Molecular Psychiatry (2009) 14, 1072–1082

www.nature.com/mp

FEATURE REVIEW

The role of genetic variation in the causation of mental illness: an evolution-informed framework

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The apparently large genetic contribution to the aetiology of mental illness presents a formidable puzzle. Unlike common physical disorders, mental illness usually has an onset early in the reproductive age and is associated with substantial reproductive disadvantage. Therefore, genetic variants associated with vulnerability to mental illness should be under strong negative selection pressure and be eliminated from the genetic pool through natural selection. Still, mental disorders are common and twin studies indicate a strong genetic contribution to their aetiology. Several theories have been advanced to explain the paradox of high heritability and reproductive disadvantage associated with the same common phenotype, but none provides a satisfactory explanation for all types of mental illness. At the same time, identification of the molecular substrate underlying the large genetic contribution to the aetiology of mental illness is proving more difficult than expected. The quest for genetic variants associated with vulnerability to mental illness is predicated upon the common disease/common variant (CDCV) hypothesis. On the basis of a summary of evidence, it is concluded that the CDCV hypothesis is untenable for most types of mental illness. An alternative evolution-informed framework is proposed, which suggests that gene–environment interactions and rare genetic variants constitute most of the genetic contribution to mental illness. Common mental illness with mild reproductive disadvantage is likely to have a large contribution from interactions between common genetic variants and environmental exposures. Severe mental illness that confers strong reproductive disadvantage is likely to have a large and pleiotropic contribution from rare variants of recent origin. This framework points to a need for a paradigm change in genetic research to enable major progress in elucidating the aetiology of mental illness.
Molecular Psychiatry (2009) **14,** 1072–1082; doi:10.1038/mp.2009.85; published online 25 August 2009

Keywords: evolution theory; genome-wide association studies; gene-environment interaction; rare variants

Introduction

The search for the genetic causes of mental illness has been following the direction taken by medical research. Clustering of illness in families, higher concordance rates between monozygotic than dizygotic twins and similarity of adoptee to their biological rather than adoptive relatives have been used to estimate the heritability of mental illness. High heritability estimates point to the importance of genetic substrate passed from generation to generation, but twin and adoption studies have been relatively uninformative as to how many genetic loci constitute such substrate and what is the strength of each locus. Pedigree-based linkage studies have been conducted to search for genetic variants with strong effects, but did not identify genomic regions that would be consistently linked to mental illness across populations.[1] A hypothesis has been formulated that common genetic variants of small to moderate effect underlie the susceptibility to common disorders: the common disease/common variant (CDCV) hypothesis.[2,3] The success of the current wave of genome-wide association studies (GWASs) crucially depends on the CDCV hypothesis, as even very large samples would not provide the power to detect individual rare variants of small effects.[3,4] The GWASs have brought some success, mainly in medical disorders, but the progress in identifying genetic variants associated with mental illness has been slower. For example, the Wellcome Trust Case–Control Consortium GWAS investigated equal numbers of cases of seven common diseases and found strong replicable associations for five of them, but not for bipolar affective disorder, the one mental illness included.[5] Two large GWASs of unipolar depression have also not identified any genetic polymorphism as associated with depression beyond reasonable doubt.[6,7] Although

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Received 16 February 2009; revised 28 May 2009; accepted 27 July 2009; published online 25 August 2009

some associations have been found,[8,9] they have a very small effect size and explain a small proportion of the presumed genetic contribution to mental disease. The difficulty in finding a molecular substrate for the presumably large genetic contribution to mental illness is one of the major questions facing psychiatric genetics.

At the same time, high heritability of mental illness is puzzling as it appears to defy natural selection. Mental illness usually has an onset early in the reproductive age and is associated with substantial reproductive disadvantage. Therefore, genetic variants associated with vulnerability to mental illness should be under strong negative selection pressure and be eliminated from the genetic pool through natural selection.[10] Still, mental disorders remain common. The question of how heritable yet harmful mental illness survived the fitness-maximizing process of evolution by natural selection is a second major puzzle that psychiatric genetic is faced with.

