres.

Lateralization and inter-hemispheric transmission of words. Monitored with slow event-related potentials individuals with schizophrenia consistently failed to achieve the left (fronto-temporal) dominance for phonological discriminations [Angrilli et al., 2009] observed in healthy controls. This suggests that the primary change in the evolution of language is segregation of the phonological engram in the frontal lobe to the left; and that in schizophrenia this lateralization is diminished or lost.

In a tachistoscopic lexical decision task for words presented to one or both visual fields, Mohr et al. [2008] found patients with schizophrenia failed to show the "bilateral redundancy gain" (BRG) of healthy individuals. In another study [Barnett et al., 2005] performance of controls improved when words were presented bilaterally, while that of patients deteriorated.

These studies identify the pathophysiology of schizophrenia as "failure of hemispheric dominance for language" [Crow, 1997b]. They suggest a concept of normal language whereby phonological engrams (particularly motor) are lateralized to the left hemisphere but associative engrams (i.e., "semantic" elements) are represented in the diversity of connexions between the hemispheres. In predisposed or affected individuals lateralization of the phonological component is retarded, and its connexions with the associative components are impaired.

Three studies relate dopamine (DA) and glutamate mechanisms to asymmetry (Table VIII).

Amygdala DA. In a post-mortem study a selective increase in dopamine content in the left amygdala [Reynolds, 1983] was correlated with (i) loss of GABA uptake sites in the left hippocampus [Kerwin et al., 1998], and (ii) loss of glutamatergic elements,

TABLE VII. Components of Language

Lateralization of structure	Method	Principal findings	Comments
Li et al. [2007]	fMRI: connectivity of Broca's and other brain areas in a visual lexical decision task	Correlations reduced in both high-risk subjects and SCHZ pts	
Walder et al. [2007]	sMRI SCHZ patients (11M:8F) vs. HC (6M:9F)	Total hippocampal volume reductions correlated with phonological, semantic and syntactic deficits in males	NB hippocampal structure in pm brain not abnormal in SCHZ [Walker et al., 1998; Highley et al., 2003]
Wisco et al. [2007]	MRI "metric distortion" of brain structure	Increase in pars triangularis of Broca's area on left in SCHZ pts	
Kawasaki et al. [2008]	MRI: structural lateralization in the pars triangularis of Broca's area and planum temporale	Skew to rightward asymmetry in pars triangularis and reduced leftward asymmetry in planum temporale in SCHZ pts relative to HC	
Bhojraj et al. [2009]	Asymmetries L > R of pars triangularis, L > R of Heschl's gyrus, L > R of supramarginal and R > L of angular gyri in HC	Asymmetry of pars triangularis reversed; Heschl's gyrus asymmetry exaggerated; asymmetries of supramarginal and angular gyri attenuated in high-risk subjects with verbal fluency deficits	
Lateralization of function			
Sommer et al. [2004]	Language lateralization in MZ twins discordant for SCHZ	Language-related activation in discordant pairs, higher in RH, not different in LH [Sommer et al., 2004]; activation by words in Broca's homologue in RH increased with familial loading [Spaniel et al., 2007]	
Dollfus et al. [2005] and Razafimandimby et al. [2007]	fMRI: speech comprehension	Lateralization to the left middle temporal gyrus, angular, and inferior frontal gyri decreased in patients [Dollfus et al., 2005] stable over time	
Walter et al. [2003]	fMRI: working memory	Verbal > left inferior frontal, spatial > right prefrontal dominance in HC, absent in SCHZ pts, that is, loss of laterality	
Mohr et al. [2008] and Barnett et al. [2005]	Lexical decision task with words and pseudowords presented tachistoscopically either unilaterally or bilaterally	HC showed bilateral redundancy gain (BRG) for words, not for pseudowords. SCHZ pts failed to show the BRG for words [Mohr et al., 2008]; SCHZ pts disadvantaged by bilateral presentation [Barnett et al., 2005]	Consistent with a deficit in inter-hemispheric information exchange
Walder et al. [2006, 2007]	31 SCHZ patients vs. 27 HC assessed with a battery of phonological, syntactic and semantic features	Male patients more impaired than male HC with least deficits in phonology; females less impaired than males but with greatest deficits in phonology	
Collinson et al. [2009]	MRI: 39 adolescent onset SCHZ patients; Dichotic listening	Impaired R ear advantage correlates with smaller L temporal lobe volume	
Angrilli et al. [2009]	Event-related, for example, slow potentials: rhyming/phonological, semantic and word recognition tasks	Phonological potentials lateralize to the left in anterior (fronto-temporal) regions in HC; lateralization absent in SCHZ pts	Exemplifies an hypothesis of the segregation of phonological and semantic traces
Jalili et al. [2010]	EEG synchronization-in SCHZ patients and matched controls (1st and 2nd order S-estimator)	Attenuated asymmetry in alpha and beta bands increasing with disease duration and negative symptoms	
van Veelen et al. [2011]	fMRI of verb generation, antonyms, and semantic decision task in 35 FES neuroleptic-free SCHZ patients	Diminished lateralization between both IFG and STG in SCHZ vs. HC; no correlation with symptoms	Loss of hemispheric differentiation is present early and is not due to medication

