Schizophrenia: Developmental Variability Interacts with Risk Factors to Cause the Disorder: Nonspecific Variability-Enhancing Factors Combine with Specific Risk Factors to Cause Schizophrenia

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Schizophrenia: developmental variability interacts with risk factors to cause the disorder

Non-specific variability-enhancing factors combine with specific risk factors to cause schizophrenia (subtitle)

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Abstract

We propose a new etiological model for schizophrenia that combines variability-enhancing non-specific factors acting during development with more specific risk factors. This model is better suited than the current etiological models of schizophrenia, based on the risk factors paradigm, for predicting and/or explaining several important findings about schizophrenia: high co-morbidity rates, low specificity of many risk factors and persistence in the population of the associated genetic polymorphisms.
Compared with similar models e.g. de-canalization, common psychopathology factor, sexual-selection or differential sensitivity to the environment, our proposal is more general and integrative.
Recently developed research methods have proven the existence of genetic and environmental factors that enhance developmental variability. Applying such methods to newly collected or already available data will allow for testing the hypotheses upon which our model is built.
If validated, our model may change our understanding of the etiology of schizophrenia, our research models and prevention paradigms.

1. Introduction: the risk-factor etiological model of schizophrenia and its limitations

Schizophrenia is one of the most severe and debilitating psychiatric disorders. The onset is usually in adolescence or young adulthood and evolution is often chronic and/or recurrent. Schizophrenia generates a high level of social and functional impairment, is a source of suffering for patients and their families, and has high societal and financial costs [1].

Symptoms of the disorder, no single one of which is necessary or sufficient for the diagnosis, are generally seen as belonging to one of three categories: positive (e.g., delusional ideas and hallucinations), negative (e.g. poverty of speech, flat affect), and disorganization of speech or behavior (e.g. loose associations, bizarre behavior) (see **Box 1**) [1–3]. These symptoms lead to severe impairments in reality testing, goal-directed activities, and social interactions [4].

Current treatment strategies are not entirely satisfactory: almost one third of patients have a poor clinical response and are considered resistant to treatment [5]. Furthermore, several primary preventive measures have been proposed to date, yet none has shown significant results [6].

Despite the fact that several genetic and environmental factors increasing the risk for the disorder have been identified (see **Box 1**) [7–9], our understanding of the etiology and pathophysiology of schizophrenia is still very incomplete. This incomplete understanding is, at least in part, responsible for the current state of treatment and prevention.

Insert Box 1 here

The risk factor (RF) paradigm is the dominant model for chronic, complex disorders [10], including schizophrenia. According to this model, diseases are caused by multiple interacting factors that might lead to disease by different pathways. Each of these factors increases the risk for the disease but no single RF is sufficient or necessary for the development of the disease.

Based on the RF paradigm and arguments for the developmental origin of schizophrenia [7, 11], the current models of schizophrenia posit that genetic and/or environmental RF impair cerebral development leading to a dysfunctional endpoint that constitutes the basis for the disorder. Some variants of this general model (e.g. the “vulnerability-risk”, “diathesis-stress” or “double/multiple hit” models) introduce a distinction among RF in that some RF precede and lay the groundwork for the action of others. A further refinement of the model includes factors that decrease the risk for the disorder: factors that increase resilience (the opposite of vulnerability [12]) and protective factors (opposite of RF).

Despite being instrumental in identifying several genetic and environmental factors that increase the risk for schizophrenia [13, 14], this model has several important limitations.

First, it does not fully explain some of the most robust facts about schizophrenia: the lack of specificity of risk factors, the extensive co-morbidity, and the persistence of genetic RF for the disorder in the population despite a reduction in fitness.

RF for schizophrenia usually have little specificity and are related not only to other psychiatric disorders but also to many non-psychiatric diseases/conditions. For instance, childhood trauma is associated with schizophrenia [15, 16], but also with mood disorders [17, 18], cardiometabolic disorders, gastrointestinal disorders, chronic pelvic pain, etc. [19, 20]. Urbanicity and migration show similar associations [21–25].

Moreover, there is a large degree of comorbidity between schizophrenia and other psychiatric (e.g. anxiety and affective disorders, addiction) or complex somatic disorders (e.g. diabetes, cardio-vascular diseases) [26–31]. The lack of specificity of RF and comorbidity are not