This review explores the possibility that the two major questions facing psychiatric genetics have a common answer: that the difficulty in finding replicable genetic associations is due to a distinct genetic architecture that is an inevitable evolutionary consequence of fundamental features of mental illness. Several streams of evidence are reviewed for this purpose. First, several aspects of various types of mental illness relevant to the origins of genetic variation are critically reviewed, including prevalence, age of onset, reproductive disadvantage, heritability and parental age effects, as building blocks of evidence to anchor theoretical considerations. Second, evolutionary mechanisms are reviewed that could have led to the persistence of harmful yet highly heritable traits. Third, the CDCV hypothesis is evaluated in light of the evolution theory and epidemiological evidence. Finally, a framework is proposed, based on evolution theory, to guide genetic research on psychiatric disorders and practical aspects of the application of this framework are considered.

Scope of this review

Previous attempts to address the question of common heritable mental disorders from an evolutionary viewpoint either have been limited to a single disorder[11] or have searched for an explanation that would be common to all types of mental illness.[10] As there is substantial evidence for both overlaps and differences between various psychiatric diagnoses, this review explores mental disorders on a spectrum, recognizing similarities and differences between them. Six representative types of mental illness covering the spectrum of severity and reproductive disadvantage are considered in detail: schizophrenia, bipolar affective disorder, unipolar depression, anxiety disorders, anorexia nervosa and autism. Addictions are excluded as the availability of highly concentrated addictive substances may be a recent phenomenon in evolutional terms.[12] Dementias are not considered as they strike well after the reproductive age and the vast majority of our ancestors did not have the luxury to reach old age. Psychopathy and antisocial behaviour are excluded as these may not be associated with reproductive disadvantage.[13] Other disorders could be largely included within the same framework as the six prototypes, but have less evidence to be considered individually.

The building blocks

Age of onset and prevalence of mental illness

The combination of high prevalence and early age of onset distinguishes mental illness from most medical conditions. As life expectancy and average age of reproduction have dramatically increased over the last several hundred years, modern humans may be burdened by a number of diseases with relatively late age of onset, such as cardiovascular illness and type II diabetes, because these did not have major impact on reproductive fitness during most of human evolution. However, the overview of prevalence and age of onset clearly shows that this is not a plausible explanation for most types of mental illness (Table 1). Nearly 50% of humans develop at least one mental illness during

Table 1 Genetic epidemiology of selected types of mental illness

	Prevalence (%)	*Age onset*	*Mortality*	*Fertility*	*Heritability*	*Paternal age effect*
Autism	0.30	1	2.0	0.05	0.90	1.4
Anorexia nervosa	0.60	15	6.2	0.33	0.56	—
Schizophrenia	0.70	22	2.6	0.40	0.81	1.4
Bipolar affective disorder	1.25	25	2.0	0.65	0.85	1.2
Unipolar depression	10.22	32	1.8	0.90	0.37	1
Anxiety disorders	28.80	11	1.2	0.90	0.32	—

Lifetime prevalence (percentage), median age of onset (years), mortality ratios (values of more than one indicate increased mortality compared with the general population), fertility ratios (values less than one indicate decreased fertility compared with the general population), heritability (estimated contribution of additive genetic effects from twin studies) and an index of paternal age effect (risk ratio for 10-year increase in fathers age above 30 years; no data are available for anorexia nervosa and anxiety disorders). All data are based on published reports referenced in the 'Building blocks' section.

their lifetime and half of them experience an onset of mental illness before age 14.[14]

There are important differences in prevalence and age of onset of various types of mental illness. Autism[15] is relatively rare and is a life-long affliction. Anorexia nervosa[16] is relatively uncommon and has an early age of onset. Schizophrenia[17] and bipolar disorder[18] have medium levels of prevalence, affecting approximately 1 in 100 humans each, and most often strike in young adulthood, during the typical reproductive period. Unipolar major depression[19] is common, affecting at least 1 out of 10 humans at some time in their life and has a more varied age of onset. Anxiety disorders[14] are widespread, with close to one-third of individuals suffering from at least one anxiety disorder at some point in their life and a median age at onset of the first anxiety disorder before puberty.

