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Neuroscience and Biobehavioral Reviews 28 (2004) 41–53

NEUROSCIENCE AND
BIOBEHAVIORAL
REVIEWS

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Schizophrenia—an evolutionary enigma?

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Received 14 July 2003; accepted 23 October 2003

Abstract

The term ‘schizophrenia’ refers to a group of disorders that have been described in every human culture. Two apparently well established findings have corroborated the need for an evolutionary explanation of these disorders: (1) cross-culturally stable incidence rates and (2) decreased fecundity of the affected individuals. The rationale behind this relates to the evolutionary paradox that susceptibility genes for schizophrenia are obviously preserved in the human genepool, despite fundamental reproductive disadvantages associated with the disorders. Some researchers have therefore proposed that a compensatory advantage must exist in people who are carriers of these genes or in their first-degree relatives. Such advantages were hypothesised to be outside the brain (e.g. greater resistance against toxins or infectious diseases), or within the social domain (e.g. schizotypal shamans, creativity). More specifically, T.J. Crow has suggested an evolutionary theory of schizophrenia that relates the disorders to an extreme of variation of hemispheric specialisation and the evolution of language due to a single gene mutation located on homologous regions of the sex chromosomes.

None of the evolutionary scenarios does, however, fully account for the diversity of the symptomatology, nor does any one hypothesis acknowledge the objection that the mere prevalence of a disorder must not be confused with adaptation. In the present article, I therefore discuss the evolutionary hypotheses of schizophrenia, arguing that a symptom-based approach to psychotic disorders in evolutionary perspective may improve upon the existing models of schizophrenia.

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Keywords: Schizophrenia; Genetics; Human evolution; Trade-off; Dysconnectivity; Brain maturation; Heterochrony; Language; Social brain; Catatonia; Symptom-related approach

1. Introduction

The term ‘schizophrenia’ originally proposed by Eugen Bleuler in 1908 in a scientific meeting refers to a group of disorders characterised by severe cognitive, emotional and behavioural symptoms [1]. These disorders usually manifest in late adolescence or early adulthood, although childhood precursor symptoms are frequent, [2]. It seems obvious that schizophrenic disorders are ubiquitous and occur in virtually every human society. The prevalence and incidence rates are supposed to be cross-culturally similar (recently reviewed in Ref. [3]). This would suggest that intrauterine virus infections, nutritional conditions or other exogenous influences during the foetal period, for example,

cannot fully explain the comparable frequencies of these disorders across cultures, let alone the clinical resemblance of psychotic syndromes in different cultures [4]. Twin and adoption studies have clearly demonstrated that genetic factors play a significant role in the transmission of schizophrenia; this, however, does not rule out that environmental influences also contribute to the manifestation of schizophrenia [5–8]. The incidence rate of ‘core schizophrenia’ of roughly 1% in human populations exceeds a mere chance effect due to high mutation rates, e.g. [9–11], and it is widely accepted that the fecundity of people with schizophrenia, particularly of males, is reduced by about 50% compared to healthy individuals [12].

These findings create an evolutionary puzzle: why has natural selection allowed genes to persist in the human genome that increase the likelihood of suffering from these devastating disorders, despite the reproductive disadvantage of schizophrenia? In fact, the persistence of schizophrenia

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suggests that (1) genes related to the disorder convey advantages in terms of survival or reproduction (genetic polymorphism) or (2) genes associated with schizophrenia may be linked to other genes that have an advantage (pleiotropy).

Evolutionary-based explanations of schizophrenia could, therefore, be informative if they accounted for (1) a plausible mechanism for the preservation of these genes in the global human genepool, (2) potential sex differences, for example, in age at onset of schizophrenia, and, most importantly, (3) the multi-faceted symptomatology of schizophrenic disorders; (4) they should, however, also be consistent with neuropsychological, developmental and evolutionary findings regarding the human brain.

A host of evolutionary hypotheses regarding schizophrenia has been published over the past 40 years or so that may be loosely distinguished according to three central topics, although considerable overlap exists: one set of hypotheses focuses on the survival advantage of heterozygous gene carriers, e.g. [9,13,14]; a second group of hypotheses concentrates on the impaired ontogenetic neurodevelopment in schizophrenia, in part related to aspects of heterochronic processes and neural connectivity [15–18]; a third array centres around the hypothesis that schizophrenia represents a trade-off of the evolution of human ‘sociality’, e.g. [19–21]. The most sophisticated theory proposed by T.J. Crow in a number of seminal articles relates schizophrenia to the evolution of language and cerebral asymmetry [10,11,22–32]. Although a number of excellent review articles on the presumed evolutionary background of schizophrenia have been published in recent years [18,33,34], none has sufficiently addressed the important question of what evolutionary hypotheses may precisely add to present-day schizophrenia research, or what the possible implications of the evolutionary approach for current psychiatric nosology are.

In the present article, I shall therefore firstly summarise the divergent evolutionary concepts of schizophrenia and secondly discuss some issues of evolutionary approaches to the understanding of psychotic symptoms.

