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Schizophrenia as one extreme of a sexually selected fitness indicator

Andrew Shaner[a,*], Geoffrey Miller[b], Jim Mintz[a]

[a] *Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles and the Veterans Affairs Greater Los Angeles Healthcare System, USA*
[b] *Department of Psychology, University of New Mexico, USA*

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Abstract

Schizophrenia remains an evolutionary paradox. Its delusions, hallucinations and other symptoms begin in adolescence or early adulthood and so devastate sexual relationships and reproductive success that selection should have eliminated the disorder long ago. Yet it persists as a moderately heritable disorder at a global 1% prevalence—too high for new mutations at a few genetic loci. We suggest that schizophrenia persists and involves many loci because it is the unattractive, low-fitness extreme of a highly variable mental trait that evolved as a fitness ("good genes") indicator through mutual mate choice. Here we show that this hypothesis explains many key features of schizophrenia and predicts that some families carry modifier alleles that increase the indicator's neurodevelopmental sensitivity to heritable fitness and condition. Such alleles increase the extent to which high-fitness family members develop impressive courtship abilities and achieve high reproductive success, but also increase the extent to which low-fitness family members develop schizophrenia. Here we introduce this fitness indicator model of schizophrenia, discuss its explanatory power, explain how it resolves the evolutionary paradox, discuss its implications for gene hunting, and identify some empirically testable predictions as directions for further research.

Keywords: Schizophrenia; Genetics; Evolution; Sexual selection; Mate choice; Fitness indicator

1. Background

Schizophrenia is a devastating mental illness with a well-established (Cannon et al., 1998; Cardno et al., 1999; Tsuang et al., 2001) but evolutionarily puzzling (Huxley et al., 1964) genetic basis. Diverse evolutionary theories have attempted to explain why schizophrenia persists at a global 1% lifetime prevalence—far in excess of the rate possible from a single deleterious mutation (Wilson, 1997). One possibility, originally suggested by Julian Huxley (Huxley et al., 1964), is that schizophrenia is but one manifestation of a pleiotropic gene. In close relatives, the same gene might confer advantages such as resistance to infection (Erlenmeyer-Kimling, 1968), healthy suspiciousness (Jarvik and Deckard, 1977), increased fertility (Huxley et al., 1964), superior language skills (Crow,

* Corresponding author. Veterans Affairs Greater Los Angeles Healthcare System, 11301 Wilshire Blvd., Los Angeles, CA 90073, USA.
E-mail addresses: Andrew.Shaner@med.va.gov (A. Shaner), gfmiller@unm.edu (G. Miller).

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1995, 2000), or other abilities that foster group splitting and migration (Stevens and Price, 2000). These advantages might enhance survival and reproduction, offset the selective disadvantage of schizophrenia, and perpetuate the responsible gene.

However, only two studies have reported possible survival advantages in relatives (Carter and Watts, 1971; Lichtermann et al., 2001) and while some studies have found reproductive advantages (Avila et al., 2001) others have not (Haukka et al., 2003). Moreover, statistical modeling, using the recurrence risk of schizophrenia found in twin and family studies, has shown that schizophrenia is unlikely to be due to a single gene or a small collection of single-gene disorders, even taking incomplete penetrance into account. In addition, linkage and association studies have failed to find genes of large effect. Consequently, investigators have concluded that schizophrenia is probably due to many genes, each accounting for a small percentage of cases (Kendler and Diehl, 1993; McDonald and Murphy, 2003; Risch, 1990; Tsuang et al., 1999). However, if schizophrenia is sufficiently polygenic, this could explain its persistence despite reproductive disadvantage. If many loci are involved, and if the penetrance of susceptibility alleles is low, then new mutations could maintain an overall frequency of susceptibility alleles at a level sufficient to produce schizophrenia in 1% of the population (for a mathematical model, see Pritchard, 2001).

But polygenic models raise another question—why would so many genes predispose to schizophrenia? In other words, why would human mental functioning be so vulnerable to mutations at so many loci? Traits important to survival tend to develop reliably despite mutations and environmental stresses (Pomiankowski and Moller, 1995; Rowe and Houle, 1996). A partial answer is that the brain systems that fail in schizophrenia are unusually vulnerable to ''developmental instability'' (DI). When manifest in body growth, DI results in right–left asymmetries and minor physical anomalies; when manifest in brain development, DI results in abnormal lateralization, unusual brain anatomy, lower intelligence, and psychopathology (Yeo et al., 1999). Although DI may explain much of abnormal development in schizophrenia, it does not explain how humans evolved this vulnerability.