Finally, it is worthwhile to consider to what extent the prevalence of mental illness varies across times and places. Although important geographical differences in prevalence have been identified for most types of mental illness, the extent of these differences varies with the type of mental disorder. For example, it has been noted that the prevalence of bipolar affective disorder is relatively consistent across countries but the prevalence of unipolar depression varies substantially.[20] Indeed, more than 10-fold differences in the prevalence of depression have been reported between countries and cultures, even when identical ascertainment procedures were followed.[19,21,22] Schizophrenia shows important but less-pronounced variations in prevalence and incidence between locations.[17] Urban environment and ethnic minority status are associated with increased risk of schizophrenia and bipolar affective disorder.[23] For autism, increasing time trends have been reported, but may be largely because of changes in diagnostic concept and ascertainment rather than a true increase in incidence.[15] Perhaps the most striking geographical and cultural differences that cannot be explained as methodological artefacts have been found in the incidence of eating disorders, including anorexia nervosa, which is strongly related to female gender, white ethnicity and exposure to western culture.[24,25]

In summary, mental disorders are common and strike early, affecting individuals in their reproductive age. The incidence of many mental disorders varies importantly with time and place.

The reproductive disadvantage associated with mental illness

According to the evolution theory, the persistence of any genetic trait in the population depends on its potential to increase fitness for individual survival and reproduction. Therefore, the fitness of individuals with mental illness is reviewed as the second building block for evolutionary consideration. Two aspects of fitness are considered: survival and fertility.

Regarding survival fitness, the evidence is overwhelming. All types of mental illness are associated with increased mortality from both natural and unnatural causes.[26–28] There are substantial differences in excess mortality between types of mental illness: it is highest for anorexia nervosa,[29] very high for schizophrenia,[17,30] autism,[31,32] bipolar disorder[33] and unipolar depression,[34,35] and moderate for anxiety disorders[26,36,37] (Table 1). A large proportion of the excess mortality, especially suicides, occurs at young age and thus shortens the reproductive period.[26] Importantly, increased mortality risk is not specific to severe disorders and extends to subclinical levels of psychopathology.[34,36]

Regarding reproductive fitness, reduced fertility is associated with most types of mental illness (Table 1). Most individuals with autism never marry and do not have children.[38] Women who survive anorexia nervosa have been found to have three-fold reduction in the rate of motherhood and poor pregnancy outcomes.[39] Marked reduction in fertility has also been found in men and women with schizophrenia[40] and bipolar affective disorder.[41] The effects of unipolar depression and anxiety on fertility are more subtle, with most studies suggesting a small reduction in reproductive fitness.[42,43] Importantly, reduced fertility associated with mental illness is not balanced by increased fertility in unaffected relatives.[40,44] In addition to the reduced fertility, the offspring of parents with mental illness have reduced chances of living till adulthood,[45] higher risk of disability, mental and physical health problems[46] and have decreased fertility themselves.[40]

In summary, mental illness is associated with reduced fitness for survival and reproduction, which extends to the next generation and is not balanced by an advantage in relatives who may be carrying disease-associated genetic variants without being affected themselves. There is a steep gradient of reproductive disadvantage across types of mental illness that is inversely proportional to their prevalence.

Heritability of mental illness

The strength of the genetic contribution to the aetiology of mental illness can be estimated from the incrementally higher concordance in mental illness between relatives who share larger proportions of their genomes. Twin and adoption studies allow disentangling the effects of genes from familial similarities in environment and partitioning of variance in the liability to mental illness into genetic (heritability) and environmental (shared and non-shared environment) components. As collection of large samples of adoptees is difficult, heritability estimates for most psychiatric disorders rely on the twin design. Twin studies suggest that most of the liability to autism,[47,48] bipolar disorder[49,50] and schizophrenia[51] is owing to genetic factors (Table 1). Heritability estimates are also relatively high for anorexia nervosa.[52] The heritability of depression is

moderate in population-based samples[53] but much larger in clinically ascertained samples with more reliable assessment.[54] For anxiety disorders, twin studies indicate a relatively lower but still substantial genetic contribution representing at least one-third of the variation in liability.[55]