incompatible with RF models, however, such models fail to predict and explain the existence of these phenomena.
Another shortcoming of models based on the RF paradigm is their inability to explain the so called genetic-evolutionary paradox of schizophrenia i.e. the fact that genetic variants that predispose to schizophrenia persist in the population despite the reduction in fitness in affected individuals [32]. The current understanding of the genetic architecture of schizophrenia is as a combination of rare variants of significant effect and numerous common variants of small effect [8]. Specific mechanisms have been proposed to account for the persistence of rare variants of significant effect (balance between *de novo* mutations and selective pressure [32]) and of common but near-neutral (i.e. only slightly deleterious) alleles (mutation-selection-drift model [33]). However, the presence, at relatively high frequencies of some of the mildly deleterious alleles implies that other specific mechanisms, that offset the selective disadvantage associated with the risk for schizophrenia, are present [32, 33].
From a quite different, heuristic, perspective the RF model also has limitations. First, the model provides no specific avenue for research. Indeed, the classical RF model proposes no specific mechanisms and no differentiation between the various RF. Although such a "black box" model (i.e. a model that is not concerned with an explanation of the association between cause and effect) could help in the early stages of the identification of etiological factors [34], it unnecessarily limits the scope of research when causal complexity, causal interactions, or multiple disorders must be addressed [35].
Furthermore, the RF model makes few explicit predictions and, as such, it is difficult to disprove. Typical studies based on this model, tend, by circular reasoning, to reinforce it. For example, any association between a factor and a disease is interpreted as proof that the factor is a RF for the disease. This reasoning disregards the fact that such studies could not, by design, ascertain that the disorder is the sole (or even the principal) outcome associated with the RF.

In order to resolve these limitations, we propose a new model in which non-specific variability-enhancing factors play an important role, alongside RF, in the etiology of schizophrenia. Although, for simplicity, in this manuscript we call these non-specific, variability-enhancing factors variability factors (VF) this is not meant to imply that they are the only possible factors that might influence phenotypic variability.
In the following sections we will first provide a detailed presentation of our model and a comparison with the RF model as well as other related models. Next, we will analyze evidence in favor of the existence of variability factors (VF) and suggest possible mechanisms for their action. We will then explore research options for testing the model before concluding with remarks on the importance of the model for research, therapeutics and prevention.

2. A new model that adds developmental variability to risk

2.1. A general outline of the model

We hypothesize that schizophrenia (and other similar, complex disorders) is the consequence of the interaction of two types of factors: RF and VF. Given the developmental origins of schizophrenia, the action of etiological factors (which, in our model, we divide into VF and RF) impacts the development of the nervous system.
RF are relatively specific for a disorder or group of related disorders and are the "direct causes" of those disorders [36]. When such specific factors are associated with positive outcomes, instead of deleterious outcomes, we call them "opportunity factors" (OF).

By contrast, VF are non-specific. They increase the capacity (or potential) of the organism to change its phenotype under the influence of risk or opportunity factors. For disorders with a developmental component, such as schizophrenia, this means a change in the developmental trajectory. The most important characteristic of VF is that they are not outcome-biased (as RF are) but rather promote multi-finality [37], and as such, are associated with various, including favorable, outcomes. Such factors will expand the range of possible responses and, finally, the degree of variability in the population hence the name we propose.
There is an obvious similarity between our model and some of the RF models of schizophrenia (e.g. vulnerability-risk, multiple hit models) in that the impact of some factors depends on the presence of others. However, unlike what is suggested by such models, in our model VF are not in themselves deleterious. They have little specificity in their interaction with RF (or OF) and, as a consequence, little specificity in outcome.

2.2. Definition of terms: direct causes, variability potential (VP) and variability factors (VF)

The developmental processes (and their final outcome) are influenced by genetic and environmental factors as well as stochastic (random) events. The impact of these inputs or "direct causes" also depends on the state of the system (i.e. of the organism) [36] as the organism could be more or less sensitive to these inputs due to genetic, environmental, or developmental factors. We call this sensitivity, which is latent and expressed only in the presence of direct causes, variability potential (VP) (see Box 2)

Insert Box 2 here

The VP might be global and therefore characteristic of each individual. Or VP might be specific to each category of direct causes (i.e. environmental, genetic or stochastic) or even very specific VP might exist – related to very specific causes (e.g. VP for a specific environmental factor like temperature) (see **Figure 1**). It is more probable that all three types of VP (i.e. general, by type of cause, by specific cause) co-exist, interact and are effective in the course of individual development (see also Del Giudice [38]).

Insert Figure 1 here

Figure 1. Schematic representation of different hypothetical levels of variability potentials

The most studied level of VP has been the intermediate level (by type of cause: genetic, environmental, or random). In the literature several terms have been used to designate this kind of VP. For those interested, the most frequently used terms and their definitions are provided in **Box 2**.
In our model the direct causes correspond to RF or, for positive outcomes, to OF. VF are the factors that increase the capacity of the organism to respond to the direct causes i.e. the VP. The opposite of VF are robustness/canalization factors, factors that diminish VP (i.e. the sensitivity to the effects of genetic, environmental or stochastic factors) and thus promote the realization of the standard outcome/phenotype.

