The Role of Schizotypy in the Study of the Etiology of Schizophrenia Spectrum Disorders

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Abstract:

Schizotypy provides a useful construct for understanding the development of schizophrenia spectrum disorders. As research on the epidemiology of psychotic symptoms and clinical risk for psychosis has expanded, conceptual challenges have emerged to comprehend the nature and borders of the space comprised between personality variation and psychosis. Schizotypy is considered in light of these more recent constructs. It is suggested that rather than being superseded by them due to their higher specificity and predictive power for transition to psychosis, schizotypy integrates them as it constitutes a dynamic continuum ranging from personality to psychosis. The advantages of schizotypy for studying schizophrenia etiology are discussed (eg, it facilitates a developmental approach and the identification of causal, resilience, and compensating factors and offers a multidimensional structure that captures etiological heterogeneity). An overview of putative genetic, biological, and psychosocial risk factors is presented, focusing on communalities and differences between schizotypy and schizophrenia spectrum disorders. The found notable overlap supports etiological continuity, and, simultaneously, differential findings appear that are critical to understanding resilience to schizophrenia. For example, discrepant findings in genetic studies might be interpreted as suggestive of sets of independent genetic factors playing a differential role in schizotypy and schizophrenia: some would influence variation specifically on schizotypy dimensions (ie, high vs low schizotypy, thereby increasing proneness to psychosis), some would confer unspecific liability to disease by impacting neural properties and susceptibility to environmental factors (ie, high vs low resilience to disorder) and some might contribute to disease–specific characteristics. Finally, schizotypy's promise for studying gene-environment interactions is considered.

Keywords: psychotic-like experiences | psychosis | psychosis proneness | risk factors | genetics | environment

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Schizotypy provides a useful construct for understanding the development of schizophrenia spectrum disorders. As research on the epidemiology of psychotic symptoms and clinical risk for psychosis has expanded, conceptual challenges have emerged to comprehend the nature and borders of the space comprised between personality variation and psychosis. Schizotypy is considered in light of these more recent constructs. It is suggested that rather than being superseded by them due to their higher specificity and predictive power for transition to psychosis, schizotypy integrates them as it constitutes a dynamic continuum ranging from personality to psychosis. The advantages of schizotypy for studying schizophrenia etiology are discussed (eg, it facilitates a developmental approach and the identification of causal, resilience, and compensating factors and offers a multidimensional structure that captures etiological heterogeneity). An overview of putative genetic, biological, and psychosocial risk factors is presented, focusing on communalities and differences between schizotypy and schizophrenia spectrum disorders. The found notable overlap supports etiological continuity, and, simultaneously, differential findings appear that are critical to understanding resilience to schizophrenia. For example, discrepant findings in genetic studies might be interpreted as suggestive of sets of independent genetic factors playing a differential role in schizotypy and schizophrenia: some would influence variation specifically on schizotypy dimensions (ie, high vs low schizotypy, thereby increasing proneness to psychosis), some would confer unspecific liability to disease by impacting neural properties and susceptibility to environmental factors (ie, high vs low resilience to disorder) and some might contribute to disease–specific characteristics. Finally, schizotypy's promise for studying gene-environment interactions is considered.

Key words: psychotic-like experiences/psychosis/psychosis proneness/risk factors/genetics /environment

Introduction

Schizotypy was introduced to represent the inherited vulnerability to schizophrenia spectrum disorders expressed as a multidimensional personality organization.[1] The interaction of this vulnerability substrate with other genetic and environmental factors shapes the risk of presenting spectrum disorders and yields a wide range of phenotypic variance. Schizotypy is associated with heightened risk for the development of psychotic disorders,[2,3] although most schizotypes are not expected to develop psychosis, and constitutes a useful framework to study etiological factors of schizophrenia spectrum disorders. Assessment of schizotypy provides an entry point for identifying individuals possessing liability to psychosis prior to the appearance of clinical manifestations. This should facilitate the study of developmental pathways to psychosis and the identification of protective factors in individuals not presenting with typical confounding factors associated with schizophrenia spectrum disorders.

