Natura Facit Saltus: discontinuities in the latent liability to schizophrenia and their implications for clinical psychiatry

Natura Facit Saltus: discontinuità nella predisposizione latente alla schizofrenia e le loro implicazioni per la psichiatria clinica

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Summary

Objective

To show that the discontinuous (i.e., taxonic) structure of latent liability to schizophrenia represents one of the most consistently replicated findings in literature addressing the latent structure of psychopathology, and to suggest that knowing the natural boundaries and estimated prevalence of latent liability to schizophrenia in the general population may be useful to the clinicians in their daily practice.

Method

Review of the empirical scientific literature.

Results

A schizotypy taxon (i.e., a latent class of subjects which are characterized by a liability to develop schizophrenia) has been found across different samples, cultures, assessment instruments, schizotypy indicators, and statistical procedures (Table I). Interestingly, studies based on non-clinical adult samples usually report a roughly 10% prevalence for the schizotypy taxon, which is approximately ten times higher than the proportion of clinically expressed schizophrenia. This estimate of the base rate for the schizotypy taxon is consistent with the theoretical conjectures of Meehl. Although there are isolated findings that are not consistent with this corpus of empirical research, such results have typically come from studies that suffer from one or another methdodological artifact.

Discussion

The relevance of these findings should be considered in the light of the literature on the associations between cannabis use and psychosis. Cannabis is a psychoactive drug, which contains tetrahydrocannabinol (THC), and is used extensively by many adolescents, young adults, and some older adults around the world. Recent research is suggestive of cannabis having a relatively greater or more potent psychotogenic effect in those individuals predisposed to psychosis, especially schizophrenia, as opposed to those not at risk for psychosis.. Thus, having accurate estimates and indicators of the presence or absence of the schizotypy taxon at the level of the individual may prove useful for accurately targeting intervention programs on cannabis use prevention. The goal of such intervention, of course, would be the reduction of a potential increase of schizophrenia in those at-risk for the illness.

Key words

Schizophrenia • Schizotypy • Taxon • Prepulse inhibition • Liability • Endophenotypes

The discontinuous (i.e., taxonic) structure of latent liability to schizophrenia represents one of the most consistently replicated findings in literature addressing the latent structure of psychopathology. Although there are isolated findings that are not consistent with this corpus of empirical research, such results have typically come from studies that suffer from one or another methodological artifact. A review of the empirical scientific literature shows that a schizotypy taxon (i.e., a latent *class* of

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subjects which are characterized by a liability to develop schizophrenia) has been found across different samples, cultures, assessment instruments, schizotypy indicators, and statistical procedures. Interestingly, studies based on non-clinical adult samples usually report a roughly 10% prevalence for the schizotypy taxon, which is approximately ten times higher than the proportion of clinically expressed schizophrenia. This estimate of the base rate for the schizotypy taxon is consistent with the theoretical conjectures of Meehl [1].

In the present discussion, the relevance of these findings is considered in the light of the literature on the associations between cannabis use and psychosis. Cannabis is a psychoactive drug, which contains tetrahydrocannabinol (THC), and is used extensively by many adolescents, young adults, and some older adults around the world. Recent research is suggestive of cannabis having a relatively greater or more potent psychotogenic effect in those individuals predisposed to psychosis, especially schizophrenia, as opposed to those not at risk for psychosis. Thus, having accurate estimates and indicators of the presence or absence of the schizotypy taxon at the level of the individual may prove useful for accurately targeting intervention programs on cannabis use prevention. The goal of such intervention, of course, would be the reduction of a potential increase of schizophrenia in those at-risk for the illness.

One of the most widely replicated findings in literature addressing the latent structure of psychopathology is evidence for a discrete latent class (i.e., a taxon) of individuals who carry a liability for developing schizophrenia – often referred to as schizotypy [1-3]. For the purposes of this discussion, schizotypy is taken to refer to a type of personality organization that harbors the genetic potential for schizophrenia. Various features – such as schizotypal signs/symptoms as well as certain endophenotypes [4] – are conceived of as schizotypy indicators. Thus, an individual within the so-called schizotypy taxon is an individual who differs qualitatively (by type or kind, not merely by degree; see [1 5 6]) from others by virtue of having the genetic liability for schizophrenia.