2. Are there selection advantages of schizophrenia-related genes outside the nervous system?

The question of a possible survival and reproductive advantage of heterozygous carriers of schizophrenia susceptibility genes was first raised by Huxley et al. [9]. They argued that the incidence rate of approximately 1% in human populations would lie well above a plausible mutation level and hence provided evidence for a balanced (poly)morphism. That is, genes that on the one hand increase the risk of developing schizophrenia, may also have beneficial effects in other domains, similar to the case of sickle-cell anaemia, where heterogeneous carriers of the allele are relatively better protected against malaria

infection than non-carriers [35]. Huxley and co-workers proposed that schizophrenic individuals might either be more resistant to infectious diseases, or had an unknown reproduction advantage (particularly female schizophrenic patients). Regarding the latter assumption they drew parallels to a possibly increased female fertility in haemophilia, whereas males having the condition faced a high reproductive disadvantage. Thus Huxley et al. [9] located the compensation of reduced fecundity of male schizophrenic patients outside the nervous system. Drawing from this hypothesis, Erlenmeyer-Kimling [13] found in a retrospective analysis of live-born offspring of schizophrenic patients that the cumulative mortality rate from birth to age 15 of females was significantly lower compared to the mortality rate of females of non-schizophrenic control families. Moreover, an increased survival rate among offspring of schizophrenic persons emerged for both sexes in the first year of life; a finding that was at odds with previous studies carried out in the 1920s [13]. More specifically in terms of what such a survival advantage could be, Carter and Watts [14] made an interesting discovery in a study assessing the resistance to infectious diseases, rate of accidents and injuries and the fertility of first-degree relatives of schizophrenic patients. They found a diminished rate of virus infections, a lower rate of accidents and increased fertility in first-degree relatives of patients with schizophrenia. They tentatively interpreted their findings in a way that suggests that genes associated with schizophrenia could convey a survival advantage in relatives and thus explain the persistence of such genes in the population.

More recently, researchers have proposed a ‘developmental instability’ model of schizophrenia that in many respects also relies on the assumption of a selection advantage outside the nervous system (reviewed in Ref. [36]). This theory suggests that schizophrenia may emerge due to an individual’s incapacity to ‘buffer’ the negative effects of multiple mutations, pathogens and toxins. Central to this line of argumentation is that the so-called ‘fluctuating asymmetry’ (FA), that is, a near-normally distributed asymmetry of bilateral characters that are on average symmetrical in the population, is greater in twin pairs concordant for schizophrenia than in discordant pairs. Greater FA may therefore indicate an imprecise expression of the developmental design due to genetic or environmental causes [36]. This could explain, for example, why patients with schizophrenia have a greater number of minor physical abnormalities such as hypertelorism that could be indicative of an incomplete early cell migration. Other characteristics putatively associated with a developmental instability in schizophrenia are a greater homozygosity of blood alleles, a lower premorbid intelligence, a reduced cortical volume, and a relative instability of functional and anatomical lateralisation of brain functions in schizophrenia [36]. Similarly, it has been proposed that the accumulation of potentially deleterious mutations, genetic variability due

to pathogen–host co-evolution and homozygosity at key alleles may affect developmental stability (and FA) in many ways (reviewed in Ref. [37]).

Early hypotheses speculating on advantages outside the nervous system have been criticised for a number of reasons: Polimeni and Reiss [34], for instance, have recently argued that the study by Carter and Watts [14] was statistically flawed by a lack of a Bonferroni corrected statistical analysis of the data. In addition, Carter and Watts did not convincingly rule out the possibility that the reduced rate of infections and injuries in first-degree relatives of schizophrenic patients could be due in part to a reduced exposure to viral diseases or accident-prone situations. These individuals might carry, for example, an increased load of schizoid personality traits, which could account for their being ‘less social’ relative to control subjects in the general population.

A more general argument refers to the fact that natural selection acts on the phenotype rather than on the genotype. Thus, potential compensatory advantages of genes associated with schizophrenia rather ought to be expected in the behavioural, emotional or cognitive domain. However, recent research has revealed a higher activity of natural killer cells in a schizophrenic sample [38], which may lend some support to the assumption of a compensatory advantage outside the nervous system. In addition, a gene that causes Tay-Sachs disease, which typically manifests in early childhood and is characterised by debilitating alterations in the central nervous system by accumulation of a GM2 ganglioside, may have been selected because it confers a relative protection against tuberculosis [39]. Thus an advantageous effect of a gene or genes associated with schizophrenia outside the nervous system is well conceivable.

The ‘developmental instability model’ [36] of schizophrenia that suggests that polygenetic design flaws related to FA may be involved in the origin of psychotic disorders, also postulates that environmental factors such as toxins and viruses play an important role. If this were the case, however, one would expect dissimilar incidence rates across different environments [32], which has in fact been controversially debated, e.g. [40], and the comparison of incidence and prevalence rates also critically depends on diagnostic conventions.

At this stage it may therefore be concluded that studies focussing on the potentially greater resistance to infectious diseases in schizophrenic patients—or their first-degree relatives—need to be replicated in larger samples. Further, the ‘developmental instability model’ requires testing in cross-cultural comparison applying rigorous diagnostic criteria. But it may well be worth pursuing these ideas, given the fact that theoretically, even the natural mutation rate could account for such a complex disease like schizophrenia, if, as Ernst Mayr pointed out, more than six loci would produce similar phenotypic effects (quoted after Ref. [14]).

3. Neurodevelopmental hypotheses of schizophrenia

3.1. Heterochrony

The term ‘heterochrony’ was coined by Ernst Haeckel [41]. It refers to changes in developmental timing of tissue or morphological structures during ontogeny in relation to the timing of their development in ancestral species. Speeding up or slowing down the growth curves of different morphological characters in relation to each other results in divergent large-scale shaping of the entire body, parts of the body or in specific changes on the molecular level. Haeckel had proposed that ontogeny briefly and incompletely recapitulated phylogeny. This view was challenged, for instance, by De Beer [42], who advocated that the reverse might apply, i.e. that phylogeny was the result of ontogeny rather than its cause. (Both positions are going to be reconciled, for instance, in the work of McKinney and McNamara [41]).