The construct of schizotypy was developed both within the individual differences and medical traditions, which has led to differences in its conceptualization.[4] The fully dimensional model of schizotypy, rooted in personality tradition, proposes schizotypy as part of normal personality, being a source of *both* healthy variation and predisposition to psychosis. This model encompasses the more restrictive conceptualization derived from the medical tradition that dimensionality in psychosis exists but is restricted to the severity of presentation (from personality

pathology to the most extreme form of schizophrenia), viewing schizotypy as a *forme fruste* of psychosis (quasi-dimensional model). These models involve different views on the usefulness of schizotypy for studying schizophrenia spectrum disorders. The medical perspective tends to view schizotypy as a risk factor and a link in the chain towards schizophrenia. The reference point is the pathological, and the relevant focus is understanding the transition from subclinical stages to psychosis. From this perspective, studying nonclinical variation is not highly informative,[4] and this has hindered integration of knowledge derived from the individual differences and clinical fields. This has also slowed down the adoption of a developmental psychopathology perspective in the field of psychosis (which recognizes continuity between normal and abnormal and puts the emphasis in the study of interindividual differences and processes contrary to traditional disease models of causation),[5] even if a number of researchers pioneered a developmental conceptualization of schizophrenia in the early 90's.[6,7] In other psychopathology domains, more fruitful research has been conducted to understand connections between personality and psychopathology.[8] This possibly relates to challenges posed by the larger phenotypic discontinuity existing between trait and disorder in the case of psychosis compared with other domains, say trait anxiety and anxiety disorders, the failure of radical "Eysenckian dimensionalism" to recognize that there *is* a transition between healthy schizotypy *personality* and psychotic *illness states* (not meaning that they are unconnected), and that schizotypy presents more challenges than other personality dimensions (eg, definition of the low end of schizotypy).[4]

This article focuses on how schizotypy can be informative for studying schizophrenia spectrum disorders. It first addresses currently unresolved conceptual issues regarding schizotypy and then offers a brief overview on candidate causal factors regarding commonalities and differences between schizotypy and schizophrenia spectrum disorders.

Conceptual Issues

Has the Usefulness of Schizotypy in Etiological Research Been Superseded by New Constructs?

As discussed in a previous article of this Special Issue,[9] there are numerous terms referring to the psychopathological space between psychological health and psychosis. These terms variously refer to individual differences, subclinical manifestations, symptom–like experiences (eg, psychotic–like experiences [PLEs]), and clinical conditions closer to psychosis but vary in terms of severity, frequency, and duration (eg, schizotypal personality disorder [SPD], prodromal or at-risk mental states, and attenuated psychotic symptoms syndrome). These constructs have often been proposed as alternatives to schizotypy, although some have been used interchangeably with schizotypy. PLEs[10,11] are traditionally defined as mild versions of psychotic symptoms, but are also used interchangeably with schizotypy. We suggest that, in most cases, these alternatives are narrower constructions interpretable as manifestations along the schizotypy continuum.

As epidemiological research on PLEs has expanded, there seem to be assumptions that PLEs are superior to schizotypy traits for assessing psychosis liability in nonclinical populations. We suggest, however, that this may reflect a misinterpretation that schizotypy simply taps incipient risk for psychosis. Indeed, PLEs are useful predictors of psychosis development,[12] because ostensibly they are psychotic symptoms, albeit in milder form. Furthermore, we suggest that PLEs, like overt psychotic symptoms, can be thought of as manifestations of positive schizotypy. Simply put, PLEs are useful indicators of schizotypy and predictors of spectrum disorder and psychosis risk in nondisordered schizotypes (although only representing one schizotypy dimension).

