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The evolutionary paradox and the missing heritability of schizophrenia

Abstract
Schizophrenia is one of the most detrimental common psychiatric disorders, occurring at a prevalence of approximately 1 %, and characterized by increased mortality and reduced reproduction, especially in men. The heritability has been estimated around 70% and the genome-wide association meta-analyses conducted by the Psychiatric Genomics Consortium have been successful at identifying an increasing number of risk loci. Various theories have been proposed to explain why genetic variants that predispose to schizophrenia persist in the population, despite the fitness reduction in affected individuals, a question known as the evolutionary paradox. In this review, we consider evolutionary perspectives of schizophrenia and of the empirical evidence that may support these perspectives. Proposed evolutionary explanations include balancing selection, fitness trade-offs, fluctuating environments, sexual selection, mutation-selection balance and genomic conflicts. We address the expectations about the genetic architecture of schizophrenia that are predicted by different evolutionary scenarios and discuss the implications for genetic studies. Several potential sources of 'missing' heritability, including gene-environment interactions, epigenetic variation, and rare genetic variation are examined from an evolutionary perspective. A better understanding of evolutionary history may provide valuable clues to the genetic architecture of schizophrenia and other psychiatric disorders, which is highly relevant to genetic studies that aim to detect genetic risk variants.

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Introduction

The evolutionary paradox of common psychiatric disorders

Common psychiatric disorders can be highly detrimental and many are associated with a shorter lifespan [1-4]. Unlike common somatic disorders, common psychiatric disorders often emerge early in the reproductive age [3, 5-9], conferring a substantial reproductive disadvantage [10-14]. Twin and adoption studies have indicated that genetic differences between individuals explain an important part of the variation in risk for many psychiatric disorders [15-20]. Estimates from 'unrelated' subjects suggest that a significant part of the variation in risk can be explained by genome-wide SNPs, with 23% for schizophrenia [21], 38% for bipolar disorder [22], and 32% for major depressive disorder [23]. According to evolution theory the process of natural selection preserves genetic variants associated with survival and reproductive advantage (fitness), while genetic variants associated with low fitness are eliminated from the gene pool [24]. Given that genetic variants associated with reduced fitness are under negative selection pressure, why is it that natural selection has not eliminated genetic variants that predispose to psychiatric disorders? This question has been addressed by many and is known as the evolutionary paradox of psychiatric disorders.

The paradox is most evident for disorders that have a high heritability and are associated with a large fitness reduction. Why are harmful psychiatric disorders that are largely genetic in origin so common? Schizophrenia is among the most heritable psychiatric disorders (heritability~70% [20, 25]) and also among the most severe. It is characterized by positive symptoms (i.e. hallucinations, delusions and racing thoughts), negative symptoms (i.e. poor social functioning, apathy and lack of emotion), and cognitive symptoms (disorganized thoughts, concentration problems, memory problems and difficulty with completing tasks) [26]. The onset is typically in early adulthood, with an earlier onset in men than in women by on average three to four years [27], and is usually followed by a lifelong course of social and professional impairment. Individuals with schizophrenia show lower reproductive success (on average 30-80% relative to controls, with affected males showing a larger reduction in reproductive success than affected females [28]) and suffer from increased mortality due to natural and unnatural causes (suicide in particular) [29]. These disadvantages suggest that risk alleles for schizophrenia should be under negative selection. Yet, the disorder is surprisingly prevalent, affecting approximately 1% of individuals worldwide [3]. A variety of evolutionary hypotheses has been proposed to explain the high prevalence of schizophrenia, despite the associated fitness reduction and high heritability [30, 31].

The evolutionary paradox and the missing heritability: A common ground?

Although schizophrenia appears to be highly heritable, most of the genetic variants remain to be identified. Genetic linkage studies have pointed at various

loci, but these loci were rarely replicated across populations [32]. It was hypothesized that susceptibility to schizophrenia may be mediated by common genetic variants with small individual effects, a view known as the common disease-common variant (CDCV) hypothesis [33, 34]. Genome-wide association studies (GWAS) have identified an increasing number of common variants that appear to modify the risk of schizophrenia but these variants together explain only a small fraction of the total amount of genetic variation that is assumed to underlie the disorder [35-38]. Recent findings from sequencing studies suggest that at least part of the genetic risk for schizophrenia may be related to rare genetic variants that are difficult to detect in GWAS [39-41]. Evidence has emerged for a role of rare structural variants [37, 42] and *de novo* single nucleotide mutations [43].

The genetic properties of populations are the result of natural selection in the past, together with mutation and random drift [44]. A better understanding of the evolutionary history of diseases may provide valuable insights into their genetic architecture and into suitable strategies to identity risk alleles. The hypothesis that common genetic variants influence the risk for common psychiatric disorders relies upon important assumptions about the evolutionary history of psychiatric disorders. Common susceptibility alleles must be evolutionary ancient and cannot have been subject to continuous strong negative selection pressure, since such variants should have reached fixation and no longer contribute to heritable variation in traits [44]. The evolutionary paradox of common psychiatric disorders and the difficulty to identify susceptibility genes ('the missing heritability' [45]) may be closely linked. The difficulty in finding replicable genetic associations for psychiatric disorders that account for a substantial part of disease risk may be explained by a characteristic genetic architecture that has been shaped by evolutionary history [46].

In this review, we address the question how genetic risk for schizophrenia may persist in the population. We consider evolutionary perspectives on schizophrenia, evaluate the usefulness of these theories in terms of explaining the persistence of heritable variation, and discuss various aspects of the genetic architecture of schizophrenia that are predicted under different evolutionary scenarios. Although schizophrenia is the central theme of most evolutionary theories, many of these theories may apply to a broader concept of psychotic illness. Non-organic psychoses (i.e. psychoses in the absence of organic brain disorder) have traditionally been divided into two diagnostic categories; schizophrenia and bipolar disorder [26]. A combination of symptoms that is intermediate of these two categories may be classified as schizoaffective disorder, however, many clinical signs are shared across all psychotic disorders and it is unclear to which degree the different diagnostic categories are aetiologically distinct. There is increasing support that there is at least partial overlap between genetic risk variants for schizophrenia and bipolar

disorder [35, 36] and such overlap may even extend to other psychiatric disorders as well [37].