With respect to schizophrenia it has therefore been suggested that the brain development in schizophrenic patients could be due to dysfunctional genes regulating the speed of maturation. On the grounds of the recapitulation theory Millar [43] proposed that schizophrenia represented a condition of insufficient recapitulation of the final developmental steps during adolescence. He argued that, according to MacLean’s distinction between the ‘reptilian’, the ‘palaeomammalian’ and the ‘neomammalian’ brain (i.e. upper brainstem, limbic system, and neocortex), many symptoms of schizophrenia could be related to an insufficient suppression of the phylogenetically old ‘reptilian’ brain system.

An opposing view, however, emerged from the so-called ‘neoteny’ hypothesis of human evolution. Since the 1920s several scientists argued that neoteny, literally ‘holding on to youth’, would account for the major physiological and behavioural changes of human beings compared to the great apes, and as such, may be called the ‘hallmark of human evolution’ (overview in Ref. [17]). This assumption was based on the observation that adult human beings superficially resembled juvenile apes, thus, it had been deduced that humans retain juvenile features into adulthood compared to apes and their putative common ancestor. Many physiological peculiarities have subsequently been ascribed to neoteny such as relative hairlessness, the rounded shape of the human skull, and eventually brain size. Moreover, in respect of behaviour it has been suggested that playfulness, curiosity and intelligence derive from a shift towards neoteny in human evolution [44]. Bemporad [45] has therefore argued that the lack of curiosity in schizophrenic patients and other behavioural symptoms may point to a ‘failure of neoteny’ in these disorders [45]. In addition, Crow [25] has reasoned that a defective neotenic development may account for an insufficiently established cerebral dominance in one or the other hemisphere (see below).

Without explicitly referring to heterochrony, Saugstad [16,46,47] has reasoned that the asymmetry of hemispheric development is related to the speed of maturation, and that psychiatric disorders may therefore arise at the extreme of maturational rates. Schizophrenia, in particular, would be related to a delay of maturation leading to reduced connectivity, reduced dendritic branching, and eventually to a diminished number of neurons due to a prolonged pruning process (the reverse condition would apply to bipolar affective disorder and to autism, the latter being associated with a premature developmental arrest). Saugstad also conjectured that acceleration (earlier onset of puberty) in the past 50 years or so might account for the alleged decreasing number of the most severe cases of schizophrenia [47], as this would counterbalance the maturational delay typical of schizophrenia. Surprisingly, Saugstad has never referred to Ewald Hecker who, on behalf of his teacher Karl Ludwig Kahlbaum, had described hebephrenia in 1871. Hecker had already speculated that hebephrenia was characterised by a lack of maturation, indicated by a 'pathologically permanent state of puberty' [48].

3.2. Connectivity theory

In relation to the issue of brain maturation in general, the aetiology of schizophrenia has been repetitively linked to a dysfunctional intra- and interhemispheric connectivity (recently readdressed in Ref. [18]). According to the connectivity theory of psychotic disorders, functional networks either may become incompletely, falsely or overly connected during ontogeny. Consistent with the time of onset of schizophrenic disorders, adverse effects occurring already during foetal cell migration may become clinically manifest only in adolescence or early adulthood when myelination is completed [49]. The sexual dimorphism in myelination with males maturing later may also explain the (converse) sex difference in onset of psychosis [49] due to a prolonged period of enhanced susceptibility. More specifically, Horrobin [50] speculated that a defect in lipid metabolism that evolved in recent hominid evolution might lead to abnormal growth and insufficient myelination of neurons in some individuals, which could manifest clinically as schizophrenia.

With respect to the fact that a normal loss of cell connections during ontogeny occurs, Feinberg [51] suggested that schizophrenia might arise from insufficient synaptic 'pruning' during adolescence. More recently, Rison [52] adopted this hypothesis, proposing that schizophrenia could be explained by a lack of normal switching from the foetal to the adult form of the NMDA-receptor during adolescence, resulting in an excess of excitatory synaptic transmission. The cost of insufficient pruning of foetal NMDA-receptors, i.e. psychosis, could be balanced, on the other hand, by a relative protection from neurodegenerative effects [52]. In a computer-simulated model of synaptic pruning McGlashan and Hoffman [53] argued,

however, conversely that schizophrenia might be characterised by an overshoot of synaptic pruning. This model predicts that an earlier onset would be associated with more rapid deterioration and reduction of hallucinations with further pruning, as is in fact the case in chronic schizophrenia [53].

Relating schizophrenia to heterochrony in human evolution, the speed of brain maturation or cerebral connectivity represents an interesting theoretical approach. However, it conveys some pitfalls. For example, I have argued elsewhere [17], in line with the work of McKinney and McNamara [41], that impaired neoteny does not provide a suitable developmental model for the existence of schizophrenic disorders, simply because neoteny is not the only heterochronic process involved in human brain evolution, and hence in the evolution of cognitive mechanisms. Rather, hypermorphosis, which involves the postponement of growth and differentiation, adds new characters by 'overstepping' the ancestral form. Hypermorphosis is, therefore, critical for brain evolution and human cognition, because the neoteny-related retention of juvenile characteristics of the ancestral species into adulthood of the descendant alone would in fact lead to reduced cognitive capacities in the descendants [41]. Needless to say that neither the mental capacities of healthy persons or of schizophrenic patients are comparable with the mentality of juvenile apes [17].