2.2. The variability and risk model for schizophrenia

The development of the central nervous system (CNS) is robust, which means that normal development is achieved with remarkable consistency despite large variation in

environmental and genetic factors. Accordingly, most, if not all, environmental and genetic factors that increase risk for schizophrenia are highly prevalent in the general population and yet the prevalence of the disorder is relatively low.
The balance between the two opposed processes (robustness and abnormal development) might be altered either by an increase in the VP under the action of genetic or environmental VF, or by an increase in the cumulative effect of genetic or environmental RF.
When the VP is sufficient for (or the robustness capacity is exceeded by) the action of RF, this will lead to the specific pathological phenotype: e.g. schizophrenia.
From the viewpoint of the influence on risk for a specific disorder e.g. schizophrenia, VF and RF are similar. However, it is important to keep in mind their fundamental difference, which can become apparent at the level of the whole individual (comorbidity) and/or of the population (increase in risk for multiple outcomes). Factors that increase VP (i.e. VF) are not outcome specific: they increase the risk for a large number of disorders while also increasing the opportunity for positive outcomes. The nature of the specific outcome(s) that is (are) realized depends on the presence of RF or OF, which are outcome specific. (see **fig. 2**)

Insert Figure 2 here

Figure 2. Diagrams of developmental outcomes

Among factors that have been associated with an increase of risk for schizophrenia, a good candidate for an environmental VF would be early stress/ childhood adversity. In support of this, early stress/adversity has been shown to increase the risk for affective disorders, asthma and other respiratory diseases, diabetes, cardiovascular diseases and cancer [39] and has even been related to positive outcomes [40–42].
Suggesting that early stress/adversity may be a VF is a departure from classical models that consider stress primarily deleterious (e.g. toxic stress [43], allostatic load [44, 45]), but also from more recent models that frame stress responses to early adversity as conditional adaptations [46]. It should be noted however, that the different roles suggested for stress/adversity are not mutually exclusive and a role for early stress as a plasticity modulator (i.e. as a VF) has been hypothesized in recent work on conditional adaptation [47].
By contrast, the RF in our model are factors that have been associated with a restricted range of related disorders and no positive outcomes (e.g. cannabis consumption, influenza infection in utero, etc.).
Thus, according to our model, VF such as early stress/adversity will increase the VP and if other more specific factors are present (e.g. cannabis consumption) this may lead to psychotic symptoms [48]. Without specific RF exceeding the robustness threshold, the outcome would be different: either the standard ("normal") outcome or, if other specific factors are present, a different one (other psychiatric or physical disorders or even favorable outcomes).
To illustrate, early stress might lead to type 2 diabetes if the subject is also exposed to a specific RF such as increased consumption of sugar-sweetened beverages [49], it might lead to asthma in the presence of air pollution [50] and/or to exceptional social achievement if the subject benefits from the positive influence of a family member or role model [40].
It is important to mention that, in our view, most VF for schizophrenia are not new factors that have never been studied. Instead, we think that the specific characteristics of VF have not been recognized and have been mislabeled as RF, as in the example of early stress/adversity discussed above.

Another example might be that of (some of) the genetic common variants of small effect on the risk for schizophrenia. Evidence of their association with several different outcomes is needed to validate this hypothesis. The association of the same variants with positive outcomes will strengthen the case for their status as VF and help explain the "genetic-evolutionary paradox" of schizophrenia: the fact that natural selection has not eliminated the genetic variants that predispose to schizophrenia, despite a reduced capacity to reproduce for those with the disorder (see also the sexual selection model below as a related, alternative, explanation). Finally, a more direct argument would be if the same polymorphisms are shown to increase variability in quantitative traits related (e.g. cognition) or not (e.g. body-mass index) to schizophrenia.

3. Comparison with other models of schizophrenia/ psychopathology

A better understanding of the specific features of our model and of its added value necessitates comparison with other models of schizophrenia and/or of psychopathology. Of special interest are comparisons with the current most accepted model, but also with other models that might share important characteristics.

3.1. Comparison with the risk factors model

The central idea of vulnerability-resilience/risk-protective models is that each factor has a specific, unequivocal effect: it either increases (as in vulnerability, RF) or decreases (as in protective, resilience factors) the risk for the disorder. The original feature of our model, compared to these models, is the notion of VF, factors that although associated with an increase in the odds for a pathological outcome are not intrinsically detrimental.

By adding VF to RF, our model has the potential to resolve some of the limitations of the current, dominant models.

The persistence of genes associated with an increase in the risk for severe pathologies that decrease reproductive fitness (e.g. schizophrenia) might be explained if they are conceptualized as genetic VF. If this were the case, they would be expected to increase not only the risk for pathology but also the chance for favorable outcomes and, as a consequence, increase reproductive fitness thus persisting in the population.

Furthermore, the frequent finding of factors that increase the risk for several psychiatric but also non-psychiatric disorders (e.g. asthma, diabetes, cardiovascular disorders) is to be expected in a model that includes VF. The same applies to the related finding of high co-morbidity between disorders.

Accordingly, the problems and explanations would be similar for the less studied case of opposite outcomes (i.e. favorable/pathological) associated with the same factor [40, 51].