Schizophrenia as an evolutionary adaptation

It has been suggested that psychiatric disorders should not be regarded as merely harmful conditions. Rather, these conditions, associated traits, or underlying genes may provide certain advantages to affected individuals or their relatives, which may have been favoured throughout evolutionary history [47-50]. Most of such advantages were proposed for cognitive domains. For example, Kellet [48] suggested that personality traits associated with schizophrenia such as inventiveness and the ability to tolerate low levels of stimulation while remaining alert may offer good territorial instincts, which could have been advantageous to territorial animals. Although this theory might explain the persistence of such traits in ancestral times, modern allele frequencies depend mainly on fitness in recent times. Irrespective of whether schizophrenia or associated traits were indeed beneficial in the past, such theories do not clarify why risk alleles for schizophrenia exist today.

Various other advantageous correlated phenotypes have been proposed, which may also be of benefit in modern times, including social skills, creativity, musical skills, intelligence and exceptional abilities. Associations of creativity with psychosis and schizotypy are well-supported by empirical evidence; individuals with a high score on schizotypy or with a history of psychosis on average score higher on measures of creativity and vice versa [51, 51, 52], and individuals with schizophrenia and bipolar disorder are overrepresented in creative and artistic occupations [53].

Several authors have suggested a link between schizophrenia and advantageous somatic characteristics. Among one of the earliest, Huxley *et al* [54] proposed that the disadvantage of schizophrenia susceptibility may be outweighed by advantages such as higher resistance to infection, heat shock and allergies. Several studies have indeed demonstrated immune-related differences in schizophrenia [54-57], but it remains unclear to which degree this characteristic is advantageous. While several studies have indicated that schizophrenia is associated with a lower risk of rheumatoid arthritis [58-60], the incidence of various other autoimmune diseases, including thyrotoxicosis, celiac disease, acquired hemolytic anemia, interstitial cystitis, and Sjogren's syndrome, has been found to be elevated [61].

Another often cited potential benefit associated with schizophrenia is lower susceptibility to cancer. Besides a possible protective effect of antipsychotic drugs in cancer development [62], several characteristics of schizophrenia itself have been proposed to provide an inherent biological protection against cancer, including a protective effect of excess dopamine [63], increased apoptosis [64], and enhanced natural killer cell activity [65]. Some studies have found a lower incidence of cancer among schizophrenic patients compared to the general population [66-68], also after correcting for risk factors

such as age, race, gender, marital status, education and smoking [66]. Yet, other studies have reported a similar or even higher incidence of several types of cancer in schizophrenia [67, 69] and mixed findings for the association between schizophrenia and cancer may be related to numerous confounders that have not been accounted for in all studies [70, 71], of which smoking could be most important [72].

Although schizophrenia may be associated with some positive aspects, these aspects obviously do not outweigh the negative effects of this disorder to affected individuals. Neurocognitive studies have highlighted that schizophrenic patients generally show marked cognitive deficits [73]. Most importantly, data on lifespan and reproduction of patients with schizophrenia show that any benefit experienced by these patients is apparently not enough to prevent them from having a lower life expectancy and fertility compared to the general population. Therefore, possible cognitive or somatic benefits to affected individuals cannot explain the survival of genetic risk variants for schizophrenia.

Schizophrenia as a fitness trade-off at the extreme end of variation

Several authors have suggested that schizophrenia may have arisen as an unfavourable but inevitable (by-) product of human brain evolution. These theories have in common that schizophrenia is approached in the traditional perspective as a disorder, that is as a phenotype that is purely disadvantageous to the affected individual. According to this view, the high prevalence of the disorder is explained by positive selection for genetic variants that allowed for higher-order cognitive functions throughout evolutionary history, despite the cost of predisposing to schizophrenia.

Schizophrenia could represent the extreme end of normal variation in cognitive skills. Farley [74] proposed that schizophrenia may be regarded as an outlier on the normal continuum of social behaviour and as the toll that humans pay for the benefit of adaptive social skills genes. Crow referred to the link between schizophrenia, language dysfunction, and cerebral flexibility to hypothesize that schizophrenia reflects the extreme end of variation underlying language capacity [75-77]. According to Crow, positive selection for cerebral flexibility during human evolution allowed for the emergence of language; however, a by-product of cerebral flexibility was the associated variation in psychological functioning, resulting in personality disorders and schizophrenia at the extremes. Dodgson and Gordon [78] proposed that certain types of hallucinations may be regarded as the evolutionary by-products of a cognitive system designed to detect threat. From an evolutionary perspective, it might be better to mistakenly believe being threatened by an approaching predator than to fail to recognize it if one is really in danger.

Randall emphasized the role of neural connections in the evolution of human brain functions [79, 80]. According to Randal, the random establishment of novel neural pathways throughout development may produce advantageous supernormal connections or non-adaptive misconnections. This “biological trial

and error of connections" may give rise to a range of behavioural variants, including schizophrenia. Horrobin focused on the biochemistry underlying such neural connections, emphasizing the role of phospholipids biochemistry in the evolution of the human brain and in disorders such as schizophrenia [81-83]. According to this theory, a boost of neuronal membrane phospholipid metabolism resulting from the introduction of a larger amount of essential fatty acids in the early human's diet triggered the evolution of enhanced neuronal micro-connectivity. Though increased micro-connectivity may have allowed for the emergence of traits such as creative thinking, the authors propose that increased neuronal connectivity may also predispose to unwanted side-effects such as schizophrenia. Finally, schizophrenia has been proposed to result from delayed cerebral maturation, which may represent a disadvantageous phenotype within the boundaries of normal variation in cerebral maturation [84].

Although the disorder is approached from a different angle, theories that consider schizophrenia to be by-product of evolution actually rely on a similar principle as theories in which schizophrenia is considered as an evolutionary adaptation; both assume that the disorder is somehow linked to beneficial characteristics. If schizophrenia has arisen as a by-product of evolution at the extreme end of variation in 'normal' traits, the question that still remains is why this extreme and maladaptive phenotype persists, or from a genetic perspective; why the genetic variants responsible for this disorder are maintained in the population.