Schizotypy – as a latent personality organization – is a latent construct that is not directly observable and is therefore inferred from manifest indicators. Members of the latent schizotypy class are thought to exhibit, in some cases, early manifestations of this liability, including (a) behaviors such as social withdrawal and flat affect [7 8] and (b) unusual sensory experiences such as perceptual aberration, magical ideation, and referential thinking [9 10]. In other instances, a person who is a valid schizotype – one who carries schizotypy – may not present clinical phenomenology suggestive of schizotypic personality or prodromal schizophrenia. In such instances, the underlying schizotypy can be detected with more sensitive measures or laboratory procedures. For example, schizotypes may reveal (a) specific patterns of item responses on objective psychological tests [11-13] or (b) deviance on established endophenotypes [4] for schizophrenia such as compromised neuromotor performance and eye-tracking dysfunction [14-17].

Although there is some degree of phenomenological similarity between schizotypic symptoms and signs and the diagnostic criteria for *DSM-IV* schizotypal personality disorder (SPD), important differences exist between the two concepts. Schizotypy refers to a latent personality organization and is essentially a broader construct linked to a developmental theory; whereas *DSM-IV* SPD is a cluster of observable signs and symptoms that tend to aggregate, and the disorder is described in an atheoretical manner [1 2]. Thus, the two concepts differ in terms of their level of analysis. It is helpful to think of schizotypic psychopathology, such as SPD or paranoid personality disorder, as a manifestation of schizotypy at the observable level [18 19].

The vast majority of the findings supportive of a latent discontinuity underlying observed schizotypy indicators comes from taxometric [20] investigations. Taxometric methods are statistical procedures designed to detect whether the structure underlying continuous observed or manifest indicators is either taxonic (categorical, qualitative) vs. non-taxonic (dimensional, continuous, quantitative). The consistency of the evidence supportive of a latent taxon underlying schizotypy indicators from taxometric investigations is compelling. Although one recent taxometric study [21] could not find evidence of a latent taxon and called into question the evidence that schizotypy is taxonic. These authors, furthermore, suggested that that limitations to the taxometric method are responsible for spurious taxonic results in all previous studies. However, several shortcomings of the of Rawlings et al. study [21] undermine their conclusions and suggest

their criticism of prior taxometric work is largely unteneable. For example, the sampling strategy used by Rawlings et al. [21] was biased and not appropriate for a taxometric study [6 22], besides the epistemological consideration that in soft sciences support for theories is derived from replication across multiple levels of analysis and that single experiments rarely if ever disconfirm theories in psychological science [22-24].

Of greater concern, in conducting their data analysis Rawlings et al. omitted all items on the Combined Schizotypal Traits Questionnaire [25] that were endorsed by fewer than 10% of participants; this procedure likely excluded from the sample those items that were valid indicators of the schizotypy taxon, whose expected base rate in the general population is about 0.10 [22].

The third major shortcoming of Rawling's et al. study [21] came from a naïve use of data simulation to accommodate variable skew, a procedure that was introduced by Ruscio and Ruscio [26] to distinguish between true low base rate taxa and spurious taxa derived from skewed variables. Despite its popularity, this procedure is not without controversy – for example, extensive Monte Carlo simulations indicate that MAXCOV is effective in distinguishing discrete from dimensional latent structure with skew values as high as 2.0 even when the taxon base rate is as low as 0.05 (e.g., [27]) – and may even performed inadequately for low base-rate taxa, with low to moderate nuisance covariance, decreasing indicator validity [28].

On the contrary, if one examines the 16 published articles (see Table I) that tried to address the issue of the latent structure of liability to schizophrenia using latent taxon unfolding techniques (either taxometric analyses or mixture models) on measures of schizotypy or SPD, he/she can easily observe the striking consistency of the results suggesting a taxonic latent structure of schizophrenia liability. Only Rawlings et al. [21] claimed that the taxometric analyses yielded evidence of a dimensional latent structure of schizotypy; inconclusive findings were reported in three selected sub-samples or measures, whereas partial evidence of dimensionality was reported in two studies with respect to selected measures of "positive symptoms" of schizotypy. All other studies supported the taxonic structure of schizotypy.