For example, we have shown in prior research that some of the factors that are usually considered RF for schizophrenia (e.g. advanced paternal age, urban birth) are also associated with a contrasted outcome (exceptional achievement) [52]. Such a result might seem counterintuitive under a RF-only model but is to be expected in a variability and risk model.

Furthermore, in contrast with the "black-box" RF model, our model makes some specific predictions that could be tested (see section 5. "Moving forward - testing the model" below).

Finally, our model could be useful for suggesting factors and mechanisms that might explain variability in response to genetic, environmental or stochastic factors.

3.2. Similar models

Given the importance of schizophrenia and, more generally, of complex chronic disorders for public health on the one hand, and the limitations of current explanatory models on the other, several alternative etiological concepts have been proposed. Unsurprisingly, some of them bear important similarities to the model presented here. The main related models as well as their similarities to, and differences from, our model are briefly presented below.

Our model hypothesizes that 1/ some factors (i.e. VF) increase the potential for alternative phenotypes, 2/ these factors are not outcome-specific and thus are associated with multiple different disorders and 3/ the same factors, depending on other associated factors (i.e. OF) might also lead to favorable outcomes.

The first hypothesis is shared with models that assign a central role to de-canalization in the etiology of complex diseases (e.g. diabetes, asthma) [53] and in particular of schizophrenia [54–56]. Canalization refers to the ability of developmental processes to recover from perturbation and attain a defined endpoint, even if by an alternate route [57]. Development, in particular CNS development, is an example of a complex canalized process.
Although there are several differences in the models proposed by these authors, the gist of their hypotheses is that the action of RF for schizophrenia is generally counteracted by canalization but leads to the disorder when de-canalization (i.e. impaired canalization) occurs. De-canalization is seen as a pathological/deleterious process and factors that promote it are seen only as RF. Thus, despite similarities with our model in the mechanism suggested, for all theoretical and practical consequences (research, prevention etc.), these proposals are not different from the multiple hit/ vulnerability-risk models mentioned before.
The existence of factor(s) that are associated with multiple disorders (our second hypothesis) is shared by models based on the hypothesis of a general factor of psychopathology – the “p” factor [58–62].
The “p” factor is a theoretical/ statistical construct that emerged from statistical analyses of the patterns of associations of symptoms that define psychopathology. The existence of a common factor associated with variation in all the domains of psychopathology studied, lead to the hypothesis of the existence of non-specific etiological factors that increase risk for all dimensions of psychopathology [60].
The main difference from our model is that we do not limit our model either to psycho- or to – pathology. On the contrary, we suggest that the same factors (VF) and mechanisms apply to somatic disorders and favorable outcomes depending on the quality of development. The hypothesis of a “p” that influences only psychopathology is, in our opinion, the direct consequence of the a priori limitation of possible outcomes in the original studies.
The sexual selection model (SSM) of schizophrenia [63–65] also posits the existence of factors increasing both positive and negative outcomes (our third hypothesis). This model is based on the concept of a fitness indicator (FI) i.e. a marker of genetic quality (fitness) that is associated with sexual attractiveness and thus influence sexual selection.
The SSM model considers schizophrenia as the “low-fitness unattractive extreme” of a sexually selected fitness indicator [63] This model postulates the existence of two types of genetic variants increasing the risk for schizophrenia: 1. non-specific deleterious variants influencing fitness and 2. genetic variants that act as “amplifiers” i.e. increase the fitness-sensitivity of the FI [65]. Amplifiers, according to this model are associated with schizotypal traits [64, 66]. They increase the occurrence of extreme values of the FI but do not modify the

mean value of the trait (FI). Amplifiers are thus not selected against and will persist in the population despite increasing the occurrence of "extremes" such as schizophrenia [65].
There are obvious similarities between VF and amplifiers as both increase the occurrence of extreme outcomes. In contrast to our model however, the SSM suggest that they are (only) genetic, specific (to a FI) and enhance variability of the FI without (as suggested by our model) changing the variability in fitness. The two models are not mutually exclusive and non-specific VF might very well co-exist and interact with amplifier factors.
The third hypothesis i.e. the existence of factors that increase the potential for alternative outcomes both positive and negative is also at the core of the differential susceptibility to the environment (DSE) theory [67]. According to the DSE theory, some subjects will prove more susceptible to both positive and negative environmental factors: "for better and for worse". The origin of individual differences in susceptibility is considered genetic [68] or set in the early, including prenatal, environment [46, 69–71].
The DSE is the theory that comes closest to our model. In fact, DSE could be viewed as one particular instance of the variability-risk model. Indeed, our model integrates not only sensitivity to the environment as DSE does but also to genetic or stochastic factors. Furthermore, we suggest that in an individual, VP is not a uniform characteristic and that it might be different for different (types of) direct causes.
In summary, based on theoretical assumptions and empirical data, several models similar to the model proposed here have been developed. Compared to these models, we propose a more complete, integrative view on the factors enhancing variability (genetic, environmental): a more complex conceptualization that includes multiple causes (environmental, genetic, stochastic) and multiple, interacting VP. Furthermore, we suggest that the same model applies to outcomes beyond psychiatric disorders i.e. to somatic/physical disorders as well as non-pathological favorable outcomes as long as they have a developmental component.