Balancing selection

Most evolutionary perspectives on psychiatric disorders rely on "balancing selection", which refers to a situation where multiple alleles may be maintained in the gene pool, if the genotypes are under different selection pressures, or if different selection pressures act upon an individual allele under different circumstances. One example of balancing selection is presented by antagonistic pleiotropy, where the effect of a genetic variant is associated with both advantageous and disadvantageous traits within the same individual, making it selectively neutral. An example is the P53 gene, which suppresses cancer, thereby increasing survival at younger ages, but also suppresses stem cell proliferation, thereby contributing to the process of aging [85]. The hypothesis that schizophrenia risk alleles are potentially protective to cancer is an example of antagonistic pleiotropy.

Another example of balancing selection is presented by balanced polymorphisms (heterozygote advantage). Thus, it has been proposed that genetic variants that predispose to fitness-reducing psychiatric disorders in homozygotes are maintained in the population because they are associated with a fitness-increasing trait in a large number of carriers (heterozygotes) [47, 54]. A classic example of a disease that is related to a balanced polymorphism is sickle-cell anemia, a severe disease that presents in individuals who are recessively homozygous for the β-hemoglobin gene [86]. The recessive allele is

maintained in the gene pool because it confers resistance to malaria in heterozygous carriers. Likewise, schizophrenia risk alleles could be maintained in the population because they provide beneficial cognitive or somatic traits in unaffected carriers of these alleles. Of note, a genome-wide scan to identify loci that have been subject to balancing selection indicated that balanced polymorphisms are probably rare [87].

Several authors have suggested that schizophrenia persists due to a benefit experienced by family members of affected individuals; e.g. schizophrenia may present in homozygous individuals, while their heterozygous relatives experience superior social skills [49], creativity [47, 50, 88] or academic success [89], thereby enjoying a selective advantage compared to the general population. Support for the link with creativity has been demonstrated for healthy siblings of schizophrenia patients [53]. Yet, similar cognitive deficits as seen in schizophrenia are often present, although to a milder degree, in relatives without a diagnosis of schizophrenia [90, 91]. Both affected individuals and their relatives perform worse than healthy controls on a range of cognitive tasks, with the most pronounced deficits observed in verbal memory, executive functioning and attention [90, 91]). With respect to cancer, conflicting findings have been found in unaffected relatives of schizophrenic patients, with some studies reporting a lower incidence of cancer in relatives [69, 92] and others reporting a higher incidence [93]. Some studies have reported increased fertility in relatives of schizophrenic patients [94, 95], however, most studies have concluded that the fertility of relatives is not sufficient to outweigh the reproductive cost of schizophrenia [11, 13, 96, 97]. So far, there is thus no evidence for the hypothesis that the fitness cost of schizophrenia is outweighed by an advantage experienced by close relatives, although one might argue that a true instance of "heterozygote advantage" is difficult to detect when it is unknown which relatives are heterozygous for the responsible genetic variant.

Cliff-edged fitness refers to the increase in fitness associated with increased expression of a trait up to a certain threshold, above which increased expression of the trait is associated with a sharp drop in fitness [98]. A classic example of the cliff-edged fitness model is provided by the tendency of some birds to lay fewer eggs than they are capable of; birds that lay fewer eggs avoid the risk that all offspring die under conditions of nutritional scarcity [99]. One theory that relies on the cliff-edged fitness model to explain the persistence of schizophrenia addresses the link between schizophrenia and synaptic pruning. Pruning; the selective elimination of weak neuronal connections, is a normal developmental process that occurs predominantly throughout childhood and adolescence. The elimination of little-used synapses improves mental efficiency; however, excessive reduction of synaptic connectivity (over-pruning) may result in spontaneous and autonomous cerebral activity, causing hallucinations and other positive symptoms [100]. The optimum level of pruning might lie just below the threshold above which psychosis may be induced.

Therefore, evolutionary processes may select towards maximal neuritic pruning, despite the potential risk of over-pruning.

The cliff-edged fitness model has also been applied to explain the persistence of schizophrenia at the level of the underlying genes. Thus, a small number of susceptibility alleles may be beneficial to the individual, for example by providing good social skills and theory of mind capacity [98]. Too many susceptibility alleles, however, may be maladaptive and increase the risk of schizophrenia. The cliff-edged fitness model also offers a potential mechanism for the other theories stating that schizophrenia has arisen as a by-product of evolution at the extreme-end of variation in some trait. Yet, the cliff-edged fitness model does not actually solve the paradox, because it is not clear why natural selection would maintain a number of harmful alleles in the population that can lead to schizophrenia in a subset of individuals, and has not rather selected a set of alleles that is beneficial to all individuals.

Another type of balancing selection is frequency-dependent selection, where the fitness of a phenotype depends on its frequency relative to other phenotypes in the population. Positive frequency-dependent selection refers to the situation in which the fitness of a phenotype is increased as it becomes more common. For example, bright warning (aposematic) coloration in a poisonous species is associated with higher fitness when it is common, since predators are more likely to avoid brightly colored individuals if most individuals are brightly colored [101]. Negative frequency-dependent selection refers to the situation where the fitness of a phenotype increases as it becomes less common. For example, female fruit flies prefer males with a rare phenotype, which is called the “rare male advantage” [102].

Selfish gene theory and group advantages

In evolutionary biology, group selection theory refers to natural selection favoring a trait that confers an advantage to the species as a whole, regardless of the effect of the trait on the fitness of individuals within the group [103]. Similarly, the selfish gene theory emphasizes that the preservation of a gene in the gene pool is determined by its ability to proliferate in the population, even if it predisposes the individual who carries it to self-sacrificing behavior [104]. Group selection has for example been put forward as an explanation for the (apparently) altruistic behavior of “helper birds” observed in many bird species, which delay their own reproductive efforts to help raising the offspring of close relatives [105]. Although such behavior decreases the individual birds’ reproductive success and survival, it promotes the survival of young relatives, thereby stimulating the propagation of the family's genes.