PLEs are also suggested to be more advantageous than schizotypy, because they are less unspecific. It should be noted, however, that both schizotypy traits and PLEs are present in samples of mood disorder patients,[13] predict mood disorders with psychotic features[14], and share genetic factors with neuroticism.[15] In fact, this is consistent with the idea of positive schizotypy conveying expression of psychosis in both schizophrenia and mood psychoses. Rather than reflecting a lack of specificity, we believe schizotypy provides a useful mechanism for linking the experience of mood and non-mood psychoses. Furthermore, it highlights the importance of not establishing one-to-one associations between personality dimensions, subclinical states and *specific* disorders, as the early stages of psychopathology are not highly specific and interact dynamically with each other.[16]

An aspect seeming to have created confusion is the dual nature of schizotypy (as any other dimension) having both state and trait manifestations. A useful analogy could be systemic disorders. Cardiovascular functioning, indexed partly by blood pressure, provides an analogy for schizotypy that is continuously distributed in the population. This trait though has a dual nature, as it also shows fluctuations according to a number of exogenous and endogenous factors, thus presenting with properties of a state.[4] Schizotypy tends to be used to refer to the stable personality structure, whereas PLEs are used to describe temporal states that fluctuate according to developmental transient states (eg, neurodevelopmental reorganizations) and are subject to environmental influences. So, on the one hand, we ascribe stability to schizotypy because we conceive of personality as a *fixed* temperamental set of stable propensities, but then it does not seem to be a good model to track the developmental pathways to clinical disorders because it is sensitive to endogenous

and exogenous variation. Most likely the problem is that true *dynamic* and developmental models of personality and psychopathology are not still well established, even if the notion of a sharp distinction between temperament, personality, and psychopathology and the assumption that personality is fixed and lacks a state component have been questioned.[17]

Another issue is whether clinical risk models are superior to schizotypy for studying schizophrenia etiology, given they have better psychosis-specificity and predictive power. As referred to in a previous article in this special issue,[9] the interpretation that schizotypy is a poor model because it has low predictive value derives from a misconception of schizotypy, as it is not expected that many individuals with high schizotypy will develop schizophrenia spectrum disorders. Furthermore, help-seeking individuals meeting clinical risk criteria have more severe psychopathology than those with subclinical symptoms in the community (comorbidity bias), so transition rates to psychosis are naturally higher in the clinically defined population.[16] Interestingly, Salokangas et al[18] found in ultra-high risk individuals that baseline self-reported schizotypy traits, specifically ideas of reference and lack of close interpersonal relationships, were associated with the risk of transition to psychosis. The co-ocurrence of these schizotypy features doubled the risk of transition at 18 months, and this risk remained significant when controlling for a diagnosis of SPD.

So What Is the "Added Value" of Schizotypy for the Study of Schizophrenia Etiology?

Schizotypy offers a number of advantages for conceptualizing the etiology, development, and expression of schizophrenia spectrum psychopathology. Firstly, it integrates a broad range of conditions including schizophrenia and related disorders, spectrum personality disorders, the prodrome and at-risk mental states, subclinical manifestations, and normal individual differences allowing for a dynamic developmental approach. This enables us to study a broad spectrum of variation, not just rare, and extreme manifestations like clinical disorders and the prodrome. This approach is consistent with NIMH Research Domain Criteria, which favor a bottom-up approach (from basic traits to higher order levels) of dimensional phenotypes.[19] Also, this framework allows the identification of factors contributing to movement along the schizotypy continuum at subclinical and clinical levels, taking into consideration that there might be different mechanisms operating within different ranges of severity along the continuum, including those that trigger the onset of clinical disorders. The study of subclinical expression should avoid many of the serious consequences of schizophrenia spectrum disorders that confound etiological research, thereby enhancing the study of psychological variables easily confounded by symptoms, severity, distress, comorbidity, and maladaptive strategies to emerging symptoms. Finally, schizotypy enhances the power of genetic and endophenotype studies that previously omitted subclinical cases or misclassified them as nonaffected.

In addition to integrating subclinical and clinical expressions, schizotypy also offers a multidimensional structure that captures the heterogeneity in the etiology, development, and expression of schizophrenia spectrum psychopathology. This heterogeneity and unique patterns of impairment in patients are not well explained by unitary models of schizotypy and schizophrenia. For example, positive schizotypy is characterized by affective dysregulation and negative schemas whereas negative schizotypy is characterized by diminished positive affect and reward, showing similar social difficulties but driven by differential mechanisms.[20,21] Furthermore, this multidimensional model should enhance understanding of the overlap and differentiation between affective and nonaffective psychosis—specifically, suggesting that both psychoses are high on positive schizotypy, but only nonaffective psychoses involve negative schizotypy.