Likewise, while there is certainly interindividual variation of the developmental speed of brain maturation, speculations on its relation to schizophrenia bear some inconsistencies. Some researchers have suggested, for instance, that schizophrenia emerges according to an extremely late maturation [47], others, on the contrary, assert that schizophrenia occurs due to a disruption of the normal developmental delay of maturation, i.e. premature ageing [45]. Moreover, recent studies have revealed partially incompatible results regarding the age at onset of psychosis and the age of menarche of the affected female individuals, a finding that does not unequivocally link schizophrenia to physical maturation alone [54]. Further, it is still a matter of debate as to whether sex differences of age at onset have been definitively established in schizophrenia [55–58].

Hypotheses regarding altered synaptic pruning or myelination in schizophrenia are, though plausible, somewhat problematic because they disregard the relatively typical 'core' symptomatology of the disorders. For example, if defective myelination or excessive pruning occurs randomly, one would expect a broader spectrum of symptoms in initial stages and possibly a more stable symptom constellation in the course of psychosis [34].

3.3. Is schizophrenia related to the evolution of 'sociality'?

As already pointed out, since selection acts on the phenotype rather than on the genotype it could be more

fruitful to relate the putative preservation of susceptibility genes for schizophrenia more tightly to the actual symptomatology that largely manifests within the social domain [21]. Kuttner et al. [19] proposed that the uniqueness of schizophrenia in human beings was specifically linked to human characteristics that separate humans from other animals. They argued that these differences would lie in the highly complex social life, the superior intelligence and language. The ‘beneficial effects’ of schizophrenic traits could, for example, be related to ‘the sphere of social behavior’, e.g. a relative protection from social stress [19]. In line with a once popular account of schizophrenia relating the development of the disorder in individuals to pathological behaviour of their mothers, Kuttner and Lorincz [59] had hypothesised even earlier that a potential survival advantage of individuals who later develop schizophrenia could be linked to the overprotective behaviour of their ‘schizophrenoid mothers’.

Kellett [60], referring to a presumed ‘heterozygous’ advantage of schizophrenia genes, related schizophrenia to the concept of ‘territoriality’. He argued that the (heterozygous) schizotype had a reproductive advantage compared with more socially adapt individuals in evolutionary scenarios where the need to establish territoriality would surpass the importance of pro-social behaviour.

Similarly, Allen and Sarich [21] argued that schizophrenia might be regarded as a condition at one extreme on a ‘sociality scale’. They concluded that the advantage of non-psychotic carriers of the gene(s) was their ability to balance their own interests against the demands of group living more effectively under ancestral conditions, which in some cases might also emerge in their greater creative potential. Moreover, they viewed schizophrenia as a ‘disease of civilisation’, because the more complex a society and the further from the ancestral hunter–gatherer existence, the more pathological conditions or deviations from the norm were tolerated. The higher tolerance of social dysfunction in ‘modern’ societies might therefore explain the maintenance of schizophrenia genes in the population.

In a similar vein, Stevens and Price [20] argued that the genetic susceptibility to develop schizophrenia emerged as an adaptation to facilitate group splitting. The group splitting hypothesis holds that the group cohesiveness of human beings is limited. As Price put it, ‘just as a cell must divide, so too must a human group divide. The capacity to form a new belief system and reject the belief system of the natal group is characteristic of cult leaders and also of people with schizophrenia’ [61]. In other words, similar to others, Stevens and Price [20] postulated that selection pressures on traits related to ‘asocial’ behaviour. This hypothesis has gained some influence, because it plausibly considers some sort of benefit of behaviour patterns that are obviously non-social, or even overtly schizoid or paranoid, which are also characteristic of the ‘Odyssean personality’ [62] or have recently been associated with shamanism and charismatic leadership [63]. Polimeni and Reiss have

proposed, for instance, that shamanism and religious leadership could have had beneficial effects on the group in human evolutionary history, which might explain the preservation of a genetic foundation of shamanism. Such traits could, on the other hand, be associated with an increased probability of developing psychotic symptoms and also account for the high prevalence of religious delusions in contemporary schizophrenic patients [34,63].

Burns [18] has recently argued that schizophrenia may be seen as a trade-off of the evolution of social intelligence involving a dramatic increase in cortical connectivity in primates. He suggested a two-step model of the evolutionary background of schizophrenia: in the first evolutionary step some 5–6 million years ago a more complex inter- and intrahemispheric connectivity emerged especially in two fronto-temporal circuits, namely the anterior cingulum bundle and the uncinate fasciculus. These brain circuits evolved due to increasing demands of the social environment of early hominids and had been crucial for increasing social cognitive capacities. In a second more recent evolutionary step 150,000 years ago, some unknown genetic mutation may have enhanced the vulnerability of these connections, which could be associated with the evolution of metacognition and ‘theory of mind’. Thus, according to Burns, schizophrenia may be seen as a trade-off of the evolution of the human ‘social brain’ [18].

A specific aspect of the evolution of intelligence is reflected in the discussion of creativity and psychosis. Data from Iceland, which is supposed to have a fairly stable genepool over centuries, suggests a connection of exceptional creative potential in relatives of psychotic individuals with psychotic illness [64], although the association is stronger for bipolar affective disorders than schizophrenia [65]. This assertion is supported by anecdotal reports of psychotic disorders in famous people such as Isaac Newton and John Nash (overview in Ref. [34]).

This multifaceted spectrum of attempts to establish an association of schizophrenia to the evolution of ‘sociality’ warrants some comments. In fact, there are a number of shortcomings in these accounts: it is very unlikely that the preservation of genes predisposing to schizophrenia have anything to do with an enhanced capacity to cope with stressful social environments. Contrariwise, schizophrenic persons are particularly vulnerable to social stress. Moreover, it is as yet unclear whether a presumed over-protective or rejecting behaviour of mothers of persons who later become schizophrenic is the cause of, or rather a reaction to, subtle behavioural abnormalities of the latter, [66]. However, careful examination of attachment patterns in infants who have a high genetic risk of developing schizophrenia later in life could be useful in clarifying the question as to what extent behavioural characteristics of mothers influence the manifestation of schizophrenia. However, this would by no means explain the probably genetically mediated vulnerability to schizophrenia.