The group selection approach has been adopted to explain the persistence of schizophrenia, by suggesting that the characteristics of some affected individuals may confer an advantage to the group. For example, Price and Stevens [106] proposed the group-splitting hypothesis of schizophrenia, which states that schizotypal traits may reflect an ancient form of behavioural specialization for hunting and gathering tribes. This hypothesis relies on the

assumption that in ancient times, proliferating tribal communities had to split from time to time to maintain optimum numbers. According to Price and Stevens, schizotypal traits in certain prominent individuals may have been advantageous to ensure survival of an offshoot group. To illustrate their hypothesis, they suggested that schizotypal traits are often found in charismatic leaders, who use "delusions, paranoia and religious themes to fraction disaffected groups and to seed new cultures". This type of leadership could be regarded as an altruistic behaviour that is maintained by group selection.

A second group selection theory of schizophrenia has highlighted the link between schizophrenia and shamanism [107]. Schizophrenia and associated traits may be advantageous for shamans to perform religious rituals. Since religious rituals and shamans are universally observed across all cultures, this activity may have a genetic basis, and may be relevant to the survival of humankind. This theory was proposed to be supported by the numerous reports of religious-based delusions in psychotic individuals [108].

A third group selection hypothesis of schizophrenia relies on the mechanism of frequency-dependent balancing selection [109]). This hypothesis states that individuals with some genetic susceptibility to schizophrenia may have a survival advantage by possessing a greater sense of individuality, and the ability to "resist shared biases and misconceptions of the group". The authors of this hypothesis propose that the integrity of a group can sustain some betrayal if there are some nonconformists; however, too many would hinder a harmonious society. It was also suggested that this theory may explain why schizophrenia is more prevalent in modern industrial societies [3]. Complex societies are more tolerant to individuals with a greater sense of individuality and may benefit from a modest number of individuals with such characteristics. Yet, as for the other group selection theories, it is difficult if not impossible to assess whether group selection mechanisms contribute to the persistence of risk alleles for schizophrenia.

Sexual selection and the evolution of fitness indicators

Traits with a high heritability that appear puzzling from an evolutionary perspective have been explained by the theory of sexual selection, which refers to the evolutionary selection of traits associated with a reproductive advantage, rather than survival advantage and includes selection due to differences in intra-sexual competitive abilities (intra-sexual competition), and selection due to mate preferences of the choosier sex (intersexual selection). Intersexual selection may stimulate the evolution of traits such as attractive bright plumage in male birds, despite the survival costs that are often associated with such traits[110]. For example, male peacocks have enormous tails that are energetically costly to grow, prevent the bird from flying, and make it an easy target for predators; however, the tails have been favored by sexual selection because they attract females[111].

Several theories have been proposed to explain why such traits attract the opposite sex. The good-genes theory states that individuals of the choosier sex prefer features of mates that advertise genetic fitness[112]. The fitness indicator theory is slightly broader, and states that mate preference traits reveal to potential mates an individual's underlying genetic quality (e.g. mutational load) and condition (e.g., nutritional status and parasite load)[113]. Selection pressures favor individuals who prefer mates with high-quality fitness indicators, since such mates are more likely to successfully produce offspring with high fitness. Fitness indicators may comprise behavioral features such as the courtship songs of birds[114]. Theoretically, the most informative fitness indicators are to a large degree influenced by genetic variation (to allow for advertising genetic fitness) and are at the same time highly sensitive to the environment (to allow for advertising overall fitness).

Visible human body traits may have evolved as fitness indicators, including male facial structure, muscularity and height[115], and female breasts[116]. Shaner *et al* [117] proposed that human mental and behavioral characteristics may also have evolved as fitness indicator. This fitness indicator may involve verbal courtship behaviors (e.g., "attracting mates by telling funny stories with creativity, social sensitivity, and emotional expressiveness"). In individuals with good genes and a favorable prenatal and postnatal environment, neurodevelopmental processes influencing these mental characteristics result in successful courtship behavior. A poor genetic background (due to harmful alleles) or environmental background, however, leads to unsuccessful courtship behavior that repels potential mates. According to Shaner *et al* schizophrenia represents the unattractive and dysfunctional extreme of a highly variable trait shaped by sexual selection. A computational model developed by Del Giudice demonstrates that the sexual selection model is compatible with reduced fertility in families of schizophrenic patients[28]. Yet, the existence of traits that advertise genetic fitness only makes sense as long as harmful genetic variants ('bad genes') are present in the population, and the question is why such variants (still) exist if they produce an 'unattractive' phenotype with lower fitness.

Recessive alleles and epistasis

One factor that is of major importance for the outcome of natural selection on a phenotype is the mode of action of the underlying genes, for example whether causal alleles act in an additive, dominant, or recessive manner [44]. If a maladaptive phenotype results from a dominant allele or additive gene effect at a locus, fitness will be decreased in all carriers of the risk allele and the risk allele will go extinct while the other allele will reach fixation. On the other hand, if a maladaptive phenotype results from the action of a recessive allele, selection will only act on individuals that are homozygous for this allele. In heterozygous individuals, the maladaptive phenotype will not come to expression and the recessive allele will be 'invisible' to natural selection. The

persistence of risk alleles for schizophrenia may therefore in part be explained by the action of recessive alleles that are difficult to eliminate by natural selection. Natural selection similarly acts more slowly on maladaptive traits that result from the interaction of multiple loci (epistasis), in which case the fitness of individuals is determined by the combination of alleles at each locus. For maladaptive traits that arise from epistatic interactions among multiple loci, a 'risk allele' is only associated with reduced fitness in individuals with the specific combination of alleles, while the same allele can be harmless in individuals with other combinations.

Negative selection pressures on recessive alleles can explain the well-described phenomenon of inbreeding depression, where a drop of fitness is observed in the offspring of related parents, because inbreeding increases the chance that offspring are homozygous for deleterious recessive alleles [118, 119]. Schizophrenia is more prevalent in populations with higher levels of inbreeding [120, 121], which supports the role of rare recessive variants, and suggests that these variants may have been subject to negative selection, although other factors, e.g. demographic, social, and economic ones may also influence such outcomes. Additional support for the role of recessive alleles in schizophrenia comes from a study of runs of homozygosity (ROH, long stretches of homozygous polymorphisms), which showed that ROH were more common in schizophrenia patients and found that several specific ROH were present in schizophrenia patients that were very rare in healthy subjects [122].