Substantial twin-based heritability estimates are commonly used as a rationale for molecular genetic studies. However, several aspects of twin methodology make such an extrapolation problematic.[56,57] First, twin studies assume that all genetic effects are additive and there is no interaction between genetic loci (epistasis) or between genes and environmental factors. Several lines of evidence indicate that this assumption is not tenable. First, combination of twin, adoption and family data sets reveals significant non-additive genetic influences on human behaviour.[58,59] Second, animal experiments reveal ubiquitous epistatic effects in determining heritable traits.[60,61] Third, the discrepancy between little or no effect allocated to shared environment by twin studies and epidemiological studies showing strong effects of family-wide social characteristics on mental illness points to the existence of extensive interactions between genotype and the aspects of environment that are typically shared within a family, such as social class and poverty.[21,56,62] In twin studies, gene–environment interactions involving aspects of environment shared within the family will be allocated to the additive genetic component and interactions involving environmental exposures not shared within the twins are allocated to non-shared environment.[56,63] As many known environmental risk factors, for example, poverty, parenting and migration, are shared within families, it is likely that twin studies estimates of additive genetic variance contain a significant contribution from gene–environment interactions. Another assumption of twin studies is that identical and fraternal twins share their environment to the same extent. This assumption has also been challenged as identical twins are more likely to be treated alike by others and fraternal twins are subject to contrast effects caused by comparison with their co-twin.[64] These points indicate that estimates of 'heritability' are likely to be inflated by epistasis, gene–environment interactions and differential sharing of environment.

A large combined extended family and adoption study has estimated the heritability of schizophrenia and bipolar disorder to be 0.64 and 0.59, respectively.[65] These estimates are significantly lower than those derived from twin studies, but still are substantial. Although the heritability estimates of twin studies are likely to be inflated, the family study estimates may be diminished owing to uncertain fatherhood and thus the twin and family estimates can perhaps be considered as the upper and lower bounds of the contribution of genetic variation to the liability to mental illness. It should therefore be concluded that mental illness is heritable and the persistence in the human population of susceptibility variants responsible for the vulnerability to harmful mental illness requires explanation, especially as the most deadly diseases associated with very strong reproductive disadvantage appear to be most heritable (Table 1). However, neither twin nor family designs can answer the question of whether the same or different genetic variants are responsible for the variation in liability to mental illness in different families.

Paternal age effects

One important question relevant to the evolutionary conceptualization is whether the genetic variants responsible for liability to mental illness are old or are of recent origin. Without knowledge of the exact molecular variants, the contribution of recent mutations can be inferred from an easily obtainable variable: the age of male ancestors at conception of offspring. As a stochastic event, new mutations arise at a roughly constant rate during each meiotic division. Although female germ cells only undergo 24 divisions and do not divide post-pubertally, male germ cells continue to divide and undergo $\sim$23 divisions every year and each division increases the cumulative risk of new mutations.[66] It has been shown that the majority of new mutations occur during divisions of male germ cells and the risk of new mutations increases with post-pubertal age of the father.[67] Therefore, the age of father is an indicator of the burden of newly arising mutations.[67] Accordingly, age of father is associated with many known genetic disorders that are associated with various newly arising mutations, including the Apert syndrome and achondroplasia.[66,67]

Association with advancing paternal age has been found for various forms of mental illness.[68–70] Strong effects of paternal age have been reported for autism,[71,72] and schizophrenia.[69,73] The risk of bipolar affective disorder is moderately associated with increasing paternal age.[74,69] On the other hand, the risk for unipolar depression shows only a weak and nonsignificant association with age of the father[69] and there are insufficient data for other types of mental illness (Table 1). The associations with increasing paternal age hold after controlling for socio-economic status and for maternal age.[71,73] Thus, the available data support the contribution of newly arising mutations to the risk of autism and psychotic illness. There is a lack of data on the effect of the grandparents' age, which could provide information on the contribution of recently arisen but inherited mutations to the risk of mental illness.

Evolutionary psychiatry perspectives

The evolution theory posits that genetic variants associated with fitness and reproductive advantage are propagated and genetic variants associated with loss of fitness and reproductive disadvantage are pruned out of the genetic pool through the process of natural selection. As a result, most mutations that are

associated with loss of fitness and the phenotypes related to such mutations are rare. In this context, the presence of common, highly heritable mental disorders that are associated with disability, mortality and reproductive disadvantage is puzzling. It is even more puzzling that the most deadly types of mental illness appear to be the most heritable ones. How is it possible that genetic variants associated with such a heavy disadvantage have not become extinct or exceedingly rare? Several theories have been proposed to explain this apparent paradox: balancing selection, mismatch between ancestral and modern environment (ancestral neutrality) and polygenic mutation-selection balance.[10] The evaluation of these three alternative hypotheses is important, as they make different predictions about the frequency of genetic variants associated with disease susceptibility.[10]