As it can be observed in Table I, the taxonic structure of latent liability to schizophrenia has been replicated across clinical and non clinical samples, self-report questionnaires and interview measures, schizotypy and SPD indicators, taxometric analyses and mixture models, as well as – most noticeably – phenotypic and endophenotypic (for instance, sustained attention and eye tracking measures) indicators. The emerging corpus of data supports several putative endophenotypes [4] as particularly promising for inclusion in genomic research and the rational expansion of the phenotype for schizophrenia [29-31]. Two endophenotypic indicators that are particularly well established are deficits in sustained attention [32-34] and impairments in smooth pursuit eye movements [35-37]. Subtle deficits in each of these neurocognitive processes are thought to tap into the latent liability for schizophrenia, or what Meehl [1 3] termed schizotypy. Prior research has established the relations between deficits in sustained attention [32] as well as eye-tracking dysfunction [35] and criteria of validity for schizophrenia liability. There are two major advantages to the use of endophenotypes that are assessed with objective laboratory methods. First, there is the increase in measurement precision. Second, endophenotypes assessed with objective laboratory measures are not subject to various measurement artifacts that could have an adverse and potentially misleading impact on latent structure analyses [38].

Overall, the consistency in findings across the various studies summarized in Table I supportive of a schizotypy taxon is impressive. It seems highly unlikely that this consistency of findings may stem from distributional artifacts. Moreover, results from studies using different approaches – particularly mixture modeling and latent class analysis approaches – are consistent with those obtained by the taxometric methodology. For example, in at least four studies mixture modeling techniques were used and supported the taxonic results [17 39-41]. Rather, it seems apparent that measures of latent liability to schizophrenia, whether phenotypic (i.e., sub-clinical schizotypic psychopathology) or endophenotypic (e.g., laboratory measures of sustained attention or smooth pursuit eye movements) in nature, almost invariably yield a discontinuous latent structure of schizotypy.

Although a detailed description of the genetic models of schizophrenia is clearly beyond the aims of this study, the studies listed in Table I suggest that what is really at issue is not the empirical evidence of a taxonic structure of schizotypy, but

TABLE I.
Summary of published findings on the latent structure of the liability to schizophrenia. *Riassunto dei reperti pubblicati sulla struttura latente della predisposizione alla schizofrenia.*

Publication	Sample	Measures[a]	Procedures[b]	Conclusions[c]
Lenzenweger and Korfine [12]	1093 undergraduates	PAb	MX	Tax
Korfine and Lenzenweger [42]	1646 undergraduates	PAb	MX	Tax
Lenzenweger [9]	429 undergraduates	PAb, MgI, RT	MX	Tax
Keller et al. [81]	1103 undergraduates	Positive symptoms	MX	Dim
		Negative symptoms	MX	Tax
Meyer and Keller [82]	809 undergraduates	PAb	MX	Tax
		MgI	MX	Dim
		PhA	MX	Tax
Horan et al. (Study 1) [83]	1560 undergraduates	MgI	MA, MX	Inc
		SoA	MA, MX	Tax
Horan et al. (Study 2) [83]	2574 undergraduates	PAb	MA, MX	Tax
		MgI	MA, MX	Inc
		SoA	MA, MX	Tax
Linscott et al. [84]	387 secondary students	PAb, MgI, RT, HT	ME, L,MX	Tax
Blanchard et al. [85]	1526 undergraduates	SoA	ME, MX	Tax
Golden and Meehl [11]	211 inpatient adults	MMPI items	L, MX	Tax
Erlenmeyer-Kimling et al. [14]	185 & 150 children	Neuromotor	L	Tax
Tyrka et al. [7]	311 children	Int, behaviour ratings	MX,	Tax
Tyrka et al. [8]	311 adults	Int	MX	Tax
Lenzenweger and Moldin [41]	707 undergraduates	PAb	MM	Tax
Fossati et al. (Study 1) [39]	721 outpatients	SCID-II; PDQ-4+; SIDP-R	MM	Tax
Fossati et al. (Study 2) [39]	537 outpatients	SCID-II; PDQ-4+; SIDP-R	MM	Tax
Fossati et al. (Study 3) [39]	225 nonclinical volunteers	SCID-II; PDQ-4+; SIDP-R	MM	Tax
Fossati et. al (Study 1) [40]	803 undergraduates	SPQ, STA, Schizotypy Scale	MX	Tax
Fossati et. al (Study 1) [40]	929 high school students	SPQ, STA, Schizotypy Scale	MX	Inc
Lenzenweger, McLachlan and Rubin [17]	311 undergraduates	Sustained attention, indices of eye-tracking	MM, MX	Tax
Rawlings et al. [21]	1073 non clinical adults	CSTQ	MA, ME	Dim