(*Continued*)

TABLE VII. (*Continued*)

Lateralization of structure	Method	Principal findings	Comments
Bleich-Cohen et al. [2012]	fMRI of verb generation HC vs. SCHZ vs. OCD patients	Lateralization and inter-hemispheric connectivity in IFG are diminished in SCHZ not OCD patients	
Thought disorder			
Shenton et al. [1992]	Structural MRI; 15 M SCHZ patients vs. 15 M HC	Thought disorder inversely correlated with left superior temporal gyrus volume	
Kircher et al. [2002]	fMRI of thought disordered SCHZ patients vs. HC	Activation in superior temporal gyrus on Left in HC, on Right in TD SCHZ pts; i.e. laterality reversed	
Horn et al. [2010]	Voxel-based morphometry (VBM)	Thought disorder negatively correlated with VBM density in left temporal pole and left superior temporal sulcus	

LH, left hemisphere; RH, right hemisphere; IFG, inferior frontal gyrus; HC, healthy controls; M, male; OCD, obsessive–compulsive disorder; pm, post-mortem; SCHZ, schizophrenia; TD, thought disorder.

assessed with D-aspartate, in the left temporal pole [Deakin et al., 1989]. It is plausible that these changes reflect a delay in lobar development (Table II), with loss of cortical inputs to the central nucleus, and relative proliferation of the DA projection on the left.

Striatal DA uptake. The right-left asymmetry of striatal dopamine uptake assessed with SPECT seen in healthy controls disappeared in a neuroleptic naive schizophrenia group [Hsiao et al., 2003], with absence of overlap between the groups.

Dopamine receptors in striatum. With positron emission tomography (PET) using <C-11> raclopride unaffected individuals from families with two or more first- or second-degree relatives with schizophrenia were found [Lee et al., 2008] to show a loss of asymmetry of D-2 receptors in the putamen, but not the caudate.

TABLE VIII. Deviations in Neurochemical/Basal Ganglia Asymmetry

Chemical variable and authors	Method	Principal findings	Comments
Globus pallidus			
Early et al. [1987]	PET: blood flow	Increased in globus pallidus on left	
Dopamine content of amygdala			
Reynolds [1983]	Post-mortem brain	Selective increase in dopamine content in left amygdala	
Kerwin et al. [1998] and Deakin et al. [1989]	Post-mortem brain	DA increase on the left correlated (i) with loss of GABA uptake sites in left hippocampus [Kerwin et al., 1998], and (ii) loss of glutamatergic elements in the left temporal pole Deakin et al. [1989]	
Dopamine uptake in striatum			
Hsiao et al. [2003] and Lee et al. [2008]	SPECT study in neuroleptic-naive SCHZ patients	No overall change in average striatal dopamine uptake but right-left asymmetry of the caudate and putamen DAT binding in HC disappeared in SCHZ pts	Complete separation of diagnostic groups
Dopamine receptors in striatum			
Lee et al. [2008]	Positron emission tomography (PET) with <C-11> raclopride; nine individuals each with two 1st or 2nd degree relatives and two MZ co-twins of SCHZ patients vs. 11 HCs	Subjects with high genetic risk showed a loss of asymmetry of D-2 receptors in the putamen in comparison with HC	