Under the *balancing selection* hypothesis, a genetic variant associated with susceptibility to a fitness-reducing trait (for example, mental illness) is maintained in a population because it is also associated with a trait that confers reproductive advantage (for example, creativity). The advantageous trait may be expressed in a large number of carriers of the susceptibility allele who are not affected by the illness and is propagated by these individuals, who benefit from the fitness-increasing trait. A classical example is sickle-cell disease, where a variant of the haemoglobin gene confers an advantage for surviving malaria but a homozygous status for the same variant leads to the deadly sickle cell anaemia. In regions where malaria is endemic, these advantageous and disadvantageous effects balance each other, so that the genetic variant is maintained in the population at a high frequency. Variants of this hypothesis have been proposed for most types of mental illness: susceptibility to schizophrenia has been proposed to be balanced by fitness-increasing traits enabling language,[11] depression by the ability to withdraw efforts in the face of failure or elicit care and sympathy,[75] bipolar affective disorder by the ability to survive long winters[76] and anorexia nervosa by the capacity to flee famine.[77] The balancing selection hypothesis would be the most convenient scenario for genetic association studies, as it is consistent with the presence of common and evolutionary ancient disease-related genetic variants distributed across the entire human population.[10] However, the balancing selection hypothesis fails on both conceptual and empirical grounds.[10] Conceptually, it has been noted that multiple cases of balancing selection would have been disadvantageous for a species and therefore alternative adaptive traits would be favoured.[10] It also fails to explain why mental disorders are maladaptive and persistent: depression persists even if environmental contingencies favour active motivated behaviour, bipolar depression is not limited to winter months and anorexia nervosa occurs in the midst of food abundance. Empirically, it has been shown that the decreased fecundity of subjects with schizophrenia is not balanced by increased reproductive fitness of their relatives.[40,44] Furthermore, not many examples of balancing selection have been found other than sickle-cell disease.[10] Therefore, balancing selection has been rejected as a relatively implausible explanation for most types of mental illness.[10,78]

The alternative *mismatch hypothesis* posits that genetic variants that have been adaptive (ancestral adaptation) or fitness-neutral (ancestral neutrality) throughout most of the human evolution have relatively recently become associated with mental illness and other chronic disorders owing to a change in environment.[10,79,80] This hypothesis predicts that older ancestral alleles rather than newly derived variants would be associated with illness. Ancestral adaptation has got some support for disorders associated with older age of onset and/or modern lifestyle. For example, the ancestral APOE*4 allele may have been associated with a 'thrifty phenotype' that was adaptive in pre-agricultural societies but is associated with Alzheimer dementia and cardiovascular disease in modern societies and is therefore being replaced by alternative alleles, which are more adaptive in current environments.[81] As the diseases associated with this allele strike late, their influence on reproduction is limited and the natural selection removes these alleles at a slow pace. This scenario is however not applicable to most types of mental illness, which strike early in the reproductive age. Although it is not possible to ascertain the level of reproductive disadvantage associated with mental illness in prehistoric societies, the low status and poor marriage prospects of individuals with mental illness in traditional cultures[82,83] suggest that mental illness was at least as maladaptive in pre-modern societies. The ancestral neutrality version of the mismatch hypothesis assumes that alleles associated with equal fitness throughout most of the human evolution may have been maintained at relatively stable proportions in the absence of any selection pressure. Keller and Miller point out that reduction in reproductive fitness by as little as 0.003% would suffice for natural selection to efficiently remove an allele from population and exact neutrality is unlikely for variants associated with phenotypic effects.[10] In addition, even functionally neutral alleles that have no effect whatsoever on fitness are predicted to reach fixation at frequencies close to either 1 or 0 over hundreds of generations owing to the process of genetic drift.[10,84] However, a nearly exactly neutral effect averaged across times and places is more likely if there are interactions between the individual genotype and changes in environments.[85] For example, it has been observed that heritable individual differences relevant for reproductive fitness can be preserved if there is repeated fluctuation of environments favouring alternative traits.[86] Therefore, the mismatch hypothesis provides a plausible explanation for the existence of strong gene–environment interactions involving common genetic variants in the causation of mental illness but is unlikely to account

for the persistence of genetic variants directly and consistently associated with susceptibility to mental illness.