Kellett's territoriality hypothesis [60] may be criticised because it does not account for schizophrenic symptoms except paranoid alertness [34], and, as de Waal [67] has pointed out, ancestral human societies were probably more hierarchically organised than territorially organised. In addition, Kellett's approach [60], like Polimeni and Reiss's shamanism hypothesis [63], relies primarily on the group-selection theory put forward by Wynne-Edwards [68]. The 'good for the species' argument as a major evolutionary force has, however, been refuted by the modern synthesis of inclusive fitness theory in light of compelling evidence that selection operates at the genetic or at best the individual level [69]. Also, the evidence that the schizoid group splitter, shaman or charismatic leader might have conveyed an adaptive advantage (which paid off in terms of reproductive success in human evolutionary history, and hence led to the preservation of genes associated with schizophrenia) is fairly weak [18,19]. It appears unlikely that at any time in our evolutionary past selection has operated in favour of the phenotype of the schizotypic shaman, charismatic leader, or group-splitter as a heterozygous carrier of genes that may cause full-blown psychosis if homozygous. If we assume, for instance, that lower back pain and a slipped disc may be trade-offs or the result of a design flaw of our upright position and bipedalism, schizotypy may be no more adaptive than minor lower back pain. Likewise, the hypothesis that schizophrenia represents a trade-off of human creativity has not been convincingly backed up by empirical studies [65,70,71], and Polimeni and Reiss cautioned us that a link with schizophrenia might be difficult to prove [34].

Burns' account of schizophrenia as a trade-off of the evolution of a 'social brain' in primates [18], in contrast, is a fruitful model because it integrates developmental brain maturation, cerebral connectivity and cross-species findings highlighting the evolutionary demands posed on individuals by the social environment in ancestral conditions. Many cognitive, emotional, and behavioural capacities 'hard-wired' in the human brain evolved as adaptations to our social environment [72]. This includes the capacities, among others, (1) to infer what others think, intend, pretend and desire, referred to as having a 'theory of mind' [73], (2) to 'read' signals of conspecifics such as facial expressions of emotions [74], (3) to travel mentally in time back and forth [75], and, (4) language [31]. In the case of schizophrenia there is good empirical evidence that the brain functions involved in social interactions such as emotion recognition and theory of mind are specifically impaired [76,77], summarised in Refs. [78]. It is also well buttressed by empirical studies in primates that some areas in the human prefrontal cortex in particular are larger than expected for a primate of human body size, and that this enlargement is associated with an increasing mass of white matter rather than grey matter. In other words, axonal connectivity probably outpaced the number of neurons over evolutionary time in primate phylogeny [79]. If increasing

white matter volume was related to a greater vulnerability this would then lend some support to Burns' and others' dysconnectivity hypothesis [18,49,53]. It is less clear and thus debatable, however, as to how Burns' proposal specifically addresses the aetiology of schizophrenia, or rather, whether it represents a model that could be applied to other psychiatric disorders as well. This issue is being addressed in more detail in the general discussion.

4. Crow's theory of cerebral asymmetry, language, and the emergence of psychosis

Crow's evolutionary theory of the origin of psychotic disorders is based mainly on the assumption that a lack of hemispheric dominance and specialisation of the language area on the left side are at the core of psychosis. Crow has accordingly hypothesised that a single gene regulating cerebral dominance was also involved in the origin of psychotic disorders, and that the evolution of language would play a central role. He proposed that—given that the genomes of the chimpanzee and humans differ only in around 1.5% of base pairs—a crucial incident must have happened since the time these two species split from a common ancestor some 5 million years ago. Central to his line of argumentation is also that the empirical evidence for Kraepelin's original dichotomy of schizophrenia and bipolar affective disorders is weak; rather, according to Crow, the 'functional' psychoses would form a 'double-continuum': from the bipolar pole to the schizophrenic pole, and from 'normal' to psychotic. The continuum hypothesis would imply that 'the disorder represents a component that is intrinsic to the individual, i.e. an extreme of variation on the normal population' [10].

One of the crucial differences between the great apes and human beings is undoubtedly the capacity of having sophisticated language. Crow conjectured that possibly only a single gene mutation might account for the huge cognitive and behavioural gap between the species and could thus be regarded as 'the speciation event'. Provided the incidence rates of 'core' schizophrenia are cross-culturally similar, the mutation in question must have occurred before the diaspora of modern *Homo sapiens* from Africa, perhaps 150,000 years ago [10].

If such a cerebral dominance gene allows the hemispheres to develop independently from one another to a certain degree, and if males and females differ with respect to their cerebral asymmetry—which is actually the case, as men usually have a greater anatomical cerebral asymmetry compared to women, and this difference is established early in ontogeny—sexual selection may be involved in hemispheric specialisation which in turn may also account for the sex differences in age at onset of psychosis [25]. Sexual selection acting on sex differences in mate choice may explain the sexual dimorphism in lateralisation of brain functions because women usually mate earlier than men and

hence would mature faster. Men, by contrast, would be more vulnerable due to a delayed maturation associated with the more pronounced cerebral asymmetry [25]. If sexual selection was involved in a single gene mutation, as Crow inferred, the most likely explanation would be to expect the gene locus to be X–Y-homologous (in early accounts Crow suggested an X–Y-homologue in the pseudoautosomal region of the sex chromosomes, but he later rejected this assumption, because such a location would not explain sex differences in age at onset, precursor symptoms and cerebral asymmetry in psychosis, as the pseudoautosomal region of the sex chromosomes is subject to crossing-over; [32]).