TABLE IX. Anomalies of Asymmetry in Individuals at High Genetic Risk

Study	Methods	Measures	Lateralized findings	Comment
Keshavan et al. [2002]	MRI of 17 offspring of SCHZ patients compared to HC	DLPFC and amygdalo-hippocampal volumes adjusted for brain size	"...Lateralized alterations in the volume of the left anterior amygdalo-hippocampal complex are evident in unaffected young offspring of schizophrenia patients..."	"And may be of neurodevelopmental origin"
Harris et al. [2004]	MRI of 16 individuals who developed SCHZ from a total of 30 at high familial risk	Volume and gyrification of cortical quadrants	Gyrification increased in DLPFC (areas 9 and 10) in male but not female cases transiting to SCHZ	Sex × diagnosis × hemisphere interaction
Bhojraj et al. [2011]	MRI of 56 offspring of SCHZ patients and 36 controls with 1-year follow-up	Freesurfer surface area and thickness AAA—planum temporale, planum polare, rostral and caudal superior temporal gyrus	Progressive reduction of surface area in left AAA selective to males	Apparent sex × diagnosis × hemisphere interaction over time
Li et al. [2012b]	MRI of 20 SCHZ patients, 21 familial high risk subjects and 48 controls	Freesurfer thickness, area and volume measures	"...Decrease of the normal left-greater-than-right anatomical asymmetry in the inferior orbital frontal area, and a increased left-greater-than-right pattern in the inferior parietal and occipital regions"	
Francis et al. [2012]	3T MRI; young adult HGR subjects (N = 46) and controls with no family history of illness (i.e., at low genetic risk LRC; N = 31)	FreeSurfer 5.0 analysis	Controlling intra-cranial volume, significantly smaller left pars triangularis (PT) ($P < 0.01$) and right pars orbitalis (PO) ($P < 0.01$) volumes and reversal of the L > R pars orbitalis ($P < 0.001$) lateralization were observed in FHR subjects	
Byun et al. [2012]	The cortical thickness of the subjects at HGR (n = 31) was compared with that of HC (n = 29) and patients with schizophrenia (n = 31)	Cortical thickness was measured by Constrained Laplacian-based Automated Segmentation with Proximities algorithm using 1.5-T structural MRI scans	Relative to HC, GHR subjects showed significant cortical thinning in the right anterior cingulate cortex (ACC), left paracingulate and parahippocampal gyrus and posterior cingulate regions. GHR subjects with two or more first-degree relatives with schizophrenia showed a greater reduction in cortical thickness in the right ACC and in the left para-cingulate cortex than those with only one first-degree relative with schizophrenia	By separating groups by degree of genetic loading this study suggests that change in right cingulate and left para-cingulate gyri is closer to the genetic core than other structural change
Li et al. [2012a]	fMRI of language task-based data from 21 patients with schizophrenia, 22 genetic high risk subjects and 36 controls were analyzed	Compared to controls, SCHZ patients and the high risk subjects showed significantly weakened network hubs in left inferior frontal and right fusiform gyri	A "unique" topology of super active and intercommunicating network hubs at left fusiform gyrus and right inferior/middle frontal gyri, which were associated with language impairment was found in the patient group, compared to the high risk and control groups	

AAA, auditory association areas; ACC, anterior cingulate cortex; DLPFC, dorsolateral pre-frontal cortex; HGR, high genetic risk; SCHZ, schizophrenia.

TABLE X. Laterality by Sex by Diagnosis Interactions

Authors	Method	Measures	Principal findings	Comments
Cortical surface lengths Highley et al. [1998]	Post-mortem study	Lengths measured dorsally over the external surface from frontal pole to central sulcus, and from central sulcus to occipital pole	Length asymmetry showed a gender × diagnosis interaction ($P = 0.002$). L > R in F, R > L in M HC. This pattern was reversed in schizophrenia. The converse effect was observed for occipito-parietal measures ($P = 0.028$). No differences for measures around the lateral surfaces of the hemispheres	The dorsal and not lateral location (i.e., in a para-sagittal rather than axial plane) suggests the interactions are in the paralimbic system rather than generalized to neocortex
Gyral volume Highley et al. [1999c] and McDonald et al. [2000]	Post-mortem study	Stereological volume measures in three gyri—superior temporal parahippocampal, and fusiform gyri	In each gyrus, asymmetry to left in HC was absent or reversed in SCHZ pts; in F pts the anomaly was greater with earlier age of onset, but in M pts the anomaly was greater with later ages of onset	
Inter-hemispheric connexions Highley et al. [1999a,b]	Post-mortem study	Fibre density	Greater in F than M HC: relative to same-sex controls decreased in F with SCHZ, but increased in M	
Savadjiev et al. [2013]	MRI	Tract-based spatial statistics & dispersion analysis to determine fibre geometry; applied in adolescent onset schizophrenia	A single area of diagnosis by sex interaction was identified in L frontal corpus callosum	PANSS negative symptoms correlate positively with increasing dispersion to the left in males and negatively in females
Ventricular size and shape Narr et al. [2001]	MRI	Three-dimensional assessment of ventricular structure	Enlargements L > R hemisphere, and diagnosis by hemisphere by sex interactions, (esp superior horn); horizontal displacement of the walls in opposite direction in the two sexes—outward in F and inward in M	
Graham et al. [2006]	MRI	Point distribution with discriminant linear analysis of shape asymmetry	M and F HC and SCHZ patients differ from each other in lateral asymmetry	
Planum temporale area Goldstein et al. [2002]	MRI	Topographic landmarks	Area asymmetry accentuated in M, diminished in F SCHZ patients	Emphasizes sexual dimorphisms
Hemisphere volume Collinson et al. [2003]	MRI	Total brain volume (TBV) and hemisphere volumes	TBV smaller in early-onset, especially for the left hemisphere in males (6.0%). A significant sex × diagnosis × hemisphere interaction: F pts reduced rightward asymmetry and M pts reduced leftward asymmetry relative to male controls. Both correlated with reduced IQ	