[a] PAb: perceptual aberration; MgI: magical thinking; RT: referential thinking; HT: hallucinatory tendency; PhA: physical anhedonia; SoA: social anhedonia; Int: interview, SCID-II: structured clinical interview for DSM-IV Axis II Personality Disorders PDQ-4+: personality diagnostic questionnaire; SPQ: Schizotypal Personality Questionnaire; STA: Schizotypy Scale; CSTQ: Combined Schizotypal Trait Questionnaire. [b] ME: MAXEIG; L: latent class method; MA: MAMBAC; MX: MAXCOV; MM: mixture models. [c] Tax: taxonic; Dim: dimensional; Incon: inconclusive.

if this empirical evidence is consistent with prominent models of genetic diathesis for schizophrenia. Meehl's [1 3] model holds that a single major gene exerts its influence during brain development by coding for a specific ''aberration of the synaptic control system'' in the central nervous system (Meehl [1], pp. 14-15). Meehl theorized a ''mixed'' model of genetic influence — namely, a single major gene with two alleles (alternate forms) operating against an additive polygenic (i.e., sum of individual genetic effects) and environmental background. Although modern genetic research does *not* support a simple single major-locus model, empirical and simulation studies have long suggested that a mixed model is clearly plausible for schizophrenia (as are several other models) [2].

According to the Meehl model, schizotypy is conjectured to have a general population base rate of 10% (see Meehl [1] for derivation of the base rate estimate). Interestingly, this conjecture was empirically supported by several taxometric studies carried out in non clinical samples [9 10 40 42] that consistently reported an estimated schizotypy taxon base rate in the 10-15% range. In other words, several studies based on phenotypic indicators of schizotypy or SPD did not replicate only the general finding of a taxonic structure, but also reported taxon base rate estimates that were highly consistent and coherent with theoretical expectations.

But is the taxonic structure of latent liability to schizophrenia consistent also with other prominent genetic models for schizophrenia? For instance, Holzman et al. posited the presence of a *latent trait* that was indicative of either schizophrenia or eye-tracking dysfunction in an autosomal dominant gene model that assumed pleiotropy [43]. The Holzman-Matthysse model, as well, suggests that one is either at risk for schizophrenia by virtue of possessing a schizophrenia-specific "latent trait" or not at risk (i.e., the latent trait is absent).

Gottesman [44 45] proposed a multifactorial polygenic threshold model that contained a pronounced *threshold* effect in an underlying continuum of schizophrenia liability. Thus, for Gottesman [44], despite a quantitative conceptualization of latent liability for schizophrenia, the threshold (much like a step function or inflection on a steep ogive) demarcates those at risk for schizotypic pathology (including schizophrenia) versus those not at risk.

Thus, what is common to all of these models (Meehl, Holzman & Matthysse, Gottesman) is the proposition that the latent liability for schizophrenia is most likely distributed in a discontinuous (or quasi-discontinuous) manner, such that one either is at risk for the disease or is not [17]. Far from being a spurious finding stemming from distributional artifacts, the taxonic structure of schizotypy is a consistently replicated empirical evidence which is expected by the prominent genetic models of schizophrenia.

Recently the epigenetic perspective [46] renewed the debate on gene-by-environment interactions in schizophrenia, as well as in other domain of normal and abnormal behavior. It should be observed that interaction effects are thought to produce qualitative differences in response rather than common effects [47]. This issue should not be overlooked in modeling the latent distribution of a variable:

In addition to consulting taxometric evidence as well as the results of other studies, there are some additional concerns regarding the detection of latent classes that should be discussed. For example, although the dimensionality of many variables in psychology seems plausible and well established, it is important to consider that the act of measuring a variable continuously does not necessarily make the latent construct continuous in nature [48]. For instance, although we usually measure intelligence in a continuous manner in the form of IQ, we speak of mental retardation as we descend into the lower tail of the IQ distribution in recognition of a readily apparent qualitative change [48].