Fitness trade-offs

From an evolutionary perspective, all phenotypes can be regarded as compromises. Evolution does not strive for perfection. Rather, it drives traits towards an optimum level where fitness and trade-offs are balanced. For example, "our immune systems could be more aggressive, but only at the cost of damaging our own tissue" [123]. Perhaps schizophrenia could have been eliminated by natural selection, but at the expense of loosing valuable cognitive traits. The capacity of natural selection to optimize traits is bounded by some important constraints [123]. Firstly, natural selection represents a stochastic process; certain mutations that could be of benefit to a species may never occur, while harmful mutations can go to fixation by mere chance. Another important constraint is path dependence, which refers to humans being the result of evolutionary forces acting on a continuous lineage from one-celled organism with no fresh start. Therefore, most aspects of the human body depend on aspects that evolved earlier in a way that suboptimal characteristics may not be set straight.

An example of a suboptimal morphological characteristic that has been suggested to reflect path dependence in evolutionary history is the recurrent (inferior) laryngeal nerve, which is a branch of the vagus nerve (tenth cranial nerve) that supplies motor function and sensation to the larynx [124]. The nerve takes a remarkable detour to reach its target: it descends from the brain into

the thorax, loops around the aorta, and travels back to innervate the laryngeal muscles in the neck. This pathway does not seem to make sense but is thought to reflect a design that originates from an ancient ancestor in which major blood vessels were located much closer to the target of this nerve. Thus, the recurrent nerve is also present in fish, in which it is the fourth branch of the vagus nerve innervating one of the posterior gills. The example illustrates that once selection has shaped a trait into a certain direction over evolutionary time, evolution cannot go back in time to reverse it if the trait becomes suboptimal later in evolutionary time. The evolution of the human brain may also have been limited by such constraints.

The triune brain concept is a model in which the human brain contains the evolutionary remnants of three ancestral brains: the reptilian brain (upper brain stem), the paleomammalian brain (limbic area), and the neomammalian brain (cortical region) [125, 126]. According to this model, each successive brain area that was introduced incorporates and modifies previous functions. Millar proposed that the introduction of each successive brain feature may have come with difficulties connecting pre-existing and novel parts, and hypothesized that schizophrenia may reflect a failure of integration between different parts, in particular between the limbus and cortex, an error that may have resulted from a suboptimal brain design due to evolutionary constraints [127]. However, the benefits of having a more complex brain that allowed for novel functions such as language may have outweighed the disadvantage that the design is sensitive to errors. But how can path dependence in the history of brain evolution explain the survival of heritable risk factors for schizophrenia? Why do errors in brain development only lead to problems in some individuals, and if there is a genetic cause for this why is it not wiped out by selection?

If a developmental outcome (brain function) is determined by the interaction of multiple areas and the development of each area is guided by its own genetic information, this suggests that the effect of an allele on an individual's outcome may depend on the presence of (many) other alleles, which implies epistasis. Yet, if there is even a very small difference in the fitness between different combinations of alleles, natural selection generally favours the most fit set of alleles, thus to maintain genetic variation there must be additional factors that play a role. Keller and Miller [128] illustrated the biological network of mechanisms that ultimately produce behaviour by using a watershed analogy: a huge number of "upstream" biological processes (e.g. neuron proliferation, dendritic pruning etc.) eventually flows into all sorts of "downstream" processes (e.g. language, learning capacity etc). One mutation in an upstream process can affect many downstream processes, and one downstream process can be influenced by mutations in many different upstream processes. Keller and Miller [128] suggested that the watershed model predicts that downstream fitness-related traits such as psychiatric disorders have a high heritability because they result from the integration of so many processes and are therefore highly polygenic. Support for the watershed model

comes from the finding that most rare structural variants that contribute to therisk of schizophrenia also increase risk of autism, developmental delay, intellectual disability, epilepsy, somatic dysmorphism, and extremes of body mass and head size [37]. Of interest to the developmental perspective, it was found that a large proportion of *de novo* mutations in schizophrenic patients were present within genes with a higher expression in the early and mid-stage fetal period [43].

Mutation selection balance

Harmful mutations are removed from the gene pool at a rate proportional to their effect on fitness. Yet, novel mutations occur all the time. The polygenic mutation-selection balance hypothesis states that the persistence of schizophrenia and other heritable common mental disorders may be ascribed to the continuous occurrence of new mutations [128, 129]. These mutations are harmful and under negative selection pressure; however, the elimination of fitness reducing mutations may be balanced by the continuous arrival of new mutations. The rate of *de novo* mutations is low (around 1.2×10^{-8} per nucleotide per generation [130]), but mental health may be influenced by many mutations, since the brain depends on the functioning of a large number of genes and their regulatory sequences. It has been estimated that human individuals carry on average 500 mutations with fitness-reducing effects on brain function that have not yet been removed by selection [128].

Polygenic mutation selection balance appears to be the most likely evolutionary explanation for the maintenance of genetic variation for psychiatric disorders with a remarkable reproductive disadvantage, such as schizophrenia [32, 128, 131]. The hypothesis may be supported by the paternal age effect that has been observed for schizophrenia, i.e. the risk of schizophrenia in offspring increases with increasing paternal age [132], and sequencing studies have shown that the age of the father at conception is associated with the number of *de novo* mutations in offspring [43, 130]. The number of *de novo* mutations was shown to increase with two extra mutations per year under a linear model, or doubled every 16.5 years under an exponential model [130].

Developmental instability and phenotypic plasticity

Schizophrenia has been proposed to represent a failure to express precisely an 'intended' developmental design due to perturbations caused by deleterious environmental influences and mutations. The developmental instability model states that during development, environmental and genetic perturbations, including pathogens, toxins, and harmful mutations introduce random effects and imprecision in developmental pathways [133-135]. An example of a feature that is thought to reflect developmental instability is fluctuating asymmetry, which is indexed, for example, by differential ear length. Though the left and right ears are on average of equal size in the population, the ears of an individual may differ slightly, and this could reflect 'noise' in development. Fluctuating

asymmetry may also affect developmental processes in the brain; an example that is thought to illustrate this is hand preference. Schizophrenic patients show greater dermatoglyphic fluctuating asymmetry and more often show atypical (mixed) handedness [136, 137]. Natural selection should favor individuals that are capable of buffering perturbations of developmental pathways, but it has been suggested that an important part of the genetic variation in developmental instability may consist of genetic variation in the ability to resist pathogens [135]. Such variation can be maintained in populations by the process of host-parasite co-evolution [138]. Of interest to this theory, the strongest genetic association for schizophrenia that has thus far emerged from GWAS is in the major histocompatability complex (MHC) region [37].