TABLE X. (Continued)

Authors	Method	Measures	Principal findings	Comments
Gyral complexity				
Narr et al. [2004]	MRI	Gyral complexity assessed by lobe and hemisphere	Frontal asymmetry to the left in M controls lost in M SCHZ patients; occipital asymmetry to the right in F HC lost in F SCHZ patients	Distribution of asymmetry according to the Gratiolettian axis, with a sexual dimorphism along the antero-posterior dimension
Paracingulate sulcus length				
Clark et al. [2010]	MRI	Length measurements	$L > R$ asymmetry increases with age in HC; trends to symmetry in SCHZ patients (M $L > R$; F $L < R$)	
Anterior cingulate sulcus volume				
Rametti et al. [2010]	MRI	BrainVisa	Reduced on L in SCHZ patients F > M	
Cortical quadrant volumes				
Mackay et al. [2010]	MRI	Torque analysis [Mackay et al., 2003]	Cortical volumes increased in M bipolar and decreased in F patients relative to sex-matched HC in L frontal and R occipito-parietal–temporal quadrants	Change follows the "Gratiolettian torque;" indicating that bipolarity cortical volume, sex, and laterality are somehow related

HC, healthy controls; SCHZ, schizophrenic patients; IQ, intelligence quotient.

The genetic influence on laterality of brain structure has been assessed in "high risk" relatives of psychotic patients. Thus in 60 young (9–25 years of age, mean 15.4 years) high risk subjects by comparison with 42 healthy controls Bhojraj et al. [2009] found reversal of the $L > R$ planum temporale asymmetry present in controls. Moreover the $L > R$ asymmetry of Heschl's gyrus seen in controls was exaggerated and asymmetries $L > R$ of supramarginal and $R > L$ of angular gyri seen in HC were attenuated in HR subjects. In an older population (mean age 25 years) at high genetic risk Francis et al. [2012] found significantly smaller left pars triangularis (PT; $P < 0.01$) and right pars orbitalis (PO; $P < 0.01$) volumes in Broca's area and reversal of the $L > R$ pars orbitalis ($P < 0.001$) lateralization.

There is little reason to doubt that changes in brain structure close in form to those present in individuals with the disease and comprising deviations plausibly related to the faculty of language are true manifestations of genetic predisposition. This conclusion challenges a primary pathogenic role for the multiple associations now identified in genome-wide association studies <see section below on the genetics of psychosis>. How could such diversity of genetic predisposition account for these relatively uniform structural deviations? The alternative interpretation is that the GWAS findings represent secondary adjustments to a primary and sex-dependent re-organization of the latest aspect of development of the human brain.

LATERALITY BY SEX INTERACTIONS

While the above findings support the argument that asymmetry is pivotal to pathophysiology some interactions with sex have been

noted [Falkai et al., 1992; DeLisi et al., 1994c; Hoff et al., 1994; Goldstein et al., 2002; Harris et al., 2004; Rametti et al., 2010; Walder et al., 2006]. A further set of findings document that the relationship is systematic:

1. Cortical surface lengths. In post-mortem brain [Highley et al., 1998] length asymmetry from the frontal pole to the central sulcus measured dorsally over the external surface, showed a gender × diagnosis interaction ($P = 0.002$). Female controls had a left-greater-than-right asymmetry, and male controls had a right-greater-than-left asymmetry. In both sexes the pattern was reversed in schizophrenia. With a similar measure in the occipito-parietal lobes ($P = 0.028$) a complementary pattern was seen. Differences between the groups were not present in measures taken around the lateral surface of the hemispheres.