One must also consider the possibility that there could conceivably be more than one schizophrenia-related (schizotypy taxon) – just as Bleuler himself viewed schizophrenia as a "group of schizophrenias" there exists the possibility that there could be multiple schizophrenia taxa. The variation in taxa could parallel the variation seen in schizophrenia symptomatology [49]. Thus, one could consider if there are schizotypy taxa that map on to the disorganized, reality distortion, negative symptom, and impaired premorbid functioning domains of phenomenology [49] (although they may not represent dissociable features of SPD, but rather represent distinct constructs, say social anhedonia vs. extraversion-introversion). Some evidence from the analysis of schizotypal PD features would be consistent with this view. For instance, it is well known that the latent structure of SPD features is not explained by a single latent variable,

but 2-4 factors are usually need to explain the correlations between measures of SPD features, with 3 factors being the most frequently replicated finding [50 51]. Although the 3-factor models of SPD show some differences, as a whole they closely resemble the 3-factor structures of Schizophrenia signs and symptoms [49 52]. At least for some 3-factor model of SPD, data suggest that the three factors of SPD are associated with patterns of cognitive asymmetry, handedness and gender in a way that is akin to what has been reported for schizophrenia [53].

Twin and family studies confirm the existence of a correspondence between psychometric complexity and etiological heterogeneity of the construct. A substantial broad heritability coefficients were reported for "affect-constricted" and "positive schizotypy" latent dimension [54-56], whereas controversial findings as to the heritability of suspiciousness features were reported [54 57 58]. Interestingly, constricted affect, odd speech, eccentricity, social dysfunction, and negative schizotypy best identified the non-psychotic relatives of patients with schizophrenia according to both recent [58-60] and "historical" family studies (reviewed by Kendler [61]) of schizophrenia.

As presently developed, taxometric methods are really only capable of detecting two latent classes if they exist (see [62]), whereas finite mixture modeling can detect any number of latent components (i.e., one, two, three, or more). Beauchaine [63] and Lenzenweger et al. [17] provided additional useful discussion of the differences between these two families of statistical methods.

Despite the possible heterogeneity of the SPD features, studies based on mixtures models of either SPD measures [39] or endophenotypic indicators of schizophrenia liability [17] consistently reported that the latent structure of schizotypy is discontinuous in nature and is characterized by two latent classes, i.e., a schizotypy latent taxon and a non-schizotypal complement.

Thus, currently little doubts exist that in the case of the latent liability to schizophrenia "natura facit saltus", i.e., there are qualitative – or quantitative-qualitative – distinctions between schizotypal and non-schizotypal subjects. This awareness is prompting a series of studies on the neuropsychological/neurophysiological functioning in the schizophrenia spectrum disorders, and the development of new "models of mind" which tries to explain both similarities and quantitative-qualitative differences between SPD and schizophrenia.

For instance, Siever and Davis [64], based on a review of neuropsychological and psychobiological studies on schizophrenia spectrum disorders, proposed that people with SPD share phenomenological, genetic, and cognitive abnormalities with people with chronic schizophrenia; for instance, subjects with SPD have been shown to share a number of psychophysiological abnormalities found in chronic schizophrenia, such as the following: 1. A failure of P50 suppression; 2. Deficits in prepulse inhibition; 3. Impairment of smooth-pursuit eye movements; 4. Errors in antisaccade tasks; 5. Poor performance on a backward masking task; 6. Reduced P300-evoked potentials; 7. Performance on the Continuous Performance Test. By the way, some of these abnormalities, such as those of P50 suppression, prepulse inhibition, eye movement abnormalities, and Continuous Performance Test performance, are quite stable in normal subjects, persist in patients with schizophrenia in remission from psychosis, and appear to be heritable, representing promising endophenotypes for genetic studies [65].

On the contrary, imaging studies evidence that while temporal volume reductions appear to be common to both groups, there may be preservation of frontal lobe volume in SPD compared to schizophrenia [64]. These consideration, as well as an extensive discussion of genetic, phenomenological, biological, and neuropsychological evidences, lead Siever and Davis [64] to propose a model in which schizotypal and schizophrenic subjects are hypothesized to share a common genetic anomaly that renders the temporal cortex particularly vulnerable to environmental insults; however, genetic factors independent of the vulnerability to the schizophrenia spectrum per se and/or more favorable environmental influences would leave the schizotypal subject better buffered with regard to frontal volume and function as well as stabilization of subcortical dopaminergic activity.

