schizophrenia risk: a) rare and *de novo* mutations, which are overwhelmingly harmful and subject to negative selection; and b) schizotypy-increasing alleles, which should be relatively common and evolve under balancing selection (a regime of alternating positive and negative selection on the same allele)[9]. Common variants that influence IQ may represent a third independent source of risk. The SSM also predicts a unique pattern of genotype-by-genotype interaction – namely, the same deleterious mutations should have a stronger effect on the risk for schizophrenia when they occur on a background of schizotypy-increasing common variants. To my knowledge, this hypothesis has never been tested in genetic research. A recent study found that strong negative selection on rare mutations contributes to maintain variation in other, physically close genes on the same chromosomes[2]. However, the authors did not test whether balancing selection may also contribute to maintain a certain amount of common genetic variation, independent of deleterious mutations.

Mating is only one component of an organism's fitness, and needs to be balanced against other critical tasks. Examples are skills acquisition, feeding, and protection of the offspring. The decisions made in allocating time and energy to these investments determine an individual's life history strategy. Life history strategies have wide-ranging implications for personality, behavior, and physiology. In humans, "fast" strategies are associated with heightened mating effort, precocious sexuality, low investment in stable couple relationships (which are conducive to parenting effort), impulsivity and risk-taking, and broad personality traits such as low agreeableness and conscientiousness. "Slow" strategies are associated with lower mating and higher parenting effort, delayed sexuality, fewer partners, self-control and risk aversion, and high agreeableness and conscientiousness.

Life history concepts can be used to develop a broad-band evolutionary taxonomy of mental disorders[10]. In this framework, schizophrenia spectrum disorders can be classified as fast spectrum conditions, together with borderline personality disorder, antisocial and conduct disorders, and eating disorders marked by behavioral dysregulation. Above and beyond their differences, these disorders share a functional link with fast life history-related traits such as heightened mating effort and impulsivity, and form a comorbidity network with common risk factors and developmental correlates[6,7,10]. They can be contrasted with slow spectrum conditions, such as obsessive-compulsive personality disorder, at least a subtype of autism spectrum disorder (mainly in the high-functioning range), and eating disorders characterized by elevated conscientiousness and self-control.

The taxonomy sketched above is still provisional and open to substantial revisions. Even so, simulations show that the life history model is already capable of reproducing the large-scale empirical structure of mental disorders, including the internalizing-externalizing distinction and the emergence of a general "p factor" of psychopathology[10]. A life history approach recasts the SSM within a broader theoretical framework and integrates its insights with those of other evolutionary models, such as the diametrical model of autism and psychosis advanced by Crespi and Badcock[5]. Together, these developments are starting an exciting new chapter in the evolutionary study of schizophrenia, with novel predictions to test and unexplored implications for epidemiology, prevention, and treatment.

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Validity and utility of the general factor of psychopathology

Psychopathology can be viewed as a variety of symptoms that are organized into first-order dimensions by their correlations. Critically, these first-order dimensions are themselves robustly correlated[1]. These correlations are problematic for categorical taxonomies[2], but provide essential information about the nature of psychopathology[3-5]. Correlations among first-order dimensions vary in magnitude, with stronger correlations among some dimensions yielding second-order factors, particularly internalizing and externalizing factors[6].

These second-order factors do not completely capture the correlations among dimensions of psychopathology, however. Rather, second-order internalizing and externalizing factors are themselves substantially correlated. We provided evidence that the correlations between internalizing and externalizing factors can be explained by a general factor of psychopathology on which every first-order dimension loads[7]. This finding has been replicated many times across the lifespan[4]. Most studies examined only prevalent forms of psychopathology, but several showed that bipolar disorder, schizophrenia and autism are strongly related to the general factor of psychopathology, suggesting that this factor is very general indeed[4].