4. Variability factors : what is the evidence?

The model presented here relies on the assumption of the existence of VF i.e. non-specific, variability-enhancing factors. Below, we summarize studies that empirically substantiate their existence and speculate on putative mechanisms by which they may act.

4.1. A selective review of research data on variability factors

Studies of factors that influence variability have been conducted using different methods, different theoretical concepts and covering different research domains. Given this diversity, any review of findings concerning VF would inevitably be incomplete.
Most of the available data concern genetic VF. Arguments for an influence of genetic factors on VP have come from studies that compare isogenic strains of model organisms. Such studies show that, for different species and for a large range of behaviors (e.g. spontaneous locomotion, startle reflex in Drosophila melanogaster, diurnal rhythms in mice) or morphologic traits (e.g. height in plants, shape and size of wings in D. melanogaster, cranial shape in mice) the degree of variability is influenced by genetic factors [72–77].
These results in turn led to studies designed to identify the polymorphisms that influence the variance of quantitative phenotypic traits (vQTLs). Such studies identified polymorphisms associated with the degree of variability [72, 74, 78], or, more specifically, the degree of variability in response to environmental [77, 79], stochastic [76, 80] or genetic factors [81, 82].
The evidence for the existence of environmental VF is not as compelling. This might be explained by the fact that, unlike genetic polymorphisms, environmental factors are not fixed

(thus they might be absent when the outcome is measured), belong to different domains/categories (e.g. social, psychological, biological etc.) and cannot be automatically and uniformly measured. However, there are studies that suggest that, similar to genetic VF, environmental factors might increase variability in response to other environmental, genetic or stochastic causes. In line with the DSE theory, preliminary data suggest that prenatal stress is associated with markers of increased plasticity of cognitive and/or psychological traits in children [70]. In D. melanogaster changes in temperature modify the degree of variability in the developmental response (wing size and shape) to genetic factors [73]. Other studies suggest that environmental factors like temperature, pollution and urbanicity in animals [83–85] enhance developmental instability i.e. variability in response to stochastic factors. Similar results have been found in studies of human subjects; traumatic experiences in mothers during pregnancy or low socio-economic status during childhood resulted in an increase in developmental instability [86–88].

In summary, studies conducted to date support the existence of genetic, and to a lesser extent environmental factors that influence plasticity, sensitivity of the organism to genetic variation or developmental (in)stability. Such studies provide preliminary empirical arguments for the existence of factors that could modify VP and thus constitute VF.

4.2. Cryptic genetic variation and epigenetics are potential mechanisms for the action of VF

Because development is under strict genetic control, mechanisms that alter genetic function/expression are prime candidates for explaining how VF might enhance the risk for schizophrenia.

Though its role in variability/robustness is still debated, one such potential mechanism involves cryptic genetic variation (CGV) and "capacitor" factors of which the best studied is heat shock protein 90 (HSP90) – see **Box 3**.

Impairment of HSP 90 function during development, by mutations or inhibition, reveals a wide range of genetic, previously cryptic, non-specific abnormalities. Given this experimental evidence, the vast interaction network of HSP 90, and the fact that its function has been shown to be influenced by genetic and environmental factors, HSP90 might be an important hub for the action of VF.

Insert Box 3 here

Epigenetic processes represent another potential mechanism by which VF might modify VP. Epigenetic processes are functionally relevant changes to the genome that are transmissible to daughter cells during cellular replication but do not involve a change in the nucleotide sequence [89].

Several different epigenetic mechanisms have been described including DNA methylation, histone modification, chromatin conformational changes, non-coding RNA interactions etc. [90] The most studied and best understood of these mechanisms is DNA methylation [91].

Methylation (and more generally epigenetic processes) is an essential mechanism for both cell differentiation and development [92]. The methylation pattern is influenced by both genetic and environmental factors. For example, DNA methylation could be modified by a wide range of environmental stimuli such as periconceptional exposure to famine, viruses or parasite infections, hypoxia [93], or childhood maltreatment [94]. Recently, methylation quantitative trait loci (mQTLs) have been identified. mQTLs are genetic variants associated with DNA

methylation at sites that are either close together (cis-acting) or elsewhere in the genome (trans-acting mQTLs) [95].
Individual factors that influence the efficiency of the epigenetic machinery might thus introduce non-specific variability in the response of the developing organism to genetic and/or environmental factors and thus constitute VF.

At this point, the proposed mechanisms are speculative. There are still missing links before any of them could explain how VF act. Furthermore, even if these mechanisms are proven to intervene in the processes of variability, it is possible, and even probable, that other mechanisms also exist.