We propose that a more complete answer lies in the one evolutionary process—sexual selection—that has historically been most successful in explaining the evolutionary maintenance of adaptively puzzling traits with persistently high heritability (Andersson, 1994; Darwin, 1871). It is no surprise that beautiful peacock tails persist. They are heritable, and males with the most beautiful tails do virtually all of the mating and reproducing (Petrie et al., 1991). The puzzle is why the ugly tails persist as they do. That paradox has been studied enough to have been named (''the paradox of the lek'') (Kirkpatrick and Ryan, 1991) and resolved (Kotiaho et al., 2001; Pomiankowski and Moller, 1995; Rowe and Houle, 1996). Much of this paper is the application of that resolution to schizophrenia.

Sexual selection concerns relative reproductive success rather than survival success. Mate choice, a major form of sexual selection, produces traits such as bright plumage or mating calls that attract opposite-sex mates (Andersson, 1994). Why such traits attract the opposite sex has been the subject of extensive theoretical and empirical research (Andersson, 1994; Kokko et al., 2003). Among the best supported theories is that many such traits function as *fitness indicators*: they reveal to potential mates an individual's underlying genetic quality (Kokko et al., 2003; Michod and Hasson, 1990; Pomiankowski and Moller, 1995; Rowe and Houle, 1996) (''fitness'' henceforth) and condition (e.g., nutritional status, parasite load). Theoretically, the most informative fitness indicators show the highest phenotypic variation in size, complexity, or quality across individuals, and that variance shows the highest correlation with underlying fitness and condition. Animals are under selection pressure to prefer mates with high-quality fitness indicators because such mates are likely to be better parents with better genes that would benefit the survival and reproductive prospects of their offspring.

The result of such mate preferences for fitness indicators is that individual variation in fitness and condition will correlate positively with the sexual attractiveness of the indicator trait. For example, a large, symmetric, colorful peacock's tail will attract many mates, while a small, asymmetric, dull peacock's tail will attract very few mates. Indicators may be morphological features such as the peacock's tail (Petrie, 1994), or behavioral abilities such as the nightingale's courtship song (Andersson, 1994). In several bird species, females prefer males with larger song repertoires, greater song

complexity, and higher song amplitude, and these measures correlate with various measures of fitness, including nestling development (Nowicki et al., 2000), immune function (Garamszegi et al., 2003), and longevity (Forstmeier et al., 2002). Other behavioral fitness indicators include abdomen drumming in wolf spiders (Parri et al., 2002) and wing song in fruit flies (Hoikkala et al., 1998). When female choice predominates, indicators evolve in males only. However, indicators can evolve in both sexes through mutual mate choice, as in many socially monogamous bird species (Andersson, 1994; Kokko and Johnstone, 2002).

Did humans evolve any fitness indicators through sexual selection? Recent evidence suggests that several human body traits may have evolved through mate choice, including male height, muscularity and facial structure (Perrett et al., 1994), and female breasts and buttocks (Etcoff, 1999; Miller, 2000b). In addition, many human mental and behavioral abilities, including language, music and humor, may have evolved as fitness indicators through mutual mate choice (Miller, 2000a). For example, suppose that in our hominid ancestors, the brain systems responsible for primitive language were sensitive to individual fitness. If so, then those who preferred verbally skilled mates would have secured for their offspring, genes for better general fitness. Moreover their offspring would inherit their parents' genes for verbal skill and genes for preferring verbally skilled mates. The increasing correlations among these three kinds of genes would set the stage for the rapid evolution of language as a fitness indicator (Miller, 2000a).

We are not the first to consider sexual selection in schizophrenia. Both Crow (Crow, 1993, 1998) and Randall (Randall, 1998) proposed roles for sexual selection, but neither addressed its effects on the genetic and phenotypic variance of sexually selected traits. Consequently, Crow postulated a single-gene model and Randall proposed that females perpetuate susceptibility alleles by reproducing before illness onset. We may be the first, however, to use fitness indicator theory (Andersson, 1994; Kokko et al., 2003; Michod and Hasson, 1990; Miller, 2000a), a relatively new branch of sexual selection theory, to explain the evolutionary origins, genetic basis, and characteristic symptoms of schizophrenia.

