The identification of individuals carrying unexpressed genetic liability to schizophrenia is crucial for both etiological research and clinical risk stratification. Subclinical psychopathological features detectable in the nonpsychotic part of the schizophrenia spectrum could improve the delineation of informative vulnerability phenotypes. Inspired by Meehl’s schizotaxia-schizotypy heuristic model, we tested anomalous subjective experiences (self-disorders, SDs) as a candidate vulnerability phenotype in a sample of nonpsychotic, genetically high-risk subjects. A total of 218 unaffected members of 6 extended multiplex families (assessed between 1989 and 1999 during the Copenhagen Schizophrenia Linkage Study) were stratified into 4 groups of increasing psychopathological expressivity: no mental illness (NMI), no mental illness with schizotypal traits (NMI-ST), personality disorders not fulfilling other personality disorders (OPDs), and schizotypal personality disorder (SPD). We tested the distribution of SDs among the subgroups, the effect of SDs on the risk of belonging to the different subgroups, and the effect of experimental grouping and concomitant subclinical psychopathology (ie, negative symptoms (NSs) and subpsychotic formal thought disorder [FTD]) on the chances of experiencing SDs. SDs distribution followed an incremental pattern from NMI to SPD. SDs were associated with a markedly increased risk of NMI-ST, OPDs, or SPD. The odds of SDs increased as a function of the diagnostic category assignment, independently of sociodemographics and concomitant subclinical psychopathology (NSs and FTD). The results support SDs as an expression of schizotaxic vulnerability and indicate a multidimensional model of schizotypy—characterized by SDs, NSs, FTD—as a promising heuristic construct to address liability phenotypes in genetically high-risk studies.

Key words: schizophrenia spectrum/schizotaxia/schizotypal personality disorder/anomalous self-experience/vulnerability phenotype/genetic high risk

Introduction

Throughout much of the last century, the search for etiologically informative phenotypes and the study of the genetic architecture of the ‘‘schizophrenia-spectrum (SzSp) disorders’’ generated a bewildering array of data.1–3 Several approaches were launched: clinical-psychopathological studies (studying clinically expressed conditions, such as schizophrenia, Diagnostic and Statistical Manual of Mental Disorders odd-eccentric cluster personality disorders, and—recently—prodromal/ultrahigh risk conditions, as the unit of analysis), genetic high-risk studies (addressing population at enhanced genetic susceptibility, mainly children of schizophrenia probands), genetic-epidemiological surveys (eg, Roscomon4), and the psychometric high-risk research (studying persons exceeding thresholds of assumed psychometric measures of schizotypy/schizophrenia proneness).5 Yet, despite all these efforts, the limits of SzSp itself remain unclear. As demonstrated by the polydiagnostic studies, even the prototype, the extreme and exemplary SzSp condition—namely schizophrenia—has variable borders, changing with the diagnostic system of reference.6,7 Furthermore, there is still a lack of agreement on the core features of SzSp, evoking relevant questions for both research and clinical practice. Hence, the ‘‘qualitative similarities’’ that inspired very notion of the SzSp of disorders of Kety et al8 remain somehow elusive and fairly unaddressed by contemporary research. This is particularly surprising because the idea of a gradient of psychopathological expressivity has been almost inescapable from the very concept of schizophrenia since its emergence.5
The Continuum Beyond the Spectrum: From Kraepelin to Meehl

Seminal observations by Kraepelin and Bleuler revealed that biological relatives of schizophrenia patients often displayed subtle formal thought disorder (FTD) and interpersonal oddities.9–11 Later (elaborating upon Rado’s original hypothesis), Meehl proposed the term schizotaxia for the “genetically determined integrative defect, predisposing to schizophrenia” and the term schizotypy for a subtly deviant psychobehavioral organization, reflective of interactions of the schizotaxic vulnerability with environmental factors.13,14 An alternative, different but related, approach reconceptualizes schizotaxia as a discrete phenotypic class characterized by slight cognitive disturbances and negative symptoms (NSs).11,15,16 assumed to occur in 20%–50% of first-degree relatives of patients with schizophrenia.15,16 Nevertheless, Meehl’s schizotaxia-schizotypy paradigm remains at the heuristic core of contemporary etiologic models of SzSp disorders.17 It assumes that schizotaxic individuals, who carry an underlying genetic vulnerability, will manifest schizotypy on a dynamic continuum of increasing severity depending on the history of developmental interaction between genes and biopsychosocial risk factors. Such continuum ranges from relative psychological health to various degrees of subclinical deviance to SzSp personality disorders to full-blown schizophrenia.13,14 Thus, it accommodates genetic and environmental contributions to liability within a developmental frame, accounting for a range of clinical and subclinical outcomes.