Studying continuities and discontinuities between schizotypy and schizophrenia spectrum disorders should enhance understanding the heterogenetity in pathways to both clinical and nonclinical outcomes and help identify protective or compensating factors. The inclusion of nondisordered individuals who are putative risk carriers for schizophrenia spectrum disorders should enhance the search for resilience factors (the very concept of resilience relies on identification of individuals with risk factors who remain healthy). For example, it has been suggested that nondisordered schizotypy, SPD, and schizophrenia share left temporal volume reductions, suggesting common genetic vulnerability, whereas striatal and frontal lobe abnormalities are not consistently seen in high schizotypy and SPD, suggesting that they may involve compensatory or protective factors.[22] Schizotypal and schizophrenic individuals may share a common genetic vulnerability that renders the temporal cortex particularly vulnerable to environmental insults. However, genetic or environmental factors that are different from those conferring susceptibility to schizophrenia, such as frontal lobe reserve or general intelligence, may decrease the impact of genetic susceptibility to schizophrenia and allow high schizotypy individuals to be more resistant to downstream effects of temporal dysfunction.[22]

A Brief Overview of Etiological Factors in Light of Continuities and Discontinuities Between Schizotypy and Schizophrenia Spectrum Disorders

In this section, we provide a brief overview of candidate etiological factors for schizotypy and schizophrenia. If schizotypy is the personality matrix that increases the risk of developing schizophrenia spectrum disorders, at least

part of the factors explaining schizotypy variance should also be associated with schizophrenia. Simultaneously, as schizophrenia spectrum disorders are not the necessary outcome of schizotypy (health or nonpsychotic maladaptations can be associated with it), it is expected that there will be factors explaining schizotypy variance but not associated with schizophrenia. The focus of this overview will be to note the overlap and differences between schizotypy and schizophrenia spectrum disorders. Additional articles in this special issue deal with associations of schizotypy with candidate endophenotypes and risk mechanisms.[23,24]

Genetic Factors

The common genetic basis of schizotypy and schizophrenia was believed to be a single dominant risk allele that, in interaction with environmental factors, leads to individual differences in schizotypy.[1,25] Current opinion, however, is that about 8300 independent polymorphisms confer schizophrenia risk.[26] These estimates have considerable implications regarding the taxonicity vs dimensionality debate, since a large number of contributing alleles supports the assumption of a continuous nature of schizotypy[27]—which, as mentioned earlier, does not preclude the existence of a functional discontinuity between high schizotypy and schizophrenia.

As for concordance rates of schizophrenia spectrum diagnoses, values in schizotypy increase with higher genetic similarity to schizophrenics. A review[28] indicated that relatives of patients primarily show elevated social-interpersonal symptoms and small elevations in cognitive perceptual and disorganized schizotypy. The reverse has also been shown,[29–31] with offspring of highly schizotypic parents being at elevated risk for schizophrenia. A large study[32] examining the heritability of schizotypy concluded that on average 50% of schizotypy variance is explained by genetics. Hereof, social anhedonia appears to be most heavily genetically influenced.[28,33,34]

A variety of genes and polymorphisms identified as relevant for schizophrenia have been found to be associated with schizotypy. The most commonly examined single nucleotide polymorphism (SNP) in schizotypy is rs4680[35] (COMT val^{158}met), which influences dopaminergic neurotransmission and has overall been consistently associated with schizotypic traits (overview in[36]). When reviewing dimensions of schizotypy, however, rs4680 appears to be differentially related to them, mainly in dependence of the instrument used. Within the Wisconsin Schizotypy Scales, the val-allele appears more heavily related to increases in negative schizotypy,[37] although others also find it coinciding with higher perceptual aberration.[38] Regarding the Schizotypal Personality Questionnaire (SPQ), the val-allele is associated with higher total scores,[38,39] higher scores in both positive and negative factors[39] or in all 3 facets (ie, positive, negative, and disorganized).[40] A reverse effect was, however, published regarding the disorganized dimension of the SPQ-B[41]. Using the O-LIFE, the val-allele is only associated with positive but not negative or disorganized schizotypy.[36] A number of the cited studies indicate the possibility of molecular heterosis, namely lowest schizotypy scores in heterozygotes compared to *both* homozygous groups. There is indication that rs4680 interacts with other relevant polymorphisms (eg, MAOA-uVNTR)[36] and with age.[42] Thus, rs4680 is indeed relevant for schizotypy, but further research in significantly larger samples is necessary to identify exactly which features are age-specifically related to which allele; this question is currently being examined by us in an international sample comprised of most samples from the aforementioned individual articles.