A third evolutional mechanism that may explain the persistence of genetic variants associated with reduced fitness in human population is *polygenic mutation-selection balance*.[10,84,87] This is the simplest explanation because it accepts that many genetic variants reduce fitness and are under negative selection pressure. Most new mutations are mildly to moderately harmful and are being pruned out of the human genetic pool at a rate proportional to their harmful effect on reproductive fitness.[88] The rate of *de novo* mutations is low ($\sim 2.5 \times 10^{-8}$ per nucleotide per generation).[89] However, as human mental health depends on the functionality of a very large number of genes and non-coding regulatory regions, the mutational target size is large. It has been estimated that an average human carries 500 mutations that have fitness-reducing effects on brain function, and there is a large individual variability in this mutation load.[10] Under the mutation-selection balance, most mutations associated with mental illness will be individually rare (<1%), evolutionary recent (<100 generations) and their combined burden will be associated with a continuous distribution of susceptibility to mental illness. On the basis of an analysis of the epidemiology of mental illness and reproductive cost, Keller and Miller have concluded that polygenic mutation selection balance is the most plausible evolutionary mechanism consistent with the prevalence rates of harmful mental illness.[10] Indeed, the types of mental illness that are associated with the strongest reproductive disadvantage, such as schizophrenia and autism, also show the hallmarks of the contribution of newly arising mutations including paternal age effects,[71,90] associations with chromosomal anomalies[91,92] and with rare structural genetic variants of recent origin.[93,94] On the other hand, common mental disorders associated with smaller reproductive disadvantage and lying on a continuum with normally distributed traits, such as depression and anxiety, do not appear to be strongly associated with increasing paternal age[69] and important regional and temporal variations in their incidence are not compatible with a stochastic causal mechanism such as newly arising spontaneous mutations.

The evolution-informed framework

There are two evolutionarily plausible mechanisms that could account for the persistence of harmful and heritable mental illness: gene–environment interactions involving aspects of environment that have periodically changed throughout evolution and cumulative effect of multiple pleiotropic variants of recent origin under mutation-selection balance. Although neither of these two mechanisms alone can explain all types of mental illness, the joint consideration of the two enables a construction of a framework that allows a genetic deconstruction of most mental disorders. On the basis of the summary of epidemiologic evidence, it is proposed that different types of mental illness will have varied degrees of contribution to their aetiology from the two mechanisms. The relative importance of each mechanism to the aetiology of a specific mental disorder can be estimated from epidemiological data (Figure 1).

The first mechanism involves interactions between common genetic variants and environmental factors.[80,85,95] This mechanism is consistent with the general properties of complex biological systems,[96,97] and with strong but individually variable effects of environmental factors on the risk of common mental illness.[62,95] It is also in agreement with moderate heritability estimates, because interactions between genetic factors and family-wide environment are included in the estimate of heritability in twin studies.[98] However, as environment sharing between twins is usually incomplete, this mechanism is less consistent with heritability estimates approaching unity. Gene–environment interactions provide a

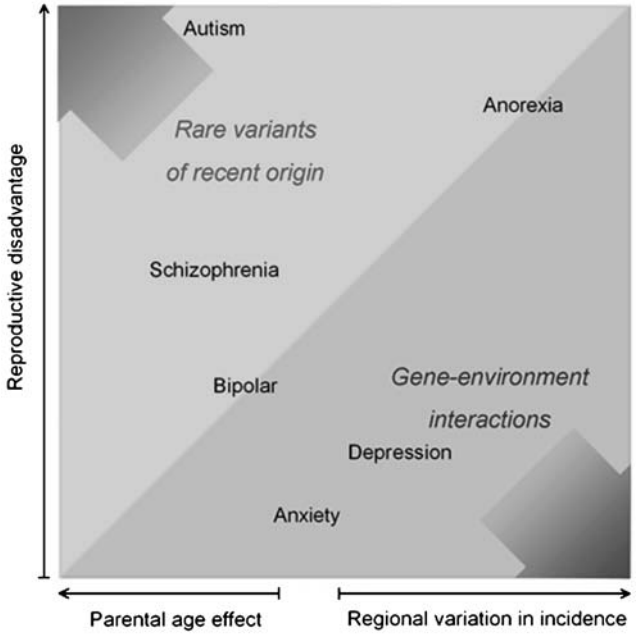

Figure 1 Estimated contributions from rare variants of recent origin and from gene–environment interactions to the aetiology of mental illness alongside a spectrum of reproductive disadvantage. Reproductive disadvantage is calculated as a product of standardized mortality ratio and the reciprocal of fertility ratio, and plotted on a log scale along the *y*-axis. The *x*-axis reflects paternal age effects (to the left) as a hallmark of the rare variants and variation in incidence across populations (to the right) as a marker of gene–environment interactions. The framework is probabilistic: disorders closer to the top-left corner are more likely to have greater contribution from multiple rare variants to the genetic portion of their aetiology. Disorders closer to the bottom-right corner are more likely to have substantial contribution from gene–environment interactions.