Self-disorders and the Schizophrenia Spectrum

Recent years have witnessed a rebirth of interest in the domain of subjectivity and its disturbances, particularly anomalous subjective experience of nonpsychotic intensity and quality.18,19 This interest is amplified by the ongoing, widespread research on the preonset stages of schizophrenia and other psychotic disorders.20–22 Curiously, such subtle (nonpsychotic) qualitative changes of subjective experience were described in the early 20th century and were thought to be intrinsic to schizophrenia, coconstituting the specificity of its characteristic gestalt. However, they were ignored by the contemporary psychiatry, mainly due to the dominating behavioristic approach.21,24

Both qualitative24–26 and empirical20,22,27,28 research consistently indicate that certain anomalous subjective experiences antedate the onset of psychosis. Clinically, anomalous subjective experiences24 encompass a broad range of phenomena—from affect, perception, and experience of cognition and action to bodily experiences more generally—all of which fall below the threshold of psychotic symptoms (ie, delusions and hallucinations). For instance, they include various disturbances in the stream of consciousness (eg, thought interference), mild perceptual aberrations, anomalous bodily experiences (eg, somatic depersonalization), lack of a sense of immersion in the world (eg, anhedonia, diminished vitality), and various other disorders of self-consciousness. (Extensive catalogs of these anomalous subjective experiences are available in the form of systematic checklists: the Bonn Scale for the Assessment of Basic Symptoms [BSABS]; the Schizophrenia Proneness Instrument-Adult [SPI-A] version; and the Examination of Anomalous Self-experience [EASEE]).29–31 For detailed phenomenological descriptions and theoretical considerations on anomalous subjective experience, see Parnas and Handest24 and Sass and Parnas.32–33

In recent years, our own psychopathological research on essential features of schizophrenia (in continuity with the Copenhagen High-Risk and Linkage Study32,33) explored a subset of anomalous experience, namely, self-disorders (SDs). SDs have been considered to be central features of the psychopathology of schizophrenia since the very foundation of the concept (Bleuler, Kraepelin, Berze, and Kronfeld [see Parnas and Handes]). They comprise unstable or attenuated sense of self-presence, lack of basic sense of self-coincidence (identity), blurred self-demarcation, disturbance in the tacit fluidity of the field of awareness, hyper-reflexivity, and difficulty in grasping familiar meanings.19

Our studies suggest that SDs form an important phenotype for the characterization of SzSp disorders, both in clinical and in genetically high-risk populations. In a study following the pilot data,34 we found that SDs discriminate International Classification of Diseases, Tenth Revision (ICD-10), schizophrenia in remission (elevated levels) from psychotic bipolar illness in remission. In a prospective longitudinal study of 155 first-admission cases, we showed that SDs aggregated selectively among the ICD-10 nonaffective psychotic patients (mainly schizophrenia patients) and in patients with schizotypal disorders but not in the diagnostic categories outside the spectrum.28,35 Finally, in an interdiagnostic study on a genetically high-risk population, we found that SDs distribution mirrors the pattern already demonstrated by the clinical samples: SzSp conditions (ie, schizophrenia and schizotypal personality disorder [SPD]) had higher SDs levels than those of other (nonspectrum) diagnostic groups or individuals with no psychiatric diagnosis.36 Independent studies of unaffected first-degree relatives of schizophrenia probands indicated that the level of SDs in such relatives is intermediate between normal control subjects and clinically overt SzSp disorders37,38 and correlates with the severity of the schizotypal traits.39

Hypothesis Generation and Rationale for Experimental Design

Against this background, we designed the current study to examine SDs as a potential phenotype to track schizotaxic liability in genetically high-risk populations. We used a multigenerational sample derived from 6 extended family pedigrees, previously assessed in the Copenhagen
Schizophrenia Linkage Study.\textsuperscript{32,40} In order to target the continuum of liability below the threshold of psychosis, we used a graded construct of schizotypy as a unit of analysis. Operatively, we assumed that detectable schizotypal traits, detectable personality disorder, and detectable SPD reflect increasing degrees of manifestation of schizotypy (in the sense of a “latent personality organization” in schizotypic individuals).\textsuperscript{12,14} We opted for such heuristic stratification because it offers recognizable anchor points of increasing clinical severity that can be directly mapped on \textit{Diagnostic and Statistical Manual of Mental Disorders} (Third Edition Revised) \textit{(DSM-III-R)} criteria (eg, criteria for Axis II disorders and criteria for SPD). Further, we hypothesized that anomalous subjective experiences (SDs) can provide points of entry for identifying schizotypic individuals at various thresholds of subclinical expressivity.

We therefore tested the following:

1. the distribution of SDs among the subgroups (assuming that it would show a gradient-like pattern);
2. the effect of SDs in moderating the risk of belonging to the nonpsychotic part of the SzSp (expecting SDs to increase the risk of belonging to the groups with higher degrees of schizotypy);
3. the effect of diagnostic assignment and concomitant (subclinical) psychopathology on the chances of experiencing SDs (expecting the assignment to be the strongest predictor of SDs odds).