Rather than being a pathological maladaptation to developmental insults, schizophrenia has also been suggested to represent an adaptively programmed phenotype that is induced by environmental adversity. Many organisms express strikingly variable morphologies in response to variable environmental conditions encountered during development, many of which are thought to represent alternative survival or reproductive strategies. The phenotypic plasticity hypothesis states that exposure to adverse environmental cues during early development may induce alterations in the expression of genes, resulting in a phenotype that is better suited for a stressful or deprived environment [139]. According to Reser [140], some of the core characteristics of schizophrenia that predict social and vocational disabilities in modern times, such as the inability to calm instinctual drives, ignore arousing stimuli, and inhibit transient desires may represent a “defensive, vigilance-based behavioral strategy that alerts the organism to salient, potentially informative stimuli and permits it to be more impulsive and vigilant”. Thus, schizophrenia may be related to physiological and behavioral characteristics that created a fitness advantage in the ancestral environment under conditions of nutritional scarcity and severe environmental stress. The link between schizophrenia and environmental adversity may be supported by several observations. Brain areas in the hippocampus and frontal lobes that become hypometabolic in schizophrenia [141-143] have also been demonstrated to become adaptively hypometabolic in response to starvation, stress and variations in ecological rigor in other mammals and birds [144, 145]. Furthermore, schizophrenia has been linked to exposure to stress during development. Thus, maternal malnutrition [146], maternal stress [147], multiparity [148], short birth interval [149] and stressful postnatal events [150] are all risk factors for schizophrenia, and certain neurophysiological characteristics of schizophrenia can be induced in animals through exposure to prenatal and postnatal stressors [151, 152].

The mismatch hypothesis

While schizophrenia may present a fitness cost in modern societies, this might not have been the case throughout the entire evolutionary history of humankind [153]. This mismatch hypothesis is supported by the fact that the prevalence of

schizophrenia seems to be quite variable across different locations [3], with the highest rates generally found in urban areas [154]. The mismatch hypothesis has been translated in various ways. Firstly, genetic variants that predispose to schizophrenia in modern times may have been adaptive in ancient environments (ancestral adaptation [155]. Secondly, schizophrenia may have been selectively neutral throughout most of human evolutionary history (ancestral neutrality hypothesis [156]. Thirdly, schizophrenia may persist due to variable selective pressures as a result of fluctuating environmental conditions [157].

Epigenetic variation as an evolutionary adaptation to fluctuating environments

How can the persistence of variation in genetic risk be explained if the outcome depends on environmental factors, as predicted by the phenotypic plasticity model? Feinberg and Irizarry [157] proposed a framework that describes how genotypes may influence fitness by regulating the variability of a trait in a population, rather than by influencing the average level of the trait. Thus, the authors suggested that certain loci regulate the plasticity of development of individuals by influencing stochastic variation in gene expression. The suggested loci are CpG islands, the density of which may vary between individuals due to genetic polymorphisms, presenting an inherited basis of variably methylated regions (VMRs). Epigenetic variation at VMRs influence variation in the expression of nearby genes [158], which can give rise to large stochastic variability in phenotypes under a given genetic background.

This type of genetically inherited stochastic variation may provide a powerful mechanism for evolutionary adaptation to variable environments. Using simulations, the authors demonstrate that under fluctuating environmental conditions, a genetically inherited propensity to phenotypic variability increases fitness of a population despite increasing disease susceptibility. In other words, the fitness of individuals may be determined in part by the ability to vary around a certain phenotypic level (or disease risk), rather than by the phenotypic level itself, as this may be the best strategy for the population when environmental factors are not constant. The model of genetically inherited stochastic epigenetic variation provides a molecular mechanism for the phenotypic plasticity paradigm, and may explain how the persistence of disadvantageous traits such as schizophrenia may be stimulated by the pressures of variable environments and at the same time have a heritable basis. Of interest, several studies have reported epigenetic alterations in schizophrenia [159-162]. The paternal age effect is also compatible with the implicated role of epigenetic mechanisms, as increasing paternal is associated with increased risk of epigenetic abnormalities [163].

Sexual and genomic conflicts at imprinted genes

Sexual conflict arises when the two sexes of a species have conflicting optimal reproductive strategies, leading to an evolutionary arms race between males and females [164]. In many species, reproduction is characterized by differential investment of the sexes in their offspring. In mammals, the mother is predominantly responsible for providing resources to offspring pre- and perinatally. As a result, the fitness of maternally derived alleles favors smaller demand on maternal resources, anticipating on the survival of future offspring, than paternally derived alleles, which are associated with high fitness if offspring exploit as much resources from the mother as possible. It is thought that the level of expression that maximizes the fitness of an allele depends on whether the allele was present in a male or a female in the previous generation.

At imprinted genes, the expression pattern of an allele depends on its parent of origin [165]. Typically, one allele is expressed, while the other is transcriptionally silent. The kinship theory of imprinting states that the evolution of imprinted gene expression originates from the conflict of interests between maternally and paternally derived alleles at a locus. Paternally derived alleles favor higher growth rates of offspring and greater demand on maternal resources than maternally derived alleles. Therefore, growth promoting loci are often maternally silenced through imprinting, whereas loci that suppress growth are often paternally silenced [166].

A well-studied example of an imprinted gene is the *IGF2* gene, which encodes a growth promoting factor that is only expressed from the paternal allele. In humans, imprinting defects that activate the silenced maternal allele result in Beckwith-Wiedemann syndrome, an over-growth syndrome characterized by a 50% increase in birth weight [167]. Conversely, imprinting defects that cause the silencing of both alleles give rise to an under-growth syndrome called Silver-Russell syndrome [168]. Imprinting is thought to be particularly important for genes expressed in the placenta, but is also frequently observed for genes with a role in brain development [169, 170]. Thus, the genetic conflict over maternal investment may also affect behavior, cognition and personality of offspring [171].