5. Moving forward - testing the model

Adopting this new model could have important consequences not only for the research, treatment and prevention of schizophrenia, but also for other mental disorders and chronic, complex disorders more generally.
Before our model could be accepted, however, more research is needed to validate putative VF, discover new VF and, finally, to uncover the mechanisms by which they may act.
In the present paper, we have suggested several potential VF for schizophrenia. Validation of their status requires formally testing the properties expected according to our model: association with various outcomes, association with increased variability in quantitative traits and potentiation of the actions of both RF and OF.
This could be achieved by designing new studies, defining and measuring new (especially favorable) outcomes but also by making use of already existing methods and data.
For example, methods of genetic analysis for identifying loci that influence multiple different disorders have already been developed [96, 97] and might be used for identifying potential genetic VF.
Estimating effects on the variance is more difficult than on the mean, requiring greater sample sizes to obtain equivalent precision and the development of adequate methods to handle potential confounding [98]. However, robust statistical methods [98, 99] and large enough samples from studies that have tested the association of environmental and/or genetic factors with changes in the mean phenotype are now available [79].
The use of quantitative phenotypes that have been phenomenologically, etiologically and conceptually associated with schizophrenia (e.g. schizotypal dimensions) has already been advocated as a means to advance our understanding of schizophrenia [100]. Using such phenotypes and methods for identifying vQTL [98, 99] might prove useful for suggesting new VF for schizophrenia. Although initially developed to identify only genetic factors (i.e. vQTL) recently researchers extended the scope of such methods to allow for the identification of non-genetic factors associated with an increase in variability [79, 99].
As mentioned before, case-control studies are, by construction, unable to differentiate between specific and non-specific etiologic factors (i.e. between RF and VF) Thus, in designing new studies, it would be important to change the case-control paradigm and instead use large, representative samples in which a diverse range of outcomes are studied (see also the similar proposal from Lahey et al. [101]).
In order to avoid spurious findings, it is important to recognize that some of the factors that have been associated with schizophrenia are either an intricate association of factors (e.g. cannabis is a mix of more than 400 compounds [102]) or markers of unknown, potentially multiple, factors (e.g. urbanicity). A well-known example is that of tobacco, which has been

associated to both negative (e.g. cancer) and positive (e.g. reduction in Parkinson's disease risk) effects. However, these different outcomes have been linked to different compounds e.g. cancer to nitrosamines [103] and Parkinson's protection to nicotine [104]. In this case, multiple effects due to multiple co-occurring risk and/or opportunity factors might be (erroneously) considered as proof of multi-finality. Thus, multi-finality must not be assumed until multi-causality has not been ruled out.

In humans, formally demonstrating multi-finality associated with the action of a factor might prove difficult especially when studying environmental factors that are difficult to isolate or might exert their action long before the phenotype of interest is apparent (as is the case for schizophrenia). This suggests that animal studies have an important role to play in testing the model. As mentioned above, several studies have demonstrated the existence of VF in model organisms. However, to date, the replication of specific findings is still needed. Furthermore, we are not aware of any study that has specifically explored factors that influence variability of measures that are used to define animal models of schizophrenia (e.g. deficits in social interactions, pre-pulse inhibition, etc. [105])

A further complication is that the same factor might have different roles depending on the time of its action. For example early stress/adversity might act as a VF but in adult life stress/adversity might be a RF.

Finally, once putative VFs are identified and findings replicated, the definite demonstration of their role would rely on uncovering their mechanisms of action. Although we have suggested some mechanisms (CGV, epigenetic modifications) none of them has been convincingly associated with any putative VF to date.

6. Conclusion and prospects

An etiological model for schizophrenia based only on the interaction of RF is not coherent with several of the most replicated research data. A more complex model that includes VFs is better suited to account for the high comorbidity, the low specificity of most causal factors, as well as the persistence of risk enhancing alleles in the population.

VFs are genetic or environmental factors that increase the sensitivity of the developing organism to a variety of influences (genetic, environmental, stochastic), and thus non-specifically promote alternative outcomes/ phenotypes. Depending on their interaction with specific RF or OF, they will lead to different disorders or even favorable outcomes.

Studies have already confirmed the existence of genetic and environmental factors that modify phenotypic variability. Furthermore, methods have been developed and data are available (or could be collected) that might allow researchers to test the pertinence of the model for schizophrenia.

Adopting this model could have important consequences for research: changing paradigms and methods, but also for therapeutics and prevention.

Identification of subjects who are more susceptible to benefit from therapeutic interventions [106] because they have a greater VP, or identification of periods and factors that increase sensitivity to effective causes might be used to enhance the efficacy of therapeutic interventions.

If this model is validated, it could also impact the design of prevention programs. Identification of subjects exposed to VF (genetic or environmental) could be useful for identifying groups in which selective preventive measures aimed at RF would be the most effective. Also, according to our model, separating RF from VF is essential. Only the former would be targeted by preventive measures. Eliminating VF could lead to unexpected and possibly detrimental

consequences by eliminating favorable outcomes and, more generally, variability in the population: variability that might be evolutionary advantageous.