Additionally, other dopamine-related genes show associations with schizotypy, such as DRD2[43], SLC6A3[36,44], and MAOA.[36] Furthermore, changes in expression patterns of dopamine-relevant genes are often reported in schizophrenia,[45,46] and a recent study shows that expression patterns of a number of these genes in human blood correlate with positive schizotypy.[47]

Other genes implicated in the etiology of schizophrenia have also been found to be associated with schizotypy, including NRG1[48], RGS4[49], PRODH,[50] BDNF[50], and ZNF804A.[51,52] Individual studies suggest both an interaction between individual polymorphisms[36] as well as additive effects.[53] However, many of the aforementioned genes (with the exception of DRD2 and ZNF804A) no longer appear as significant hits in the latest schizophrenia Genome-Wide Association Study (GWAS).[54] This underpins the usefulness of schizotypy as a research framework for schizophrenia: A critical issue of GWAS is the treatment of both cases and controls as homogeneous groups, as nondisordered schizotypes would be in the comparison group despite carrying the presumptive underlying vulnerability for schizophrenia. Additionally, all schizotypic variance within both groups is ignored. Furthermore, it must be considered that "*negative studies should never be weighted as strongly as positive* [ones]"[55] and "*researchers need to look at the cumulative evidence for a gene's involvement, be it genetic or biological*."[55]

Thus, polymorphisms not related to schizophrenia in GWAS, but consistently and plausibly linked to schizotypy, should not be easily dismissed. Grant[56] has suggested that there are at least 2 groups of genetic factors. The first group mainly explains schizotypy variance and increases *proneness* for psychosis. The second group, which marks the *risk* of transition between high but healthy schizotypy and clinical schizophrenia, is probably independent of schizotypy, but conveys unspecific neuronal resilience. Thus, it is extremely likely in case-control designs that SNPs explaining small schizotypic variance (both *between* and *within* groups) are lost due to the potentially far stronger effects of SNPs that explain the transition between healthy high schizotypy and schizophrenia. In other words, effects of SNPs that strongly but unspecifically influence whether a

person will be healthy or sick may overshadow the effects of SNPs that have specific but individually weak effects on schizotypic variance.

Further support for this hypothesis is given by the nature and function of the genes identified by GWAS.[26] There is currently no theoretical basis for many of the identified SNPs, most of them only reach genome-wide significance when samples from bipolar patients are included, most are involved in basal cellular metabolism, and many are well established as risk factors for unrelated somatic conditions. Recently, Ripke et al[54] published new results, identifying 108 schizophrenia-associated loci (83 being new). Thus, further study of these 108 genetic markers is necessary regarding their role in schizotypy and their specificity to the psychosis continuum.