Indeed, there is some empirical evidence in support of Crow's 'speciation' theory. Children who later develop psychotic disorders are more likely to be ambidextrous and have more language disorders and behavioural disturbances than children who as adults do not become psychotic. More precisely, psychomotor retardation, delayed language development and other cognitive impairments were specifically observed in subjects who later developed schizophrenia from the age of three on, compared with children who later suffered from other 'functional' psychoses or non-psychotic disorders; other emotional and interpersonal problems occurred across all diagnostic categories [80]. In addition, Crow, Done and Sacker [81] found pre-psychotic children to be impaired in reading abilities and in lateralised hand skills at the age of 7 and 11 years, relative to control subjects. These findings suggest that psychosis-related developmental disturbances may be associated with a delayed or incomplete hemispheric specialisation or unsuccessfully established dominance in one hemisphere.

Moreover, some studies have revealed a reduced cerebral asymmetry in schizophrenic adults compared with healthy subjects, and sex differences of normal asymmetry have been found disrupted in schizophrenia [82]. In addition, there is a disparate spatial and verbal intelligence in persons with aneuploidies of the sex chromosomes; in Turner's syndrome (X0) verbal intelligence, a function of the dominant hemisphere, is better preserved relative to spatial abilities, the latter represented in the non-dominant hemisphere; whereas in Klinefelter syndrome (XXY) the reverse applies, suggesting that the sex chromosomes are involved in establishing hemispheric dominance. Crow argued, however, that, since normal males (XY) only have one X-chromosome, but similar spatial and verbal intelligence, it is likely that the presumed hemispheric dominance gene is also represented on the Y [32]. Crow [32] further assumed that the structure of language in terms of its spatial and temporal organisation is segregated such that the spatial or 'logical' component is represented in the non-dominant hemisphere and the temporal or 'phonetic' aspect in the dominant hemisphere [10,31]. Therefore, for normal language the interaction of the two hemispheres is crucial. From this perspective it is plausible to draw parallels to the nature of 'first rank symptoms' in schizophrenia, because they may reflect a disruption of the normal transcallosal

connection of the two hemispheres. In other words, an imprecise timing of the logical and the phonetic aspect of language could produce symptoms such that an individual's own thoughts are perceived alien [30]. In support of this assertion, DeLisi [83] found chronic but not first episode schizophrenics to have a reduced sentence complexity. This finding was more evident in male patients, which could therefore be consistent with Crow's hypothesis of anomalous lateralisation.

With respect to the proposed gene locus on X–Y homologous regions of the sex chromosomes, a candidate area could be a sequence that was apparently transposed from the X to the Y chromosome after the separation of the human and the chimpanzee line. More specifically, the Xq21.3 region that was obviously transposed to the short arm of the Y, was subsequently split in a paracentric inversion on the Y. A gene called 'ProtocadherinXY' might therefore be involved in establishing hemispheric dominance [32,84,85], although Kalsi and colleagues [86] previously failed to find a linkage of the XY pseudoautosomal region associated with increased susceptibility to schizophrenia. Psychotic disorders could then arise at the extreme of variation due to a high mutation rate at this gene locus, or due to epigenetic factors such as genomic imprinting or X-inactivation [32]. A recent study, however, failed to replicate the result of a positive linkage of schizophrenia to any particular region of the X-chromosome, indicating that in the first place epigenetic factors are involved in the predisposition of psychosis [87].

There are several objections against the validity of Crow's evolutionary theory of psychosis as 'the price *Homo sapiens* pays for language', though plausible and consistent with many empirical studies. Firstly, Crow's claim that schizophrenia emerges in hominid evolution as a trade-off of lateralisation and functional specialisation of the hemispheres when language evolved in the 'speciation event' some 150,000 years ago is questionable, because gradual evolution of language is more likely than a saltatorial emergence of such a complex faculty, although complex syntactical and semantic qualities of human language might indeed have evolved from proto-language in a relatively short period of time [88,89]. Asymmetry of the planum temporale as the key region of the functional specialisation of Wernicke's language area is, however, already present in the chimpanzee [90], suggesting that a functional differentiation might have already evolved in the common ancestor of humans and other apes, thus clearly preceding the advent of modern humans. In addition, as recently pointed out by Corballis [91], cerebral asymmetry of vocal control can be found in many 'primitive' animals such as frogs and birds, whereas right-handedness is probably a human characteristic that evolved much later. Therefore, there is no unequivocal link of handedness and language to a single mutation in which cerebral dominance could have been established. Furthermore, the claim that schizophrenia is characterised by a less pronounced lateralisation could not

be replicated in a recent study [92]. Likewise, from a genetic point of view, the evidence of a X–Y homologous gene involved in cerebral asymmetry and the evolution of language is at best moderate. In addition, there are susceptibility genes of schizophrenia located on various autosomal regions, suggesting that a single gene mutation is unlikely to fully account for the emergence of psychotic disorders [93–101]. Two recently published meta-analyses failed to provide evidence for any particular candidate gene locus for schizophrenia [102,103]. With respect to the presumed speciation event it is important to note that a crucial difference that genetically separates human beings from other apes is that the human genome comprises 46 chromosomes, including the sex chromosomes, whereas the other great apes have 48 chromosomes. It is a well established finding that at some point in our hominid evolution the chromosomes 12 and 13 found in the chimpanzee and in the gorilla (and probably also in our common ancestor) were combined to form the large human chromosome 2 [104].