2. Hypothesis

We propose that schizophrenia is the unattractive extreme of a mental and behavioral ability that evolved as a fitness indicator (or set of indicators) through mutual mate choice in humans. If so, then the processes of neural development that go awry in schizophrenia should show high sensitivity to fitness and condition. In an individual with high genetic fitness (e.g., a low deleterious mutation load) and a favorable prenatal and postnatal environment, these neurodevelopmental processes should result in an adult brain capable of attractive courtship behavior. However, at the opposite extreme, given poor fitness and condition, neurodevelopment should result in an aberrant brain prone to unsuccessful courtship behavior that repels potential mates. It is this unattractive extreme which we recognize as schizophrenia (Fig. 1). Schizophrenia itself is not adaptive. Rather, it is the unattractive and dysfunctional (Wakefield, 1999) extreme of a highly variable trait that evolved for courtship.

What is the courtship trait? The question is difficult to answer. Biologists usually analyze fitness indicators starting from the attractive extreme, observing that individuals with the highest-quality indicators (e.g. the brightest plumage or loudest call) attract the most mates. In contrast, our theorizing began at the other extreme, with the observation that schizophrenia reduces marriage rates and reproductive output (Nanko and Moridaira, 1993). We speculate that behaviors symptomatic of schizophrenia (such as delusions, disorganized speech, reduced emotional expressiveness, social awkwardness, and poor sense of humor) reduce reproductive success largely through impairing courtship ability. If so, then what is the normal mental adaptation that goes wrong in schizophrenia?

One possibility is that the behavioral symptoms of schizophrenia are maladaptive versions of uniquely human verbal courtship behaviors (e.g., attracting mates by telling funny stories with creativity, social sensitivity, and emotional expressiveness). By "verbal courtship" we mean more than successful pick-up lines by males to attract females. Instead, we imagine a complex verbal "dance" of mutual mate choice and display, a process in which each potential mate attempts to model the other's mind and use the

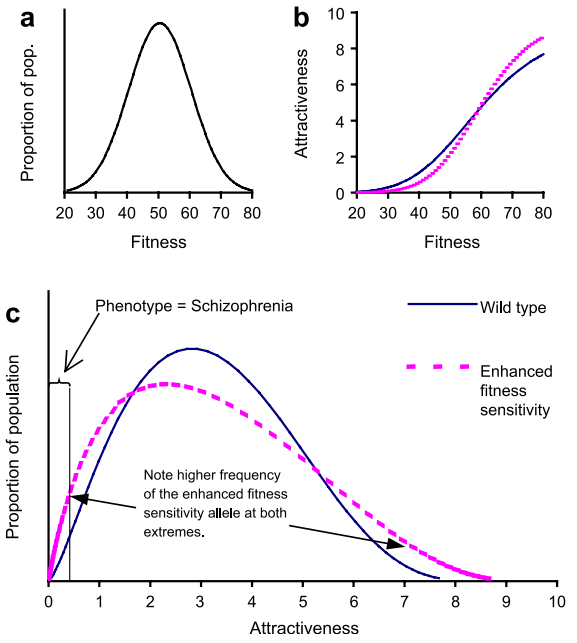

Fig. 1. Hypothetical relationships among fitness, the attractiveness of an indicator trait and the prevalence of schizophrenia. (a) Fitness (i.e., genetic quality) in the general population as a simple normal distribution (Gaussian) displayed as *T*-scores with mean set at 50 and SD=10. (b) Attractiveness (on an arbitrary scale from 0 to 10) expressed as two similar sigmiodal functions of fitness. (c) Attractiveness in the general population. This is the result of applying the functions in (b) to the distribution in (a). We assumed that half the population has the wild type indicator and half have the enhanced fitness sensitivity indicator. Arbitrary parameters were set for both functions to illustrate how the "enhanced-sensitivity" function could produce greater proportions of the population at both the attractive and unattractive extremes. We chose a threshold that defines an unattractive extreme (which we hypothesize is identical to schizophrenia) containing one percent of the total population. In this illustration, that 1% comprises about one quarter percent with the wild type indicator and three quarters percent with the enhanced-sensitivity indicator.

evolving model to determine the other's desirability and to improve conversational gambits.