Conflict of Interest

The authors declare no conflict of interest.

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Box 1. Schizophrenia – clinical features and etiology

Schizophrenia is a complex disorder on many levels including clinical presentation and etiology.
Although several characteristic symptoms (see below) are described no single one is sufficient for diagnosis of the disorder and none is present in all cases.
Symptoms are usually grouped in three categories:
- Positive symptoms which are mainly delusions (fixed beliefs that are not amenable to change despite conflicting evidence [107] the most frequent being persecutory) and hallucinations (perception-like experiences in the absence of an external stimulus [107] the most frequent being auditory i.e. "voices")
- Negative signs/ symptoms which are normal characteristics that are diminished or lacking in patients e.g. diminished emotional expression and avolition (decrease in motivated, self-initiated purposeful activities)
- Disorganization of thought/speech (e.g. speech characterized by a succession of unrelated/ unconnected ideas, or shifting abruptly from one subject to another) and behavior (e.g. unpredictable agitation, difficulties in performing goal-directed behaviors).
The diagnosis of schizophrenia supposes the presence of additional severity criteria (number of symptoms, duration and social/ functional impairment) and exclusion of other possible causes (e.g. affective disorders, physiological effects of a substance or another medical condition)

Comorbidity of schizophrenia with other psychiatric (anxiety, affective and substance-related disorders) and non-psychiatric (obesity, diabetes, cardio-vascular, pulmonary disorders) conditions is the rule rather than the exception.

Although the etiology of schizophrenia remains unknown, there is a strong genetic component with a heritability estimated around 80%. The genetic architecture of schizophrenia is thought to involve highly penetrant rare variants and numerous common variants with small individual effect sizes but which are able to explain up to 25% of the genetic variance when added in a polygenic score [8, 108].
Several environmental factors, including season of birth, infections, malnutrition, obstetric and perinatal complications, increased paternal age, urbanicity, migration/ethnic minority, childhood trauma, and cannabis use have also been associated with an increased risk of schizophrenia [109, 110].

Box 2. Key concepts for understanding our model: abbreviations, definitions and similar concepts in the literature

Direct causes = genetic, environmental or stochastic factors that are at the origin of specific changes in the development. Risk and opportunity factors (v. infra) are direct causes. Their impact depends on the characteristics of the developmental system i.e. its sensitivity or variability potential.
Risk factor (RF) = an environmental or genetic factor that increases the risk for a negative outcome (e.g. a specific disorder like schizophrenia). A RF acts in interaction with other RF and none of them is necessary nor sufficient for a disorder to occur.
Opportunity factors (OF) = the equivalent of a RF but for positive outcomes (which increase fitness).
Variability factor (VF) = an environmental or genetic factor that increases the capacity of the organism to change its phenotype under the influence of direct causes (see variability potential below). The most important characteristic of VFs, in our model, is that they are not outcome-biased but are associated with various, including positive, outcomes.
Variability potential (VP) is the capacity of the organism to change its phenotype in response to environmental, genetic or stochastic direct causes. This "sensitivity" is latent, depends on VF and is expressed only in the presence of direct causes.

A variety of terms are used in the literature to designate VP in relation to different categories of direct causes.
For environmental causes the VP (VPE) is usually called developmental plasticity [111] and the opposed characteristic (i.e. insensitivity to variation in the environment) developmental robustness [81].
To our knowledge, no specific term has been used to describe VP in response to genetic variation (VPG). Its opposite, i.e. the capacity of the system to resist genetic variation is known as genetic robustness [81].
Finally, the term developmental stability has been used to designate the capacity of the organism to buffer its development against random noise [80]. Conversely, developmental instability represents the susceptibility of development to the effects of random noise i.e. random VP.

Box 3. HSP 90 and cryptic genetic variation interaction – a potential mechanism for regulating variability/robustness

Heat shock protein 90 (HSP90) was discovered (and named) because of its specific elevated expression during the heat shock response. It is also one of the most abundant proteins in the cytosol in physiological/basal conditions and is highly conserved throughout evolution from bacteria to humans [112].
HSP 90 is a protein chaperone assisting in the structural rearrangement/folding essential for the function of a large number of protein substrates (called HSP 90 clients) [112]. Many of these substrates are key regulators of development [113]. HSP 90 has also been implicated in the stress response and refolding of damaged or abnormal proteins [114].

Cryptic genetic variation (CGV) is genotypic variation that is not expressed as phenotypic variation under normal circumstances. CGV and mechanisms by which it is buffered or released is hypothesized to play an important role in evolution and in the etiology of complex diseases [115]. Factors that contribute to buffering the expression of CGV have been called "capacitors" [116] because they are related to the accumulation of silent genetic variation.