plausible explanation especially for common disorders that are associated with moderate reproductive disadvantage, such as unipolar depression and anxiety disorders. A hallmark of disorders with a large aetiological contribution from gene–environment interactions will be marked regional and temporal variation in incidence, such as that detected for unipolar depression[19,20] and eating disorders.[16,25] Quantitative and molecular studies show that gene–environment interactions are likely to have a major contribution in the causation of depression.[99,100]

The second mechanism involves a cumulative effect of multiple mildly deleterious pleiotropic mutations that are under negative selection but are still present in the genetic pool as they are of relatively recent origin.[10,84,87] This mechanism is compatible with the presence of harmful yet heritable mental illness associated with a strong reproductive disadvantage and relatively consistent prevalence across times and places, such as autism, schizophrenia and bipolar affective disorder. It is compatible with very high estimates of heritability, as even *de novo* variants are usually shared by monozygotic twins. The hallmark of a contribution from rare mutations of recent origin is association with increasing paternal age as has been found for autism, schizophrenia and bipolar disorder.[71,73,74] Indeed, associations with multiple rare variants have already been reported for autism and schizophrenia.[93,94] As mutation rate is a stochastic event, multiple rare variants of recent origins as a main causative mechanism are not consistent with major variances in incidence across times and places. Therefore, some contribution from gene–environment interactions is still likely for disorders such as schizophrenia, which show moderate regional variation in incidence and effects of social environment. Rare variants of recent origin probably contribute much less to the aetiology of common mental disorders, such as unipolar depression and anxiety, which show strong regional variations of incidence and do not appear to be related to increased paternal age.

Figure 1 shows the estimated contributions from gene–environment interactions and from rare variants of recent origin to the aetiology of selected types of mental illness. Specific types of mental illness are ordered on a spectrum of reproductive disadvantage, obtained as a product of excess mortality and decreased fertility. This index is strongly negatively related to prevalence and positively related to heritability and to paternal age effects. Outliers from these overall relationships are likely to represent special cases. For example, anorexia nervosa is associated with strong reproductive disadvantage, but high variability in incidence across places, times and cultures in tandem with moderate heritability points to a major contribution of gene-environment interactions. Unfortunately, the paternal age effect has not been investigated in anorexia nervosa or other eating disorders, and thus it is difficult to assess the role of rare variants of recent origin.

Applications of the framework

The evolution theory summarized in the framework has implications for the CDCV hypothesis and by extension to the GWASs. The CDCV hypothesis is commonly attributed to two articles published in 1996.[2,3] Although these two papers concentrate on the practicalities and statistical power of GWASs, they do not analyse the biological plausibility of common variants contributing to common disease. When such analysis was performed, it clearly suggested that direct association of common genetic variants with common harmful conditions is unlikely and that multiple rare variants of moderate effect are a more plausible explanation for the genetic contribution to common diseases.[84,88] Given the early age of onset and large reproductive disadvantage, this conclusion is even more valid for mental illness than for most common physical conditions. Although some positive results of association studies have been interpreted as supporting the CDCV hypothesis,[101] it has been shown that this is likely to be an artefact of statistical power[4] and that there is no clear relationship between the frequency of the associated tagging variant and the frequency of the causal functional variant.[102] It has also been shown that rare variants incompletely tagged by more common genotyped markers are more compatible with the familial risk for common disorders.[102] The current analysis of epidemiological data and evolution theory points in the same direction and suggests that much of the current efforts in psychiatric genetics are being misled by methodological opportunities and convenience. Two alternative approaches are likely to provide more meaningful results: a systematic search for gene–environment interactions and summary investigation of rare variants.