Two studies investigating the relation of a polygenic risk score derived from GWAS[26] indicate *inverse* associations with PLEs[57] and schizotypy (Hatzimanolis et al, in prep; Athens Study of Psychosis Proneness and Incidence of Schizophrenia [ASPIS]) in healthy participants; that is, high polygenic risk was associated with *less* PLEs and lower schizotypy scores. In both studies, single genes did not account for differences in schizotypy or psychotic experiences, but there was a trend for an association of the gene ZNF804A in the direction previously reported for schizophrenia and schizotypy. Considering that the studies only included healthy participants, there might be an involuntary sampling bias in these studies, as those individuals with high polygenic risk scores *and* high schizotypic traits would be more likely to develop spectrum conditions than to be in a healthy sample, whereas those persons with high but healthy schizotypy *should* have a lower polygenic risk score. If one assumes 2 independent factors, namely *schizotypy* and *health/resilience*, then it is plausible to propose that individuals with high schizotypy *and* low resilience would rarely be in the healthy population but, rather, develop schizophrenia. Thus, a polygenic risk score comprised of many genetic variations involved in a number of medical conditions (and therefore unlikely to be specific to schizotypy) *should* actually be inversely related to schizotypy in nonpatients. In sum, this would suggest that the association between genetic risk and schizotypy is not generally inverse compared to schizophrenia, but rather differentially related, depending on the function of individual genes; thus, lack of genetic susceptibility for disease is protective for healthy schizotypes. Vice versa, genetically based low resilience may incur risk for a number of medical conditions, but only coincidentally high genetic schizotypy markers would lead to an incidence of schizophrenia.

Biological Environmental Factors

As mentioned previously, heritability studies estimate that genetic factors explain about 50% of schizotypic variance. The remaining variance is explained by environmental factors that can be roughly divided into psychosocial and (neuro-) biological factors.

Supporting neurodevelopmental models, many biological environmental factors are consistently shown to be involved in schizophrenia development; especially antenatal maternal viral infections, obstetric complications, elevated stress hormones, advanced parental age, and cannabis use.[58,59] Some of these factors have also been investigated regarding schizotypy, most notably in large Finnish studies.[60] A number of pre- and perinatal complications have been associated with schizotypy. A large study[61] found that individuals whose mothers had been exposed to influenza during the H3N2-epidemic in 1969 while in the sixth gestational month presented with higher schizotypy as adults. Additionally, obstetric complications and low birth weight are associated with retrospective childhood schizotypal traits in adult schizophrenia spectrum patients[62] and with schizotypy.[63] Others[60] found effects of lower birth and/or placental weight as well as head circumference, but only in women and limited to positive schizotypy traits. Associations of maternal diabetes and viral infections (especially in the first and second trimester) with PLEs in adults are also reported,[64] but the numbers of affected individuals are minor in comparison to the numbers of individuals with identical complications without PLEs. Finally, examination of other birth-related factors with regard to schizotypy[65] showed no associations, although 60% of individuals within the high-schizotypy group reporting a schizophrenia spectrum diagnosis were born in winter.

Cannabis use has been extensively studied in cross-sectional and longitudinal designs in healthy samples. Overall, findings indicate associations of schizotypy and PLEs with cannabis use[66] and earlier age of initiation of use,[67] although there are also contrary findings.[68,69] The association is found for the positive and disorganized but not for the negative dimension.[70] As for the temporal sequence, some longitudinal and age-stratified studies suggest inverse causality, namely that the development of schizotypy influences the subsequent use of drugs.[66,71,72] Also, studies controlling for effects of childhood schizotypy[73,74] find that the effect of cannabis on PLEs is reduced when childhood schizotypy is included in the model. It should be noted, however, that both studies cannot fully exclude the possibility of early childhood "oddness" playing a role in the onset of cannabis use.

Finally, a number of studies examined links between indicators of early developmental insults and schizotypy. Hereof, neurological soft signs connected with schizophrenia were found mainly to correlate with negative[75,76] but also with positive[75,77] and disorganized schizotypy.[77] Also, dermatoglyphic anomalies have been associated with positive[78] and negative schizotypy[79] as well as SPD.[80] These findings add to the understanding that schizotypy also shares a common nongenetic biological contiuum with schizophrenia.