Badcock and Crespi suggest that the “genetic war” at imprinted genes for brain development may give rise to mental disorders if expression is pushed too far towards the benefit of one of the parental alleles. Paternally biased expression of genes involved in brain development may give rise to a self-oriented child that is highly demanding to its mother, extreme cases being recognized as autism. In line with this theory, Beckwith-Wiedemann patients have an increased risk of autism [172], and individuals with autism tend to show increased *IGF2* expression [173]. Badcock and Crespi hypothesized that small deviations in imprinted gene expression towards a maternal bias may lead to offspring that are energetically ‘cheaper’ and easier behaviorally to mothers, i.e. more placid, less demanding and better capable of interpreting and

understanding the mental states of others. Large maternally biased deviations may lead to psychosis. The authors suggest that several characteristics of autism and psychosis may be regarded as opposites in the context of parental demand, i.e., autistic spectrum conditions are characterized by deficits in theory-of-mind skills, or 'hypo-mentalism', whereas psychotic spectrum conditions involve the opposite: 'hyper-mentalism'. For example, people with autism are characterized by a defective detection of gaze and inability to appreciate what goes on in groups, while individuals with schizophrenia may experience paranoid delusions of conspiracies and being watched by others.

Some empirical support for the theory of Badcock and Crespi is provided by findings in a region that contains several imprinted genes on chromosome 15. Paternally biased expression of this region causes Angelman syndrome, a disorder that is highly comorbid with autism, while maternally biased expression of the same region causes Prader-Willi syndrome, a condition that is often accompanied by psychotic symptoms [174]. Several genes have been found to contribute to risk of autism, schizophrenia and bipolar disorder at the same time [175], but it remains to be established whether these genes are imprinted and whether the expression of the genes may differ across disorders. To conclude, fluctuations in imprinted gene expression that result from the ongoing conflict between reproductive strategies of males and females may contribute to the persistence of fitness decreasing conditions such as schizophrenia. Because epigenetic mechanisms that regulate imprinting can be influenced by genetic variation [157], this theory is compatible with the persistence of heritable variation.

Wilkins addressed the situation of imprinted genes with pleiotropic effects, and suggested that natural selection can systematically cause a loss of fitness and fixation of maladaptive phenotypes due to genomic conflicts [176]. At imprinted loci, selection is driven exclusively by the fitness of the active allele. When a phenotype is influenced by multiple oppositely imprinted loci, an interlocus conflict arises, because any given level of the phenotype will be associated with differential fitness effects for the underlying maternally vs paternally expressed loci. Using a mathematical model to describe a pair of antagonistic imprinted genes (one paternally expressed and one maternally expressed) with pleiotropic phenotypic effects (i.e., both genes influence multiple phenotypic aspects), it was demonstrated that the genomic conflicts that arise can cause natural selection to drive phenotypes away from their optimum values, resulting in a maladaptive, but selectively favored, evolutionary trajectory. According to this theory, mental disorders that occur at high frequencies despite reducing individual fitness, such as schizophrenia, may be related to pleiotropic effects of imprinted gene expression in the brain.

Conclusions

We have presented a variety of evolutionary perspectives of schizophrenia and addressed how they might explain the persistence of genetic risk variants for

schizophrenia in the population. The different evolutionary scenarios make different assumptions about the genetic architecture of schizophrenia, which is relevant to genetic studies that aim to identify genetic variants.

The polygenic mutation-selection balance model offers an explanation for how fitness-reducing genetic variation is maintained in the population; harmful mutations are under negative selection but variation persists, because the removal of alleles is balanced by the occurrence of new mutations in the population. Of interest, a study of the rate of *de novo* occurrence and overall frequency of ten large and rare recurrent DNA copy number variants (CNVs) that have been associated with schizophrenia and other neurodevelopmental disorders indicated that all of these variants are under strong negative selection [177]. The highest selection coefficients were observed for the rarest CNVs, and given the observed selection pressures, *de novo* CNVs at these loci appear to persist in the population for only a few generations. To date, various studies have identified rare SNPs and structural variants that are associated with the risk of schizophrenia [37, 42, 43], and the polygenic mutation-selection model predicts that many more rare genetic variants are likely to contribute to the risk of schizophrenia in the population.

Theories that propose that schizophrenia is in some way linked to adaptive traits, such as social skills, creativity or pathogen resistance suggest that genetic risk variants persist through balancing selection; alleles that confer risk to schizophrenia are maintained in the population because they are of benefit to unaffected individuals. These theories imply that genetic risk variants are common. Other mechanisms that may account for the maintenance of common genetic variants that contribute to disease risk include genomic and sexual conflicts, and the maintenance of genetic variation at CpG sites as an adaptation to fluctuating environmental pressures. It is often thought that environmental approaches cannot explain the paradox of psychiatric disorders, because environmental explanations do not seem to be compatible with the high heritability. However, we have discussed how environmental pressures may in fact contribute to the maintenance of heritable variation in areas that regulate gene expression.

An important difference exists between perspectives that assume that the fitness cost associated with schizophrenia is balanced by increased fitness in relatives, and those that see schizophrenia as a maladaptive by-product of evolution, or fitness trade-off that persists at the benefit of humankind. Distinct mechanisms have been proposed to account for these alternative scenarios, which make different predictions about the genetic architecture of schizophrenia. The “heterozygote advantage” model proposed to account for increased fitness in relatives may be the most convenient evolutionary scenario for genetic association studies (e.g. GWA studies), as cases and controls are expected to differ at common polymorphisms (with adaptive heterozygote genotypes being overrepresented among controls). Yet, current data on fitness of relatives does not appear to support this model, nor does the fact that

genetic variants with large effects on the risk of schizophrenia have not emerged from GWAS.