Thus, the study of the latent liability to schizophrenia has provided a conceptual framework that is providing new opportunities also to disentangle the genetics and pathophysiology of schizophrenia [1 2 19]. By contrasting and comparing schizotypal, schizophrenic, and healthy volunteer subjects, commonalities and distinctions between schizotypal personality and schizophrenia are being mapped using neurochemical, imaging, and phar-

macological tools, and not only at psychometric or taxometric level.

Thus, studies on the latent structure of schizophrenia liability have an immediate relevance for research on the etio-pathogenesis and pathophysiology of schizophrenia. Thus, the relevance of the dimensional-vs.-taxonic debate on the latent structure of schizotypal personality should *not* be viewed as an arcane academic discussion of little relevance for the clinical psychiatrist. We think that this is not the case if we consider the prevention of schizophrenia. For example, if a taxon exists for schizophrenia liability, then we should come to know it for several reasons. First, knowledge of the existence of a latent taxon may aid in accurate detection of potential schizotypes by application of the decision rules obtained from the taxometric analyses. Second, the presence of a schizotypy taxon may be useful in predicting treatment response or course of illness (e.g., as a moderator of treatment or course). Third, if a schizotypy taxon exists, then future measures of schizotypy could be developed with this in mind. Finally, the existence of a schizotypy taxon could provide information useful to genomic investigations of schizophrenia.

Schizophrenia is among the most severe mental disorders and it deeply compromises psychic activity, emotions, self-perception and social interactions, causing social impairment and disability; the lifetime prevalence of schizophrenia is roughly 1% in the general population and increases 5-10 times in relatives of schizophrenic patients (see for a review [66]). Schizophrenia is an aetiologically complex disorder that arises from the interaction of genetic (and possibly epigenetic [46]) and environmental factors [67 68].

Knowing that the latent distribution of schizophrenia liability is discontinuous allows for the estimation of the base rate of putative taxon members in the population, i.e., subjects who are at risk to develop schizophrenia. As it was pointed out above, taxometric studies [9 10 40 42] consistently reported a base rate estimate for the schizotypy taxon in the general population in the 10-15% range. Thus, usually one-tenth of the high-risk subjects actually develops schizophrenia. However, not all those subjects at risk for schizophrenia will develop the illness in clinical form. Thus, raising the possibility of successful intervention efforts for thwarting the emergence of the illness. Recalling that only 10-15% of high risk subjects develop schizophrenia, we must confront the fact that there are many individuals at risk for schizophrenia who do not display any of the dramatic symptoms of schizophrenia (perhaps displaying only subclinical/mild positive and negative symptoms of SPD). Moreover, we must consider why those cases of schizophrenia did develop in those at risk for the illness. Were they exposed to environmental stressors that potentiated their underlying schizophrenia liability (i.e., schizotypy)? Relatedly, could clinical schizophrenia be prevented by keeping those who carry the liability for the illness from exposure to potential risk increasing stressors in adolescence or early adulthood?

For instance, amphetamine-induced psychosis was first described in the 1950s [69], and has been more fully examined in recent years in a large cohort (n = 163) of methamphetamine users who also developed psychosis [70]. These investigators reported that methamphetamine users with psychosis presented a clinical picture that mimicked the positive symptoms of schizophrenia [70]. Interestingly, being at risk for schizophrenia appeared to play a role in increasing susceptibility to methamphetamine-related psychosis: individuals who had no family history of schizophrenia could abuse the drug without developing psychosis, whereas those with a greater familial predisposition to schizophrenia were more likely to experience psychotic symptoms, and not to recover if they developed psychosis [67 70].

A meta-analysis of twin studies estimated that the heritability of liability to schizophrenia is approximately 80% [71]. This degree of heritability includes not only genetic factors but also interactions between genes and environmental factors. One of these environmental factors is cannabis. Recent meta-analytic studies [72 73] of prospective studies showed a significant, albeit moderate, effect size for the association between cannabis use and schizophrenia. However, it should be observed that only a small minority of cannabis users actually develops schizophrenia [67]. Thus, even if cannabis use increases the risk for schizophrenia, it is not sufficient in itself to cause the illness. It is more likely that cannabis is a component cause of schizophrenia; that is, it may lead to the onset of schizophrenia only in the presence of other components in the various causal mechanisms [74]. These factors are largely unknown, but, given the high degree of heritability of liability for schizophrenia [71], there

is probably an interplay between genetic liability for psychosis and cannabis use with regard to the development of psychosis [75].