In addition to SDs, in order to map salient psychopathological dimensions in nonpsychotic genetically high-risk subjects, we used assessments of NSs and FTD. Indeed, both original descriptions from Kraepelin and Bleuler and studies of relatives of schizophrenic patients\textsuperscript{41–44} indicate that the negative and disorganized dimension of schizophrenia may be a part of the constellation of features that mark genetic vulnerability for the disorder.

\textbf{Methods}

\textbf{Sample}

The sample included 218 nonpsychotic members of 6 extended multiplex families, previously assessed in the Copenhagen Schizophrenia Linkage Study. The Copenhagen Schizophrenia Linkage Study began in 1989 and was directly inspired by the findings from high-risk studies (such as the Copenhagen High-Risk Study\textsuperscript{33} and the Danish Adoption Study\textsuperscript{8}) that confirmed the existence of a SzSp disorder, described as nonpsychotic pathological conditions significantly aggregating among biological relatives of schizophrenic individuals.\textsuperscript{45} Experimentally and logistically, the Copenhagen Schizophrenia Linkage Study was an outgrowth of the Copenhagen High-Risk Study\textsuperscript{33} and was guided by a hypothesis that extended pedigree information—comprising phenotypes such as schizotypal disorder and markers such as thought disorder index\textsuperscript{40} and eye tracking dysfunction\textsuperscript{32}—might substantially contribute to mapping the alleles implicated in schizophrenia.

The Copenhagen Schizophrenia Linkage Study targeted 6 families (whose genograms are reported in Vaever et al\textsuperscript{40}), identified through the following procedure. Originally, 6 individuals with a diagnosis of schizophrenia were identified in the Copenhagen High-Risk Study, whose pedigrees were found to have the following characteristics: (1) many living members (minimum age 15 y, no maximum age), (2) at least 2 first-degree family members with a reliable diagnosis of schizophrenia (based on clinical documentation and mental health registry), and (3) reports from family members and from psychiatric case register of distant relatives with any psychiatric problem. Each pedigree was centered on 1 of the 6 original schizophrenic probands’ nuclear families; this proband was used as the starting point for extending the family trees both horizontally (eg, siblings, cousins) and vertically (eg, parents, grandparents, offspring). It should be noted that the investigators favored pedigrees that could be extended (ie, families with many siblings, aunts, cousins, etc), which represented up to 6 generations, including the nuclear families (eg, there was a family with 12 offspring, and one pedigree consisted of 175 living members).

Pedigree information was collected on 618 subjects (see Matthysse et al\textsuperscript{32} and Vaever et al\textsuperscript{40}) of which 347 were personally interviewed and assessed on multiple domains (sociodemographic, psychopathological, neuropsychological).\textsuperscript{32,36,40}

Two senior clinicians administered the Copenhagen Interview of Functional Illness\textsuperscript{46} to all the enrolled participants, blind to any diagnostic information, clues to the kinship status, and surnames of the subjects. The interview contained the psychosis section from the Present State Examination\textsuperscript{47}; an abbreviated Personality Disorder Examination (PDE)\textsuperscript{48}; the Thought, Language, and Communication (TLC)\textsuperscript{49} Scale; Scale for the Assessment of Positive Symptoms and Scale for the Assessment of Negative Symptoms (SANS)\textsuperscript{50,51}; Schedule for Affective Disorder and Schizophrenia—Lifetime Version (items concerning all nonpsychotic disorders)\textsuperscript{52}; a list of anomalous subjective experiences mostly derived from the sections C (ie, cognitive thought, perception, and motor disturbances) and D (ie, impaired bodily sensations) of a preliminary version of the BSABS\textsuperscript{29}; and single interview items used in the Copenhagen Adoption\textsuperscript{8} and High-Risk\textsuperscript{33} studies.

Complete psychopathological data on SDs were available in 305 participants.\textsuperscript{30} From this subgroup, we extracted the final experimental sample on the basis of a heuristic operationalization of Meehl schizotaxia-schizotypy construct. We excluded those with any comorbid \textit{(DSM-III-R)} Axis I condition\textsuperscript{($n=29$) schizophrenia or other psychoses, $n = 22$ affective disorders, $n = 18$ alcohol/substance-related disorders, $n = 10$ other Axis I disorders}. This restriction
was motivated by our intention to address subclinical features of vulnerability to SzSp disorders, and thus, besides excluding schizophrenia, we wanted to avoid confounders due to other major Axis I clinical disorders (eg, affective disorders, alcohol, or drug abuse). Finally, we did not include the few (n = 8) schizoids and paranoid (too few to be a class for itself) because the meaning of these terms in their post-Meehl DSM-III-R definition has been transformed into suspiciousness or egosyntonic introversion, with a dubious or no familial affinity to schizophrenia (see Parnas et al for a very extensive review of the matter).