2. Gyral volumes. In the same brain series, consistent changes of asymmetry were observed in three gyri—superior temporal [Highley et al., 1999c], parahippocampal, and fusiform [McDonald et al., 2000]. In each case, an asymmetry of volume to the left observed in the control population was absent or reversed in patients of both sexes, but age of onset separated the sexes—in female patients the anomaly was greater with earlier age of onset, as might be expected, but in male patients the reverse was the case—the anomaly was greater with later ages of onset.

3. Inter-hemispheric connexions. On histology of the corpus callosum [Highley et al., 1999a] fibre density was greater in females than males: compared to same-sex controls in female patients with schizophrenia density was decreased, whereas in males it

was increased. A similar sex by diagnosis interaction was seen in the anterior commissure [Highley et al., 1999b].

4. *Hemisphere volumes.* In an MRI study total brain volume was reduced in a group of individuals with early-onset psychosis [Collinson et al., 2003], especially for the left hemisphere in males (6.0%). Female cases had reduced rightward asymmetry relative to female controls, and male cases tended to have reduced leftward asymmetry relative to male controls. Both reductions were correlated with reduced IQ.

5. *Ventricular size.* In a three-dimensional MRI analysis Narr et al. [2001] observed enlargements of the ventricles greater in the left hemisphere, and diagnosis by hemisphere by sex interactions, particularly in the superior horn (Fig. 2). The changes include a vertical displacement upward of the roof of the ventricle present in both sexes, and a horizontal displacement of a large segment of the walls, extending from the trigone to the ventral surface of the superior horn, and including the dorsal surface of the inferior horn, that is in opposite direction in the two sexes—outward in females and inward in males. The shape of that part of the ventricle that encircles the Sylvian fissure has changed in a way that differentiates the sexes.
   With linear discriminant analysis significant differences in lateral asymmetry between the sexes were observed alongside sex-specific deviations in schizophrenia [Graham et al., 2006].

6. *Gyral complexity.* Along the Gratiolettian axis asymmetry to the left in the frontal lobes in control males, and to the right in the occipital lobes in females was lost in the respective male and female patient groups [Narr et al., 2004].

7. *Cingulate sulcus continuity.* Interruptions of the cingulate sulcus have been reported to be more common in high-risk individuals and in those with schizophrenia, in both hemispheres, compared to controls [Meredith et al., 2012]. Notably when separated by gender, the finding was present in males only in the left hemisphere and in females only in the right hemisphere.

FIG. 2. Reproduced with permission from [Narr et al., 2001]. Color averages indicate group differences defined by sex and diagnosis. (Blue: male schizophrenic patients; green: male control subjects; purple: female patients; yellow: female control subjects; RH, right hemisphere; LH, left hemisphere).

8. *Meta-analysis of* Bora et al. [2012]. Perhaps the most cogent evidence of an interaction between sex and asymmetry comes from a study in which meta-analyses of the MRI literature on brain structure in schizophrenia and bipolar disorder were conducted first with all studies included, yielding the predicted excess of males with a diagnosis of schizophrenia, and second confined to studies in which the sample sizes were balanced with respect to sex.

In the first analysis structural deficits were detected in schizophrenia in the insula and paralimbic structures (cingulate and paracingulate gyri) on both sides. In the second analysis there was reciprocal laterality between the disorders: in schizophrenia the deficits in the insula were focal to the left side, and more posterior, whereas in bipolar disorder they were focal to the right side, and more anterior. In the paralimbic system (cingulate gyrus) sidedness was reversed—the deficits were predominantly to the right in schizophrenia and to the left in bipolar disorder.

Three telling conclusions can be drawn: (a) that the anatomical bases of bipolar disorder and schizophrenia are intimately related. The structures implicated in schizophrenia include all the structures implicated in bipolar disorder, (b) the conditions are distinguished by the direction of deviations in lateralized brain structure, and (c) laterality interacts with sex to determine form of psychosis.

Together these findings indicate that the interaction between sex and asymmetry is intrinsic to psychosis. What is the meaning of such an interaction? How is laterality apparently involved in so many aspects of psychosis? Here it is argued that psychosis can be understood only in relation to the mechanism of sexual selection, and that such selection relates to a feature that defines a species.

SEXUAL DIMORPHISMS AND SPECIES DIFFERENCES

How do quite different sexual dimorphisms come to characterize closely related species? Since Darwin [1871] introduced the concept the relationship between sexual selection (as an explanation of the origin of sexual dimorphisms) and natural selection (as the mechanism of adaptation to the environment) has been debated.