The requisite brain systems are likely exceedingly complex and their development may therefore be vulnerable to mutations at many loci and to a wide range of environmental hazards. For example, suppose that successful verbal courtship requires an unconscious capacity to generate many possible conversational gambits, and then to internally critique, practice, and improve the gambits to produce interesting utterances and enjoyable conversation. Disrupted development of the required brain systems might produce an abnormally conscious awareness of the internal critique, experienced as the derogatory auditory hallucinations typical of schizophrenia. Disrupted development might also impair the effectiveness and accuracy of the internal critique resulting in socially inappropriate utterances that include disorganized speech and delusions—also typical of schizophrenia. Further support for this speculation is that language abnormalities are common in schizophrenia (DeLisi, 2001) and that people with schizophrenia appear to have deficits in verbal humor and the ability to represent the beliefs, thoughts and intentions of other people (Corcoran et al., 1995; Frith, 1996, 1992).

To illustrate our hypothesis, we have focused on mate choice as the mechanism of sexual selection that drove the evolution of human language as a fitness indicator. However, some sexually selected fitness indicators may have evolved both as weapons, used in contests over mates, and as ornaments, used to attract (or manipulate) the opposite sex (Berglund et al., 1996). For example, among deer, males use antlers in contests over mates and those with the largest antlers have an advantage. In addition, females prefer males with larger antlers (Fiske et al., 1998). Similarly, human language may have evolved for both contests and courtship. Those who could model the minds of sexual rivals and produce more intimidating verbal gambits could have used the same brain systems to model the minds of potential mates and produce more attractive (i.e. either more pleasing or more manipulative) verbal gambits (Miller, 2000b). Disrupted development of brain systems evolved for contests with sexual rivals might lead to inaccurate detection of rivals—expressed as persecutory delusions and derogatory hallucinations—and poor attempts at intimidation—expressed as grandiose delusions.

3. Explanatory and predictive power

This hypothesis that schizophrenia represents the unattractive extreme of sexually selected verbal courtship abilities is just one possibility—a special case of our more general claim that schizophrenia is the unattractive extreme of some type of sexually selected fitness indicator (SSFI). This more general

claim can be evaluated without specifying the precise nature of the SSFI, because SSFIs have some generic properties that explain many puzzling aspects of schizophrenia and lead to several testable predictions. If our general claim holds up, then further research will clarify the nature of the SSFI that goes awry in schizophrenia. Below we outline seven key generic properties of SSFIs and show how each is relevant to understanding schizophrenia. We show that they explain many otherwise puzzlingly facts about schizophrenia and lead to surprising but testable predictions.

3.1. SSFIs are displayed during courtship

If schizophrenia is aberrant courtship, its symptoms should begin at the age when courtship typically begins in normal individuals, and its symptoms should become more severe under socio-sexual conditions that promote courtship and sexual competition. As the brain systems underlying successful courtship mature in normal individuals under hormonal control, those same brain systems may begin to produce psychotic symptoms in individuals at risk of schizophrenia. This explains schizophrenia's typical post-puberty age of onset: although neurodevelopmental precursors of schizophrenia can be observed long before puberty (Woods, 1998), schizophrenia itself is rare before puberty, and most cases begin between the ages of 15 and 26 (Hafner et al., 1993), the age of peak mating effort in humans. Because the age at onset of courtship varies across populations, we predict that across different human groups (e.g. sexes, ethnic groups, races, and birth cohorts), schizophrenia's average age at onset will be correlated with courtship's average age at onset (e.g., as measured by the proxy of age at first sexual intercourse). Because courtship effort varies with age, we predict that schizophrenia symptoms will peak in severity at the age-peak of mating effort.

Moreover, if schizophrenia is aberrant courtship, anything that stimulates courtship and sexual competition in normal individuals should precipitate or worsen schizophrenia, and anything that inhibits courtship should improve schizophrenia. For example, dopamine agonists stimulate courtship in a wide range of species including humans; dopamine antagonists have the opposite effect (Melis and Argiolas, 1995; Neckameyer, 1998; Wood, 1995). This may explain why dopamine agonists worsen schizophrenia while dopamine antagonists improve it (Kahn, 1995). In addition, it suggests that other drugs that reduce courtship behaviors may prove therapeutic in schizophrenia. More generally, it suggests that disturbances in animal courtship may provide useful models of schizophrenia. Finally, social situations that stimulate courtship and sexual competition in normal individuals (e.g., dating, falling in love, being derogated by a sexual rival, getting divorced) should precipitate or worsen schizophrenia.