Secondly, from a clinical perspective, although plausible regarding some first rank symptoms of schizophrenia, Crow's theory hardly accounts for other psychotic or behavioural symptoms such as catatonia, negative symptoms, and affective disturbances, although Crow asserts that echolalia and echopraxia may arise from impaired communication between the two hemispheres [31]. Thirdly, Crow's explanation of sex differences in age at onset of psychosis appears somewhat circumstantial; he suggests that later brain maturation renders male brains more susceptible to psychosis and might therefore account for the earlier onset of psychosis in men, whereas earlier maturing female brains are relatively protected against the disorder. In Crow's view sex differences in mate selection may cause the divergent speed of brain development, with men favouring younger (and therefore faster maturing) women, relative to women who prefer older men as potential sex partners. To me, this line of argument appears in some respect circular. Furthermore, the gender effect on age at onset of schizophrenia is possibly even reversed in populations where infant mortality is high [105], a scenario which may more closely resemble the conditions of the 'environments of evolutionary adaptedness' of our species. Fourthly, Crow [29] proposed a 'double' continuum of psychosis. On the one hand, schizophrenic and affective disorders are more accurately described as 'dimensions of variation' rather than categories or disease entities; on the other hand, along with Kretschmer [106], psychotic states may arise at the boundaries of personality traits. Indeed, there are many clues that this might be true. For instance, several studies on psychotic symptoms in non-clinical populations have confirmed that phenotypic differences between patients and non-patients are quantitative rather than qualitative [107–109]. Also, obsessive-compulsive disorder and delusions may overlap [110]. Many more examples exist in favour of the continuum hypotheses. This

poses, however, a problem for Crow's evolutionary theory of schizophrenia, because it becomes, then, speculative whether the presumed stable incidence rate across cultures is a valid finding, and this problem may even persist if restricting the schizophrenia concept to nuclear symptoms [10]. Moreover, with respect to cross-cultural similarity, mild male preponderance and earlier age at onset is probably not unique to schizophrenia, since the same applies, for instance, to obsessive–compulsive spectrum disorders.

Crow's evolutionary theory of schizophrenia is nevertheless a very useful concept for addressing psychiatric disorders from an evolutionary perspective. There is no doubt that language plays a key role in both human evolution and psychosis; however, his theory is too narrowly focused on a supposed single gene mutation [111]. In a more general vein, a gene on a X/Y homolog region such as the ProtocadherinXY could conceivably be involved in regulating the heterochronic growth of the two hemispheres, possibly reflecting a hypermorphic shift on top of a general neotenic developmental trend in humans relative to the other great apes.

5. General discussion

A wealth of evolutionary hypotheses has addressed the question of apparently constant incidence rates of schizophrenic disorders across different cultures and environments, despite the fact that individuals suffering from schizophrenia have a reduced fecundity compared with the general population. Evolutionarily speaking, natural selection should have eliminated susceptibility genes of schizophrenia, if the apparent reproductive disadvantage was not compensated for by any survival or reproductive advantages in heterozygote carriers or by advantageous effects of pleiotropy. However, none of the evolutionary hypotheses put forward so far meets all criteria mentioned in the introduction, i.e. providing a convincing mechanism for the preservation of genes in the human gene pool associated with schizophrenia, explaining potential sex differences, and accounting for the multifaceted symptomatology. Thus none can be entirely refuted or accepted on the basis of the currently available evidence, although those invoking group selection would seem least consistent with modern evolutionary theory, neither are they substantiated by empirical studies. However, most hypotheses outlined above are open to empirical testing. They are therefore not evolutionary 'just so stories' comprising more or less plausible but unstable explanations of schizophrenia.

One needs to keep in mind the possibility that this line of research is like chasing an illusion. For example, evolutionary hypotheses of schizophrenia that propose an adaptation of heterozygous carriers of alleles are at risk to fall prey to the erroneous belief that every psychiatric disorder can always be explained as an adaptation in one way or another

[112,113]. As Weiss Lane and Luchins [114] have pointed out, a common fallacy in evolutionary psychiatry is to assume that ‘a trait is adaptive by virtue of its existence or prevalence’. Traits or constellations of traits may also be prevalent in a population due to processes unrelated to adaptation such as random mutation, genetic drift, and segregation distortion (‘meiotic drift’).

Another problem that is probably most imperative to schizophrenia research, relates to the fact that there is not one single psychopathological symptom, biochemical or structural marker that is specific or unique to schizophrenia, such that Bentall and colleagues have even recommended abandoning the whole concept of schizophrenia [115]. Similarly, the question raised by Crow [23,29] of continua versus ‘disease entities’ is not only critical for the evolutionary discussion of schizophrenia but also for the validity of the classification of psychiatric disorders in general. It could eventually well turn out that our diagnostic system relies on arbitrary and empirically flawed categories. In other words, we must not overlook, as Burton-Bradley [116] put it, that our Western diagnostic system is, particularly in a cross-cultural context, only of limited value because it originated ‘in a few limited geographical areas of Europe, notably in Vienna, Munich, and Zürich’.

However, from a pragmatic point of view, simply discarding the concept of ‘schizophrenia’ might not only be difficult to sell to clinicians; more importantly there also ought to be some alternative that is superior to the current (anachronistic) account and may, at least in part, resolve the diagnostic dilemma.