Perspectives in which schizophrenia is considered to represent a maladaptive by-product of genetic variants required for complex cognitive functions suggest that every individual carries some genetic susceptibility to schizophrenia, and whether individuals are affected may depend on the number of susceptibility alleles they carry (cliff-edged fitness), or on the combination of alleles across multiple loci (epistasis). The cliff-edged fitness paradigm predicts that inter-individual variation in cognitive characteristics is not so much determined by the particular genotype at each locus. Although susceptibility alleles generally give rise to favorable cognitive traits, too many alleles result in schizophrenia. Since many combinations of susceptibility alleles may predispose to schizophrenia, as long as the total number of alleles is large enough, this scenario is a difficult one for case-control association studies or linkage studies. The scenario would in fact be in line with the variable linkage results that have been reported, since affected individuals might be distinguished from non-affected relatives by the additional presence of any copy from the total pool of susceptibility alleles. Thus, although the genetic architecture of schizophrenia under the cliff-edged fitness paradigm could be in line with the CDCV hypothesis, it may explain the limited success of gene finding studies, since the success of detecting susceptibility alleles under this scenario critically depends on the study design. Epistasis likewise implies that single-SNP tests as usually conducted in GWAS are not the optimal strategy to identify common risk variants for schizophrenia, although main effects are expected to exist for individual alleles, which should be identified when sample sizes are large enough. Yet, as the overall effects of these alleles on fitness are expected to be very small from an evolutionary perspective (otherwise they would have been eliminated by natural selection), the individual effects of these alleles when compared between cases and controls are likewise expected to be very small.

The hypothesis that genetic variants that predispose to schizophrenia may have been favoured by natural selection is supported by some empirical evidence. Several genes that have been linked to schizophrenia appear to show signs of positive selection in the human lineage, including Disrupted in Schizophrenia 1 (*DISC1),* Dystrobrevin Binding Protein 1 (*DTNBP1)* and Neuregulin 1 (*NRG1)*, each of which is thought to play an important role in brain development [178]. Several genes related to energy metabolism that have been implicated in the pathophysiology of schizophrenia also appear to have undergone rapid changes in the human lineage [179]. It thus seems that at least some of the variants associated with schizophrenia may have been favoured by natural selection.

Perhaps the strongest evidence for the role of common genetic variants for schizophrenia comes from the estimate that 23% of the variation in disease risk can be explained by all genome-wide SNPs from SNP arrays

together [21]. Though some of this signal may come from rare genetic variants, strong evidence for the importance of common genetic variants is implicated. Common variants can only persist in the population if they are maintained by some sort of balancing mechanism (e.g. antagonistic pleiotropy, fluctuating environments or genomic conflicts), or if the individual effect of risk variants on fitness is so small that relatively high frequencies (e.g. higher than 5 %) can result from random drift. The latter scenario is not unlikely if the risk of schizophrenia in the population is determined by thousands of genetic variants.

Though some theories cannot on their own explain the maintenance of harmful genetic variation in the population, they do provide a framework that allows us to understand how evolution has shaped the brain, and that it is not strange from an evolutionary perspective that this design can be sensitive to errors (e.g. path dependence, fitness trade-offs and developmental instability). Several theories imply that environmental exposures are important, including the mismatch hypothesis, the phenotypic plasticity hypothesis, the fitness indicator theory and the theory of stochastic epigenetic variation. These perspectives are closely linked to each other, and they all predict that gene-environment interactions and epigenetic variation contribute to the etiology of schizophrenia. Genetic variants that predispose to schizophrenia may confer risk to the condition by increasing environmental sensitivity [180] and may therefore be associated with the amount of variation in the phenotype rather than with a specific mean level. Detection of such genetic variants will require novel methodologies and statistical approaches. This evolutionary scenario is also in line with variable linkage and association results across different populations, since different populations may show different levels of the relevant environmental exposures. Part of the heritability of schizophrenia may reflect genetic variation that contributes to the exposure to certain environments (gene-environment correlation), as several 'environmental risk factors' of schizophrenia, for example smoking [181] and cannabis use [182], are known to be to heritable to some extent.

An important point of critique that has been raised in response to evolutionary approaches of schizophrenia is that most take for granted that schizophrenia represents a trait that is 'visible' to natural selection. Thus, one of the core assumptions of evolutionary psychiatry and biomedical psychiatry in general is that schizophrenia and other mental disorders are natural kinds, i.e. bounded entities with discrete biological causes [183]. Given the phenotypic heterogeneity of schizophrenia and the assumed underlying genetic heterogeneity [184, 185], the 'construct' schizophrenia may not have a discrete biological cause, but may rather represent an umbrella concept that covers a heterogeneous group of disorders. The heterogeneity hypothesis predicts that genetic studies of schizophrenia may benefit from focusing on underlying mechanisms with a more homogeneous biological foundation, rather than disease status (affected versus unaffected) as determined by clinical guidelines. Several authors have proposed a unitary model of psychosis [186-188]

and this hypothesis should also be kept in mind when considering the evolutionary history of schizophrenia. In fact, both from evolutionary and genetic perspective, diagnostic categories of psychiatric disorders can be arbitrary, and it seems likely that many genetic variants may contribute to the risk of multiple disorders at the same time.

An important general issue in evolutionary biology is the debate over the level of selection, which refers to the question which level of the biological hierarchy is touched by natural selection. Does natural selection act on organisms, genes, groups, populations or species? Classical Darwinian theory states that it is the differential survival and reproduction of individual organisms that drives the evolutionary process [24]. However, natural selection can operate simultaneously at different levels of the biological hierarchy (multi-level selection theory [189]. In fact, the direction of selection may differ between different hierarchical levels. For example, a trait may be selectively disadvantageous to individuals, but selectively advantageous at the group level. This issue is also important for evolutionary psychiatry and the debate over the evolutionary paradox, i.e. if fitness is reduced in schizophrenia and the fitness of relatives is equal to that of the general population, should it be concluded that schizophrenia risk alleles are merely maladaptive? The pluralist view of natural selection states that the distinction between different levels is a conceptual mistake; different levels of selection represent a matter of perspective rather than empirical fact [190]. Psychiatric disorders are probably subject to a combination of selective pressures, and different evolutionary perspectives may shed light on different aspects and levels of selection.

To conclude, we have discussed a variety of theories that contribute to our understanding of how heritable risk factors for schizophrenia persist in the population, providing insight into the genetic architecture of the disorder and into useful strategies for gene finding. Many of the evolutionary perspectives of schizophrenia may to some extent also apply to other common psychiatric disorders.

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