3.2. SSFIs affect the probability of mating

As the unattractive extreme of an SSFI, schizophrenia should impair the ability to attract and retain mates. This explains reduced rates of marriage (15–73% of normal) and reproduction (30–70% of normal) in schizophrenia (Haverkamp et al., 1982). Since married schizophrenics report near normal numbers of children, the reduced reproduction of unmarried schizophrenics probably results from failure to attract a mate, rather than physiological infertility (Haverkamp et al., 1982; Nanko and Moridaira, 1993).

3.3. SSFIs show predictable sex differences

Sexual selection theory predicts that males will typically invest more time, energy, and risk than females in mating effort (Andersson, 1994). This may explain why schizophrenia imposes more frequent and severe symptoms on males than on females (Jablensky, 2000)—the genetic, hormonal, and neurophysiological sex differences that amplify male mating effort also amplify any abnormality, such as schizophrenia, that represents the unattractive extreme of an SSFI. Also, females generally prefer older males and males generally prefer younger females. As a result, younger males and older females must try harder to attract and retain mates, so the peak of mating effort is younger for males than for females (Miller, 2000a). This may explain schizophrenia's earlier average age of onset in males (Hafner et al., 1993; Jablensky, 2000), despite earlier puberty in females.

3.4. The development of SSFIs is sensitive to fitness and condition

This fitness-sensitivity permits SSFIs to perform their main evolutionary function—to convert otherwise subtle variation in genetic quality into obvious phenotypic variation and thereby to make it easier for the opposite sex to choose high-quality mates. If schizophrenia is the unattractive extreme of an SSFI, the fitness-sensitivity of SSFIs explains several facts about the disorder. (1) Neurodevelopmental abnormalities are increased in schizophrenia (Woods, 1998; Yeo et al., 1999) because disordered development is one mechanism by which SSFIs indicate poor fitness and condition. (2) Polygenic inheritance underlies schizophrenia (McDonald and Murphy, 2003; Tsuang et al., 2001) because SSFIs typically show high additive genetic variance to serve as fitness (“good genes”) indicators (Houle, 1998; Houle and Kondrashov, 2002). (3) Environmental hazards such as prenatal exposure to viral infection (Buka et al., 2001), famine (Hulshoff Pol et al., 2000), and hypoxia (Cannon et al., 2002) increase risk for schizophrenia because sensitivity to environmental hazards is one mechanism by which SSFIs indicate genetic quality. (4) Increased mortality, mostly from a wide range of natural somatic causes (Brown et al., 2000) complicates schizophrenia because the unattractive extreme of an SSFI indicates poor fitness and condition.

3.5. Fitness-reducing mutations produce most of the heritable variation in the attractiveness of SSFIs

A balance between deleterious mutation and stabilizing selection produces a positive equilibrium frequency of fitness-reducing mutations in most animal populations. Thus, most heritable variation in general fitness may reflect individual differences in the number of evolutionarily transient, fitness-reducing mutations (“mutation load”) (Houle and Kondrashov, 2002; Michod and Hasson, 1990; Rowe and Houle, 1996). Therefore, our hypothesis suggests that most susceptibility alleles for schizophrenia will be evolutionarily transient, lineage-specific mutations that reduce general fitness. This explains why schizophrenia shows substantial heritability in twin and adoption studies, but why decades of gene-hunting in psychiatric genetics have failed to find any schizophrenia susceptibility alleles that replicate across human populations (McDonald and Murphy, 2003; Tsuang et al., 2001): the evolutionary half-life of such susceptibility mutations may be only a few hundred generations, so they do not spread widely across human populations. Yet every population has a substantial equilibrium number of distinctive fitness-reducing mutations that maintain the continuing heritability of SSFIs and, therefore, of schizophrenia.