One concept of what defines a species is the "specific mate recognition system" [Paterson, 1985, 1992], an externally detectable characteristic that distinguishes individuals of the same from other species, but also distinguishes members of one sex from the other. How might such a system evolve? A recent view [Kaneshiro, 1980; Kaneshiro and Boake, 1987; Carson, 1997] is that sexual selection and speciation are related, and that speciation is initiated by a change in a male that is then selected by females. This suggests initiation by the Y chromosome; but the X is also involved. Haldane's [1922] rule—that when in a hybrid cross viability or fertility is reduced it is the heterogametic sex that is most affected is generally held to implicate a locus on the X chromosome [Coyne and Orr, 1989; Presgraves, 2008] in speciation in mammals (and more generally across orders the homogametic chromosome).

A region of XY homology is implicated by the following account: Each speciation event is initiated by a change (often the addition or subtraction of gene sequences) on the Y chromosome, and
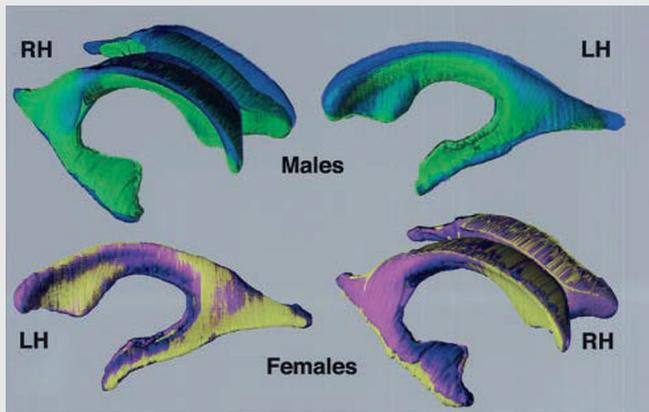
completed by change (in this case at the level of DNA sequence) in a region of homology on the X chromosome.

Each species is identified by the configuration (the pattern of paired and unpaired sequences) of the X and Y chromosomes achieved in the XY body (the compartment that separates the X and Y from the autosomes in male meiosis [Namekawa et al., 2006]). The configuration arrived at by steps (1) and (2) is "validated" (sealed by an epigenetic modification yet to be identified) by a unique conformation of the zinc finger motif of the Prdm9 gene [Oliver et al., 2009] that plays a role in both speciation and identifying sites of recombination within species. Recombination sites are selected by the new conformation of the Prdm9 zinc finger motif [Myers et al., 2010]. For each species an engram that encodes the species-defining function (a unique combination of X and Y chromosomes) is passed, with its associated variation, between generations as an epigenetic imprint [Crow, 2000, 2004b, 2008, 2012]. In Homo sapiens it is argued this variable specifies the torque (laterality) of the cerebral hemispheres.

MALE MEIOSIS AND THE EPIGENETIC IMPRINT

Male meiosis, in which X and Y gametes are generated and the diploid is reduced to the haploid number of chromosomes, takes place in two nuclear compartments, one containing the autosomes, and the other a structure termed the XY body [Namekawa et al., 2006] the only location and time at which the X and Y chromosomes come into apposition [Crow, 1991]. Homologous regions pair and unpaired regions are inactivated by a process referred to as "meiotic suppression of unpaired chromosomes" (MSUC) [Baarends et al., 2005; Turner, 2007] that reflects the distribution of X–Y homologies. The resulting imprint persists through fertilization [Huynh and Lee, 2003] to the embryo.

What happens when a structural re-arrangement, such as the Xq21.3/Yp11.2 duplication [Sargent et al., 1996; Schwartz et al., 1998] that created the X-transposed region (XTR) of the Y, occurs? In the rare event that the change is advantageous (through female selection) the new arrangement of the Y will increase in the population. At this stage a change in the X sequence that increases the distinction between the phenotypic character in males and females will have an advantage because it facilitates mate recognition with respect to the new feature. Thus a change in the X sequence that separates the interaction of the X protein with itself from its interaction with the Y protein (e.g., of the Protocadherin11XY (PCDH11XY) gene pair described in the section below) will generate a marker that distinguishes the species and separates males from females in terms of a single dimension.

According to this account the process of speciation generates the "lock and key" (the interaction between X and Y chromosomes) that passes as an encoded message (with unpaired segments epigenetically inactivated) between generations to identify the new species. The gene Prdm9 that includes a zinc finger motif highly variable between species, and a histone3lysine4 tri-methylation capacity relevant to modifications of chromosome configuration may encode and apply the imprint. Thus Prdm9 represents a component of the hardware of speciation while segments of the X and Y chromosomes constitute the software on which Prdm9 acts.