Psychosocial Factors

Growing research on the effects of psychosocial adversities on the brain is challenging the assumption that endophenotypic anomalies identified in schizotypy and schizophrenia only result from genetic and biological factors. For example, early life stress/maltreatment has been found to produce brain functional and structural alterations,[81] and there is evidence from animal models indicating that certain environmental exposures can cause behavioral and brain phenotypes analogous to those observed in schizophrenia.[82]

A substantial body of work has shown that a range of social and interpersonal environmental factors are associated with schizophrenia and schizotypy, with evidence appearing to be more robust for the positive dimension (reviews in).[11,82–84] Although some findings are conflicting and demonstration of a causal status is challenging,[85] increasing agreement is emerging that psychosocial factors are not mere triggers of a genetic vulnerability but rather coparticipating factors in the psychosis continuum. Specifically, it has been suggested that epigenetic mechanisms might mediate environmental effects on gene function by 'switching' on and off gene transcription throughout development, constituting a mechanism for rapid genome adaptations to the environment.[86]

In terms of macroenvironmental factors, there is strong evidence linking urbanicity during development with increased likelihood of both psychosis and PLEs, with dose-response relationship reported in a number of studies.[87,88] The association of schizophrenia and poverty has been mixed, even if poverty seems more strongly associated with psychosis than with other psychiatric conditions.[89] Furthermore, poverty showed a unique association with SPD dimensional scores in a general population survey examining all Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) personality disorders.[90] An association has also been reported between socioeconomic disadvantage and risk for delusional–like experiences.[91]

Accumulating evidence indicates that minority position has an important role. Migrant status has been associated with increased risk for psychotic disorder as well as with greater prevalence of PLEs.[11,92] The risk for psychotic disorder is increased in both first- and second-generation immigrants, suggesting that the post-migration context, rather than migration itself, may have a more prominent role.[92] For example, the extent to which an individual at risk of experiencing exclusion/discrimination is an exception with regard to the greater social environment has been suggested as a mechanism underpinning the increased rates of psychotic phenomena in ethnic minority individuals.[93] Thus, ethnic minority individuals living in areas with high levels of ethnic density appear to have a protective effect in relation to psychotic disorders and experiences.[94,95]

As for microenvironmental risk factors, a meta-analysis of 20 studies showed that parental communication deviance is associated with heightened risk for psychosis[96] and perceptions of parental behavior, particularly lower perceived care, are also related to psychotic disorders and schizotypy traits.[97] One of the most researched interpersonal factors is childhood adversity, with a recent meta-analysis indicating that trauma increases the risk of psychosis (including both clinical and subclinical expressions) with an odds ratio of 2.78[98]. Childhood abuse, neglect, and bullying have all been linked to schizotypy, with some studies having controlled for relevant potential confounders (eg, family history of psychosis) and using prospective designs (reviews in).[99,100] In general, the evidence suggests that experiences involving an "intention to harm" element appear more strongly related to psychotic symptoms and experiences than adversities of a nonintentional nature, like the death of a close person.[101]

Conclusions

Overall, schizotypy and schizophrenia seem to have a substantial overlap in terms of etiological factors at the genetic, biological, and psychosocial levels, which support the notion of not only phenomenological but also etiological continuity and the claim that schizotypy is a useful framework to investigate both normal individual differences and the etiology of schizophrenia spectrum disorders. Additionally, some differential findings were found, which are as relevant as similarities in order to define a complete account of the schizophrenia spectrum and to identify protective factors. The overview of recent genetic studies supported that there might be sets of independent factors playing a differential role in schizotypy and schizophrenia; some would influence variation specifically on schizotypy dimensions (ie, high vs low schizotypy), some would confer unspecific susceptibility to disease by impacting neural properties and susceptibility to environmental insults (ie, high vs low resilience) and still some might contribute to disease-specific characteristics. In addition, complex patterns of gene-gene, environment-environment, and gene-environment interactions likely contribute to shape differential liability to clinical disorders, as suggested by the fact that the majority of individuals carrying genetic risk or exposed to environmental risk do not exhibit elevated rates of schizotypy or schizophrenia spectrum disorders. The study of differential effects of the same environmental factors in genetically diverse individuals (gene-environment-interaction) is challenging, but has already shown its potential to understand the development of spectrum disorders.[102,103] Schizotypy provides a useful construct for studying gene-environment effects because it broadens the phenotype (and avoids misclassification of nondisordered schizotypes as unaffected), allows for the examination of etiological factors without the confounds of the

consequences of schizophrenia, enhances identification of protective mechanisms by including the nondisordered members of the schizophrenia spectrum phenotype and, thus, promises to increase the power of such studies.

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