In order to elucidate the aetiology of common mental disorders, such as unipolar depression, it will be important to venture a systematic search for gene–environment interactions. It is important to note that biological gene–environment interaction is not necessarily equivalent to a statistical interaction in a given sample.[103] Depending on the prevalence of an environmental exposure in a specific sample, the same biological causative mechanism may lead to a finding of a statistical interaction, a main effect of gene or no association whatsoever.[104] On the basis of a convenient assumption that gene–environment interactions should be accompanied by main effects of genes, testing gene–environment interactions has been commonly relegated to a planned follow-up to successful GWASs.[105] However, as common genetic variants with phenotypic impact are only retained if their effect on fitness averaged over ancestral environments is very close to 0, crossed interactions with no main effect of genes are much more plausible.[85,97] A main effect of genes may or may not be detected in a case–control association study, depending on sampling from various parts of the distribution of environments.[104] However, as most samples for GWASs are assembled

from multiple varied environments, no overall main effect of genes is the most likely scenario. Most (but not all[106]) gene–environment interactions identified to date are not accompanied by a direct genetic association.[100,107] A probable gene–environment interaction can be inferred from marked heterogeneity of association results across samples. This strategy has been successfully applied in asthma[108] and may well prove successful in psychiatry. However, the most important strategy will be a systematic genome-wide search for gene–environment interactions. Even if narrowed down to relatively common polymorphisms, this will be a daunting task given the difficulties with accurate measurement of environmental exposures[109] and the limited power of statistical tests of interaction.[110,111] However, progress is being made towards making genome-wide search for gene–environment interactions more efficient.[112,113]

A second strategy to elucidating the aetiology of mental illness, especially its more severe types, will consist of a systematic exploration of rare variants of recent origin. The challenges associated with this approach are of a different nature. First, as rare variants are not comprehensively covered in available databases and cannot be reliably imputed from tagging markers, sequencing of a large number of subjects will be required. Second, as each variant will be individually rare in both controls and cases, it cannot be tested as a single predictor in a traditional genetic association paradigm. Solutions for these challenges are starting to emerge. Thus, sequencing may be focused to genomic regions identified in a population-based linkage analysis[1,114] or haplotype tests adapted to rare variants.[115] The finding that most new mutations are mildly deleterious[88,116] provides a rationale for aggregate tests for the total number of non-synonymous variants in a gene or gene set, which makes a powerful association test feasible.[117,118]

The framework indicates that the architecture of genetic aetiology varies across types of mental illness. However, it should be noted that the various types of mental illness lie on a continuum and in individual cases, it is often difficult to establish a specific diagnosis with high certainty, or multiple diagnostic categories have to be used to describe an individual's presentation.[119] Consequently, it is not surprising that major overlaps in genetic susceptibility between diagnoses have been found. Major genetic overlaps have been reported between schizophrenia and bipolar affective disorder,[65,120] bipolar affective disorder and unipolar depression,[50] unipolar depression and generalized anxiety.[121] As these pairs of disorders are neighbours on the spectrum of reproductive disadvantage, the proposed evolutionary framework is consistent with these overlaps.

Caveats

Although the above-proposed framework is compatible with available data, important gaps in evidence have to be acknowledged. First, data on fertility of unaffected relatives are limited to psychosis and no reports have been identified on fertility of unaffected relatives of individuals with non-psychotic disorders. Although the rejection of balancing selection relies on both evidence and conceptual grounds, exploration of fertility in relatives of individuals with depression and anxiety is needed to complement the framework. Second, no data were found on paternal age effects in anxiety or eating disorders. The low contribution of rare variants of recent origins in these disorders is deduced from high comorbidity with depression and large regional variations in incidence. However, a direct exploration of paternal age effects in these disorders is warranted. Third, although heritability estimates from extended family and adoption design are available for schizophrenia and bipolar disorder, the heritability estimates of other types of mental illness are based on twin studies. There is a general asymmetry of evidence with disproportionately more biological research efforts being directed to schizophrenia than other types of mental illness. Hopefully, the present article may help to stimulate research that will fill these important gaps in evidence.

Conclusions

Epidemiological data and evolution theory indicate that mental disorders are likely to be caused by various proportions of gene–environment interactions and multiple rare variants of recent origins. As the CDCV hypothesis is unlikely to hold for most instances of mental illness, a paradigm change is needed to advance psychiatric genetics. An evolution-informed framework is suggested to guide future research into the aetiology of mental illness and initial strategies are indicated that are likely to bring major advances towards the understanding of the causation of mental illness.

Acknowledgments

I thank Michael Rutter, Cathryn M Lewis, Ulrike Schmidt, Peter McGuffin and Iain Campbell for their helpful comments on previous versions of the paper.

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