It has recently been reported [Frans et al., 2011] that in addition to the well-established increase with age of the father at the time of birth of the child [Malaspina et al., 2001] risk of psychosis also increases with age of the maternal grandfather. Selectivity to the maternal rather than the paternal grandfather suggests X linkage, but an influence of paternal age cannot be transmitted to a son if it is carried by the X chromosome [Crow, 2012]. Therefore if these apparently epigenetic effects are related they reflect interaction between X and Y chromosomes.

Models of epigenetic transmission between generations [Morgan and Whitelaw, 2008] including that, at least in mice, such transmission relates to mate preference, that is sexual selection [Crews et al., 2007], are of particular interest. In man parental influence on the cerebral cortex has been related differentially to area in paternal and thickness in maternal transmission [Shaw et al., 2012].

SPECIATION IN THE HOMININ LINEAGE

Human speciation is cast in this wider context. The hominin lineage is defined by the Xq21.3 to Yp11.2 duplication [Sargent et al., 1996] that took place 6 MYA (million years ago), close and perhaps causally-related to the divergence of hominin and chimpanzee lineages [Williams et al., 2006] (PAR2 was established later [Freije et al., 1992]). Within this homologous block the gene pair Protocadherin11XY (PCDH11XY) is expressed as two complementary cell surface adhesion factors from the X and the Y chromosomes respectively; playing a role in cell-cell recognition [Priddle and Crow, 2013a]. PCDH11Y has been subject to 16 non-synonymous substitutions since the common human-chimpanzee ancestor. PCDH11X has been subject to five amino acid substitutions including addition of two sulfur-containing cysteines [Williams et al., 2006]. In post-natal ontogeny [Weickert et al., 2009] the PCDH11XY gene pair has the largest expression among the earliest expressed sexually dimorphic genes in the human brain. The potential significance of the Protocadherin11XY gene pair in the development of the capacity for language [Priddle and Crow, 2013a, b] is illustrated by the case of a 4-year-old boy with severe language delay found to have independent deletions of the PCDH11 gene on both the X and the Y chromosomes detected by micro-array and confirmed by fluorescence in situ hybridization [Speevak and Farrell, 2011]. More generally the sequence of changes within the X-transposed region and in PCDH11X, and the acquisition of PAR2, can be seen to be relevant to the course of hominin speciation over the past 6 million years. Within this context a hot-spot of recombination identified within PAR2 [Sarbajna et al., 2012] is of potential relevance to human diversity.

THE GENETICS OF PSYCHOSIS

Attempts to identify genes for psychosis by linkage have not yielded findings consistently replicable across studies or populations [Crow, 2007]. Until recently genome-wide association studies (GWAS) have also failed to identify markers closely associated with psychosis, but with a steady increase in sample size and in density of markers across the genome there are indications that a small number of genes (including CACNAIC and ZNF804A it is

suggested) are consistently associated with schizophrenia and/or bipolar disorder [Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013 2013], although through associations that are small in magnitude.

From the observation that combinations of autosomal SNPs (single nucleotide polymorphisms) predicting schizophrenia in one sample also predict illness in independent samples it has been argued [Purcell et al., 2009] that heritability is highly polygenic with perhaps more than a thousand genes each contributing a very small effect. These authors postulate a causal relationship between genes in LD with these SNPs and the disease. Since only a fraction of the heritability can be accounted for a sex chromosomal contribution is not excluded, as argued here, alongside but independent of autosomal polygenes. The question arises why genes on the sex chromosomes have not hitherto been examined in GWAS. The current state of microarrays in relation to the XTR presents a particular problem in that a distinction must be made between variability of sequence arising from true polymorphisms (between individuals) and X–Y differences fixed in the population [Trombetta et al., 2010]. A map of these two classes of variation has yet to be constructed.

A parsimonious hypothesis is that autosomal and sex chromosomal contributions are related through adaptive changes that follow the speciation event. Here it is postulated that a new species is established on the basis of a structural change on the Y chromosome selected by females, followed by change in homologous sequences on an X chromosome that consolidates a new system of mate recognition [Paterson, 1992]. The novel configuration of X and Y chromosomes carries into the new species a subset of autosomal variation that operates in an environment dominated by a new mate recognition principle. Some alleles will be unsuited to the milieu of both male and female cells in the novel environment and will be selected out, but others will be suited more to the cells of one sex than the other.