Impairing HSP 90 function by mutations or chemical inactivation reveals a wide range of genetic abnormalities (previously cryptic) in model organisms [116–118]. Because of this, it has been suggested that HSP 90 could have a role in buffering genetic variation in normal conditions [116]. It has been further hypothesized that in natural conditions similar decreases in the buffering capacity of Hsp90 might occur in the case of severe stresses (e.g. heat shock). In this case the increase of HSP90 chaperone activity to assist the recovery of correct folding and function of stress-damaged proteins might entail a diminished availability/activity of HSP 90 for buffering CGV.

However, the importance of HSP 90 as a "genetic capacitor has been questioned on several experimental and theoretical grounds [119]. For example, it has been shown that the same chaperone function of HSP 90 might, in some cases, potentiate the expression of mutations [113, 120]. Furthermore, some theoretical models consider robustness and variability to be properties of complex systems/networks and as such question the potential importance of any individual "capacitor" [120, 121].

a. $Ph \leftarrow (G + E + R)*VP$

b. $Ph \leftarrow G*VPG + E*VPE + R*VPR$

c. $Ph \leftarrow \sum_{i=0}^{n}(G_i * VPG_i) + \sum_{i=0}^{n}(E_i * VPE_i) + \sum_{i=0}^{n}(R_i * VPR_i)$

Ph= Phenotype (might be a disorder e.g. schizophrenia);
* = interaction
E, G, R = effective causes [Environmental, Genetic and respectively Random] i.e. RF or OF
VPE, VPG, VPR = variability potentials [Environmental, Genetic and respectively Random]

Figure 1.

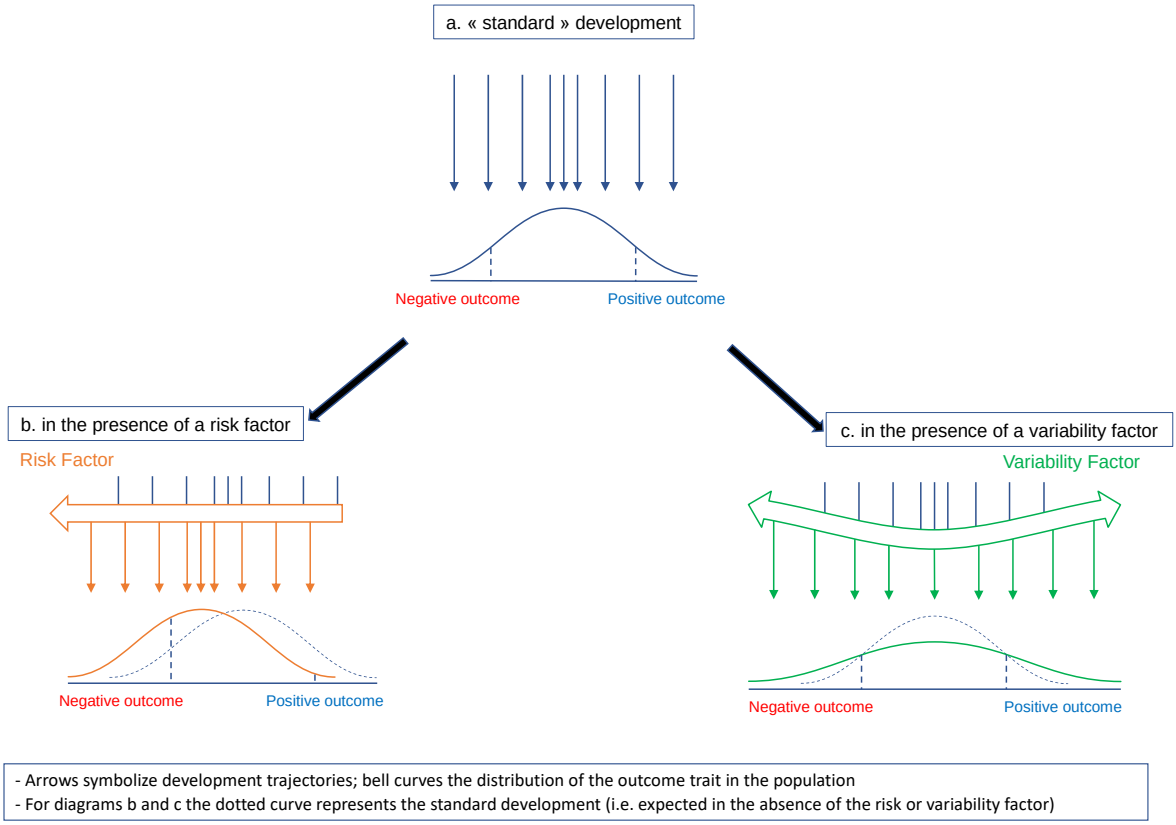
a. « standard » development
Negative outcome
Positive outcome
b. in the presence of a risk factor
Risk Factor
Negative outcome
Positive outcome
c. in the presence of a variability factor
Variability Factor
Negative outcome
Positive outcome
- Arrows symbolize development trajectories; bell curves the distribution of the outcome trait in the population
- For diagrams b and c the dotted curve represents the standard development (i.e. expected in the absence of the risk or variability factor)

Figure 2.