For instance, Henquet and co-workers [75] investigated the interaction between cannabis use and predisposition for psychosis, defined as scores above the 90th centile on the 'paranoid ideation' and 'psychoticism' sub-scales of a symptom checklist. In a large population-based cohort of 2437 young people, the risk of psychotic symptoms after 4 years' follow-up was 15% for individuals with no predisposition for psychosis, but when they used cannabis the risk increased to 21%. In the group with a predisposition for psychosis, however, the risk was 26% for those who did not use cannabis and 51% for cannabis users, suggesting that cannabis could have a stronger effect on the development of psychotic symptoms in individuals with a predisposition for psychosis.

These findings were supported by recent studies that tried to evaluate directly a gene-by-environment interaction in the relation between cannabis use and schizophrenia. Caspi et al. [76] studied a functional polymorphism of the catechol-*O*-methyltransferase (COMT) gene. They obtained DNA from 803 members of the Dunedin birth cohort at age 26 years for whom information on cannabis use was available. Adolescent cannabis use was associated with an increased risk for schizophreniform disorder in adulthood among Val/Val individuals (i.e, high COMT activity) and, to a lesser extent, among Val/Met individuals (i.e, intermediate COMT activity), but not among Met/Met (i.e, low COMT activity) individuals. These findings remained statistically significant after adjustment for confounder effects (e.g., other drug use, presence of psychotic symptoms preceding cannabis use, IQ, etc.).

Henquet et al. [77] confirmed and extended these findings in an experimental study with a randomized, double-blind, crossover design; the authors reported a significant interaction effect when participants were classified according to high or low psychometric psychosis liability, independent of case–control status and assessed before the administration of THC with a self-report instrument measuring sub-clinical psychosis-like symptoms. In other terms, carriers of the Val allele were more sensitive to psychotic experiences induced by THC than individuals with the Met allele, but only when they had prior high psychosis liability.

By the way, recent Veling et al. [78] findings clearly showed that genetic predisposition for schizophrenia did not predict cannabis use. However, despite the relevance of these findings, they should be considered as provisional; for instance, they have been not replicated in a recent study by Zammitt et al. [79]. Moreover, some psychometric measures of predisposition to psychosis may not represent accurate measure of genetic liability, because they may reflect early symptoms of psychotic illness rather than genetic liability [80].

One might consider how the schizotypy model jibes with empirical studies of clinical and subclinical psychotic (or psychotic-like) experiences in the general population, which suggest that at the manifest level psychotic symptoms appears to lie on a continuum of severity [86-92]. Despite the large size of the samples, most of these studies have been concerned merely the *observed* distributions of the features/symptoms that were examined. These studies did not address the question of the underlying structure of the data and, therefore, for the most part did not employ statistical analyses directed at discerning whether the latent structure is qualitative vs. quantitative in nature. Even prior studies of psychotic-like symptoms that used latent class analysis pointed to multiple classes – *not* to a single class with gradations within the class. Thus, although many prior investigators have examined the frequency distributions of sub-clinical psychotic (or psychotic-like) features in large samples, the visual inspection of such distributions cannot resolve the issue as to the nature of the *latent* structure of such symptoms. This type of question – the so-called "taxonic question" – can only be answered using techniques that can aid in the determination of the qualitative vs. quantitative nature of the data at hand.

Summarising, we argue that these findings regarding both the nature of the latent structure of schizophrenia liability, gleaned though the study of phenotypic (i.e., cognitive, affective, behavioral, and interpersonal features) and endophenotypic indicators, as well as the natural boundaries and estimated prevalence of latent liability to schizophrenia in the general population may be useful to the clinicians in their daily practice. At individual level, the knowledge of the manifest personality characteristics of subjects having a liability to develop schizophrenia may help preventive inter-

ventions (i.e., secondary prevention efforts), for instance, entering these subjects into educational programs designed to avoid using illicit street drugs – or to facilitate stop using illicit street drugs if the subjects is already using them - which are usually perceived as not harmful, such as cannabis, but which may be deleterious to the mental health of schizotypes. At the social-interpersonal level, these results provide psychiatrists with evidence-based information to develop psycho-educational interventions designed to change the social perception of drugs, as well as to develop targeted intervention programs in order to prevent a possible dramatic increase of the incidence and prevalence of schizophrenia.

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