Mate recognition dominates fecundity in the new species. It aligns the force of selection along the male-female axis. The new principle drives growth of certain structures (in particular those concerned with signaling between individuals) and sustains maxima of discriminability and reproductive capacity in the two sexes. Existing variation un-coordinated with the new sexual dimorphism will need to adapt. Systems previously unidirectional or "monomorphic" are driven to distinct peaks of activity compatible with a system operating in a dimorphic manner. Thus the transition between sexual dimorphisms (in the formation of the new species) is the driving force in creating diversity and conflict in the genome.

If the primary change in speciation of modern Homo sapiens is in the Protocadherin11XY gene pair secondary changes, for example, in calcium delivery, neural connectivity and myelination in the central nervous system may be expected. Such change may take place over many generations, and a range of individual variation that is less than optimal viewed in relation to the dimorphism as a whole will be retained. The spectrum of variation in the new species thus comprises a primary dimorphic core entrained through secondary mechanisms each associated with genetic variation positive in one of the dimorphic states but neutral or negative in the other. Such genes are predicted to be sex-related in expression, although

autosomal in location (see, e.g., the findings relating to CACCNAIC [Strohmaier et al., 2013]).

Brain size increased at least twice in the hominin lineage: at the transition from Australopithecus to Homo habilis or Homo ergaster, and at the transition between Homo heidelbergensis/antecessor and the large brained Homo neanderthalensis and Homo sapiens. Such increases were presumably achieved by a prolongation of brain growth and, according to the above argument, through a new sexual dimorphism. The relevant genes are predicted to be "late developmental" [Pogue-Geile, 1997] and to encode a range of diversity expressed at the reproductive peak rather than early in the course of development. Recent evidence from dental striations [Volpato et al., 2012] indicates that directional asymmetry almost certainly was present in Homo neanderthalensis, and its absence earlier although controversial [McGrew and Marchant, 1997; Palmer, 2002; Lonsdorf and Hopkins, 2003; Hopkins, 2007] has been documented within [Chapelain et al., 2011] and across [Holder, 1999] species. It is possible that directional asymmetry on a species basis entered at the Australopithecus/Homo ergaster transition. This suggests that hominin species prior to Man had a capacity for "proto-language," and that this underwent a transformation at the origin of modern Homo sapiens 150 thousand years ago [Priddle and Crow, 2013a]. In this case a plausible genetic correlate is the paracentric inversion of the duplicated block in Yp11.2 as this will have brought the X and Y sequences of PCH11XY into register thus increasing the likelihood of pairing, with a concomitant increase in diversity and complexity of late development.

The corpus callosum goes on expanding into the third and fourth decades, and this expansion is delayed in females relative to males [Cowell et al., 1992; Pujol et al., 1993] perhaps because the cortex is wider, and a critical fraction of myelinated axons is reached later. Fibre density is greater in females [Highley et al., 1999a,b]; in female patients it is reduced, and in male patients increased, relative to same sex controls. Thus myelination of inter-hemispheric connexions is a leading candidate as the target of the disease process [Crow, 1998a]. The functions most directly affected are those that are most recently evolved and sapiens-specific, including the capacity for language [Crow, 1996, 1997a, 1998b; DeLisi, 2001], and its putative anatomical correlate cerebral asymmetry [Crow et al., 1989a]. In evolutionary terms, psychosis can be described as "the price that Homo sapiens pays..." [Crow, 1997a] and its pathology as the "...failure of lateralization..." [Crow, 1997b] for language.

According to this concept the variation that underlies psychosis: (1) relates to the most recent change (the cerebral torque) in hominin evolution, established at the transition to modern Homo sapiens, (2) is epigenetic (non-Mendelian) in form, being generated and modified in male and female meiosis, (3) is formed around the configuration of X and Y chromosomes that pair in male meiosis, and (4) includes variation relating to the most recently acquired XY homologous gene pair. The PCDH11XY gene pair generates a sexual dimorphism that may constitute the human mate recognition system as the foundation of the capacity for language.

Direct tests of this hypothesis can now be framed as predictions concerning epigenetic modifications of expression of the Protocadherin11XY gene pair either through methylation of DNA

sequences, in part excluded by Ross et al. [2003], or modifications of other elements of epigenetic control at the level of histone structure. Parallel predictions relate to the diversity generated in relation to genes such as SPRY and VAMP in PAR2. Such predictions may be testable within a discordant MZ twin paradigm [Rosa et al., 2008]. Quested et al. [2010] asked "Is loss of gender dimorphism a unifying theme in schizophrenia findings?." In the wider context of schizophrenia and bipolar disorder the relevance of this question is pinpointed by Bora et al. [2012]. Neither the morphological changes nor their genetic basis can be understood unless the factors of sex and laterality and the interaction between them in the psychoses are taken into account.

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