I would like to suggest, in line with Bentall et al. [115] Burns [18] and Crow [23,29], an approach based on individual symptoms inserted into an evolutionary framework that explicitly appreciates the concept of continua rather than disease entities in psychiatry. As previously discussed elsewhere [113] an observation-driven evolutionary ‘bottom-up’ analysis may be most appropriate to address symptoms and syndromes. Many dysfunctions we call ‘disorders’ may arise due to a mismatch of our modern environmental conditions with the ancestral conditions to which our human mind once adapted. Others may rather be regarded as trade-offs or design flaws, because ‘optimality’ in nature is nonexistent (otherwise, evolution would not happen). As such, many psychotic symptoms and syndromes may be considered trade-offs, primarily manifesting themselves in domains related to the evolution of our ‘social brain’ [18,72,117].

Such social brain disorders include, as already mentioned, an overly active ‘theory of mind’ mechanism of cheater and deception detection such as in paranoia, or the incapacity to represent one’s own mental states as self-generated and to understand the beliefs and desires of others [76]. This faculty of the mind is likely to have evolved from the capacity in primates to monitor biological motion [118]. Interestingly, there is a clear link of theory of mind and language, which might also throw some light on symptoms

of ‘core schizophrenia’, since schizophrenic patients with pronounced thought and language disturbances have been found to be also markedly impaired in their theory of mind abilities, e.g. [119]. As Sperber and Wilson [120] have reasoned, the pragmatic use of language requires an intact theory of mind because for proper conversation it is not sufficient to comprehend the literal meaning of utterances but also the ‘metaphorical’ content, and the latter is ultimately linked to a person’s capacity to connect to the mentality of her interlocutor. Thus this aspect of ‘social brain’ evolution may well be reconciled with Crow’s emphasis on the evolution of syntactical and semantic qualities of human language.

Two further examples may illustrate how evolutionary driven hypotheses can inform about individual symptoms associated with (but not specific to) schizophrenia: (1) Researchers have recently detected a novel cell type in the anterior cingulate which is specific for great apes and humans while absent in monkeys and other mammals [121]. Contrary to previous assumptions that the anterior cingulate cortex (ACC) would represent a primitive stage of cortical evolution, these so-called spindle cells have increased in size and number over evolutionary time indicating encephalisation during recent hominid evolution, and hence being a novel adaptation. Functionally they may be involved in control of impulsive behaviour, error recognition, and perhaps other aspects of social behaviour [122]. Lesions of the ACC, for instance, produce akinetic mutism and other behavioural deficits such as resisting the performance of automatic subroutines [123], which strikingly resembles symptoms that may occur in schizophrenia such as stupor, mutism and stereotypies. Moreover, the fact that spindle cells in humans emerge only postnatally, and findings that the survival of neurons in the hippocampus critically depends on environmental input and enrichment, while stress reduces their production, suggests that the development and arborisation of spindle cells may also crucially rely on environmental input. In other words, stress during early development may impair the functional development of the ACC [121], and hence may induce psychopathology, including psychotic symptoms. (2) Another cell type, referred to as ‘mirror neurons’ due to their selective firing when observing and imitating certain behaviours of conspecifics, particularly hand movements, has been located in the ventral premotor cortex of monkeys that is probably homologous to Broca’s area in humans [124]. Mirror neurons also exist in Broca’s area and the superior temporal sulcus in humans. They are also selectively active when observing hand and mouth movements and when executing the observed behaviour [124]. This has given rise to the hypothesis that human language evolved in the first place from gestural communication, and that the human Brodmann area 44 is also involved in action understanding and imitation [125]. Now, with respect to psychotic symptoms it could be worth assessing, for example, whether a disinhibition of mirror neuron activity is involved in a subset of

catatonic behaviours, namely echopraxia, echolalia, automatic obedience, and perhaps *mitgehen* and *mitmachen*. Again, this may converge on certain aspects of Crow's framework. He argued that echophenomena may arise due to speech or other input being carried through to output untransformed by a failure of transcallosal communication between the language centres represented in the two hemispheres [31].

6. Conclusions

This review has sought to provide a comprehensive overview of evolutionary hypotheses of the origin of what traditionally has been referred to as 'group of schizophrenias' [1]. While the evolutionary approach to psychiatric disorders is considered extremely useful—because of its potential to render psychiatric symptoms and syndromes open to empirical testing, and because to date evolutionary theory provides the only scientific framework to integrate findings from various subspecialties as divergent as genetics, brain imaging and biochemistry and psychotherapy—it is suggested that the way to look at schizophrenia should start with an understanding of individual symptoms in evolutionary perspective. This includes consideration of the putative selection pressures that led to the emergence of neural networks underlying human cognitive, emotional, and behavioural functioning, an understanding of primate 'precursors' (where such exist) of human characteristics, and of the nature of psychological adaptations to specific environmental conditions in our evolutionary history [72,126,127]. This could, in a second step, improve upon existing research on the underlying genetics of schizophrenia and other psychiatric disorders. For instance, it could prove fruitful for Crow's evolutionary theory to specifically focus on a subgroup of schizophrenia with marked thought, language and communication disorders [128]—given the possibility that an XY homolog gene may be involved in one type of psychosis we subsume under the term schizophrenia, whereas other, genetically unrelated, psychotic disorders such as 'deficit schizophrenia' may be better understood as a result of developmental instability [36].

The case of schizophrenia may also exemplify that the evolutionary perspective of psychiatric disorders could eventually radically challenge our diagnostic systems, since Kraepelin's [129] expectation of creating a classification according to 'natural disease entities' would then need to be revised. Until then, however, schizophrenia, traditionally seen, will remain an evolutionary enigma.

Acknowledgements

The author is grateful to the unknown reviewers for their very helpful comments on an earlier version of this paper.

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