3.6. Genetic differences between lineages may affect the fitness-sensitivity of SSFIs (Pomiankowski and Moller, 1995; Rowe and Houle, 1996)

Why does schizophrenia run in families? Our SSFI perspective suggests two complementary reasons: some families may have lower than average general fitness (i.e. higher than average mutation loads), and some families may have higher than average fitness-sensitivity in the SSFIs that can go awry in schizophrenia. Here we focus on this second possible source of heritability. Consider a hypothetical allele that increases the fitness-sensitivity of an SSFI: it increases the correlation between general fitness (Fig. 1a) and the quality of the SSFI, such that low-fitness individuals grow much worse-than-average fitness indicators, but high-fitness individuals grow much better-than-average fitness indicators (Fig. 1b). For example, such an allele might dramatically increase the verbal courtship abilities of high-fitness family members, but might also increase the susceptibility of low-fitness family members to schizophrenia. If the reproductive benefits in high-fitness individuals balance the reproductive costs in low-fitness individuals, this allele for higher fitness-sensitivity will persist in the population (Pomiankowski and Moller, 1995). In families with higher fitness-sensitivity alleles, we would expect to see several unusual features: (1) higher between-individual variance in the SSFI and its neurophysiological basis, (2) higher correlation between fitness and SSFI quality (Fig. 1b), and (3) higher variance in attractiveness and reproductive success (Fig. 1c). Prediction 3 may explain the higher than average reproduction rates sometimes observed in unaffected relatives of schizophrenics (Avila et al., 2001).

Higher fitness-sensitivity in SSFIs would be favored under conditions of more intense sexual com-

petition, especially in societies with high rates of polygyny and/or extra-pair copulations (“infidelity”). The degree of polygyny and infidelity has probably varied geographically and temporally across human evolution, so different modern human populations may include different proportions of higher fitness-sensitivity alleles that were favored under intense sexual competition, and lower fitness-sensitivity alleles that were favored under monogamy. Schizophrenia rates should be highest among populations in which sexual competition has historically been most intense, and in which the SSFI associated with schizophrenia (e.g., verbal courtship) has been most valued in mate choice.

3.7. Mate preferences for the SSFI co-evolve with the SSFI (Andersson, 1994; Kokko et al., 2003)

As a trait evolves greater fitness-sensitivity, it becomes a more informative fitness indicator, and mate preferences should evolve to pay more attention to it, so high-quality versions of the SSFI are perceived as highly sexually attractive, but low-quality versions of the SSFI are perceived as sexually repulsive. The unattractiveness of psychosis is both in the mate-choice adaptations of the beholder, and in the objectively poor quality of the SSFI. If schizophrenia is the low-fitness extreme of an SSFI, this may explain why people with schizophrenia suffer so much stigmatization across cultures (Dickerson et al., 2002). This view also predicts that anti-schizophrenia bias should increase after puberty (when mate choice systems mature), and should be more severe in females (who are typically choosier about their sexual partners), especially when females are ovulating (when it is most important to focus on good-genes indicators) (Gangestad et al., 2002; Penton-Vaok et al., 1999).

4. Conclusions

In summary, our hypothesis explains many key features of schizophrenia, including onset in adolescence and early adulthood (Hafner et al., 1993), greater severity and earlier age at onset in males (Jablensky, 2000), reduced reproductive rate (Nanko and Moridaira, 1993), substantial heritability (Tsuang et al., 2001), polygenic and multi-factorial basis (Jablensky, 2000; Tsuang et al., 2001), frequent developmental abnormalities (Woods, 1998), increased reproductive success of unaffected relatives (Avila et al., 2001), and the treatment efficacy of dopamine antagonists (Kahn, 1995). Finally, our hypothesis resolves the evolutionary paradox that has baffled schizophrenia researchers for decades: its persistence across generations and cultures despite impairing both survival (Brown et al., 2000) and reproduction (Nanko and Moridaira, 1993), and despite its substantial heritability (Tsuang et al., 2001) (which should have allowed selection to eliminate it) (Huxley et al., 1964). The attractive extreme of any SSFI is attractive precisely because its development is so easily disrupted by fitness-reducing mutations and environmental hazards; therefore, every SSFI must also include a low-fitness, unattractive extreme. If, as we propose, schizophrenia is the unattractive extreme of an SSFI, then schizophrenia persists as an inevitable and distinctively human side effect of sexual selection for some distinctively human mode of courtship, perhaps involving language and social cognition.

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