Before deciding that the general factor of psychopathology is useful, we must know if it is only an artifact of systematic measurement error. The general factor almost certainly partly reflects nuisance correlations due to the same informant reporting on all psychopathology dimensions, but it must also capture something

substantive to have utility. We have addressed this issue rationally[4], but ultimately it reduces to an empirical question of criterion validity. If the general factor is more than a measurement artifact, it will be significantly correlated with variables that are external to its definition but central to its validity. Critically, the general factor is robustly correlated with measures of cognitive ability and the dispositional dimension of negative emotionality. Furthermore, controlling for internalizing and externalizing psychopathology, demographic factors and intelligence, the general factor robustly predicts both concurrent and future adaptive functioning, even when symptoms and functioning are measured by different informants[4].

Can the general factor facilitate studies of the nature of psychopathology and ultimately improve prevention and treatment? We have hypothesized that first-order dimensions of psychopathology are correlated because they have shared causes. Large twin and sibling studies of children, adolescents and adults indicate that the general factor is moderately heritable[8] and that phenotypic correlations among the first-order dimensions are largely attributable to shared genetic influences[9], with less than half of the genetic variance on most first-order dimensions being dimension-specific[5].

These findings support the view that genetic risk factors for psychopathology often function pleiotropically[10], but they suggest a previously unsuspected breadth of pleiotropy, with a significant proportion of genetic factors non-specifically increasing risk for *all* dimensions of psychopathology. This implies that genetic research will be facilitated by letting genetic correlations – rather than ICD and DSM committees – define optimal phenotypes. In concrete terms, if a genetic variant that is robustly related to the general factor were instead tested for association with, say, depression, all cases in which the variant was present but the individual exhibited high levels of any other dimension of psychopathology would erroneously counted as "misses" instead of "hits".

The general factor of psychopathology also implies that first-order dimensions of psychopathology do not each have their own entirely unique pathophysiologies. Dimensions of psychopathology are too highly correlated and there is too much sharing of genetic and environmental influences at the level of higher-order factors not to hypothesize that variations in some neurobiological systems non-specifically underlie multiple dimensions of psychopathology.

We recently proposed a formal causal taxonomy of psychopathology in which the robust correlational structure of first-order dimensions is attributed to a hierarchy of increasingly specific etiologic influences[4]. In this model, some non-specific etiologic factors increase risk for all first-order dimensions of psychopathology to varying degrees through the general factor. Other non-specific etiologic factors increase risk only for all first-order dimensions within the internalizing or the externalizing domains, and each first-order dimension has its own unique causal influences.

This causal taxonomy addresses more than just the sharing of causal influences. It also supports novel hypotheses regarding the equally important heterogeneity of causes and mechanisms underlying each first-order dimension of psychopathology. Each first-order dimension is heterogeneous in its etiologies and mechanisms for the same reasons that different dimensions are correlated. That is, the etiologic influences on each first-order dimension of psychopathology are heterogeneous largely because they arise from (at least) three separate and largely orthogonal sources. Some persons exhibiting high levels of symptoms in any dimension of psychopathology may carry only risk genotypes that pleiotropically increase risk for all dimensions of psychopathology through the general factor. Other persons with the same symptoms may carry only genotypes that increase risk for all externalizing (or all internalizing) dimensions, and others may carry only genotypes that are specific to that dimension of symptoms. Many others will carry varying combinations of genotypes from each of these sources. The result is an intractable degree of heterogeneity in the genetic influences if first-order dimensions are studied individually. It should be far more efficient to identify such diverse etiologic influences and their related mechanisms at their source – by modeling higher-order phenotypes – than by attempting to fractionate each first-order dimension into its diverse etiologies and mechanisms.

This causal taxonomy suggests the need for major changes in how the etiologies and mechanisms of apparently diverse forms of psychopathology are conceptualized and studied. Case-control samples are the current standard for such research. They are optimized for identifying dimension-specific causes, but bias correlations among first-order dimensions of psychopathology, making the modeling of higher-order phenotypes complicated or impossible. In contrast, large representative samples that include sufficient variation in all psychopathology dimensions to model higher-order factors of psychopathology can inform every level of the hierarchy.

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