The final experimental sample was therefore composed of 218 subjects with a clinical expressivity ranging from no mental illness to personality disorders (ie, DSM-III-R, Axis II conditions).

During the Copenhagen Schizophrenia Linkage Study, DSM-III-R “lifetime” psychiatric diagnoses of each participant were determined by consensus among 4 research psychiatrists/psychologists using all available data sources. Interrater diagnostic reliability was assessed and prevented from drift via regular group interview sessions (interviews conducted by J.P.). The mean interrater reliability ranged between 0.900 and 0.956, similar to that reported in Parnas et al.33

Study Variables

Phenotypic Manifestness of Schizotaxia: Categorical Divisions of Schizotypy and Sample Stratification. In order to capture in a reproducible way, the subtle manifestations of schizotaxic diathesis within a genetically high-risk, mainly nonsymptomatic (ie, below the clinical caseness level) population, we operationalized the continuum of schizotypy according to the available clinical diagnostic information. This subdivision was motivated by a rational-pragmatic approach to Meehl’s schizotaxia-schizotypy model and based on clinically recognizable thresholds. We considered subjects with no signs of mental illness and no schizotypal traits as a reference category. A second threshold was the presence of some schizotypal traits in the context of an otherwise nonpathological personality organization (ie, not fulfilling the criteria for any DSM-III-R personality disorders). A third threshold was the presence of a “pervasive pattern” of behavior and experiences configuring a personality disorder. The final threshold was the presence of the specific “pervasive pattern” of behavior and experiences indicative of SPD. We assumed that those thresholds could approximate distinguishable escalating manifestations of schizotypy in Meehl’s sense.14

Hence, we stratified the sample as follows:

1. No personality deviations and no schizotypal traits; the corresponding sample, termed no mental illness (NMI), included 79 participants.
2. Few schizotypal traits but no personality deviations; the corresponding sample, termed no mental illness with schizotypal traits (NMI-ST), included 24 participants. Operatively, in order to set a clinically tangible threshold, the subjects included in the group needed to fulfill at least 2 of the DSM-III-R criteria for SPD; subjects fulfilling only one of the SPD criteria were included in NMI (group 1).
3. Personality deviations, reaching the threshold for a DSM-III-R personality disorder but not fulfilling the criteria for full-fledged SPD. The corresponding sample, termed other personality disorders (OPDs), included 62 participants, 56 of whom also had comorbid schizotypal traits.
4. SPD, subjects reaching the threshold for the relevant DSM-III-R diagnosis and with no comorbid Axis I psychotic conditions. The SPD sample included 53 participants.

Psychopathological Dimensions: SDs, NSs, and FTD A broad range of anomalous subjective experience was explored through the Copenhagen Interview of Functional Illness,46 which contains items derived from the BSABS29 and the PDE.48

The items derived from the BSABS were originally adapted to the specific study population of the Copenhagen Schizophrenia Linkage Study (ie, non–help-seeking genetically high-risk subjects) in order to assess the lifetime prevalence of subtle enduring distortions of subjective experience, conceived as trait features. The original coding of these items was 0 (not present), 1 (doubtfully present), or 2 (definitely present). However, because only few participants received score 1, this score was recoded into 0 (not present) and 2 redefined as 1 (present).

The SDs score used for the current data analysis was based on a rational selection of items considered pertinent to the construct. That scale yielded excellent internal coherence (Cronbach $\alpha = .81$) in the same genetically high-risk population.36 Further details on the SDs score generation and item composition are available open access36 and recapitulated in the Appendix.

Briefly, the SDs score for each subject was calculated as a sum of ratings of the individual scale items (which had values 0 or 1). Clinically, the SDs score addresses a comprehensive set of self-experience, ranging from subtle de-personalization, perplexity, sense of anonymity, and interference of thoughts to more thematic or explicit levels of identity disturbance. See the Appendix for the specific item composition.

NSs and FTD were assessed with the SANS51 and TLC Scale.49 Dimensional scores were computed for the purpose of data analysis.

Statistical Analysis

We explored the sociodemographic and psychopathological features of the samples using $\chi^2$ test for categorical variables and Welch weighted analysis of variance for continuous variables. We then used multinomial logistic
regression to estimate the risk of belonging to the experimental categories (ie, NMI-ST, OPDs, and SPD, with NMI as reference class) as a function of SDs, contextually controlling for sociodemographic and other psychopathological variables. We chose multinomial logistic regression, rather than ordinal logistic regression, because the proportional odds assumption could not be made, ie, we could not assume that the postulated SDs effect on the dependent variable (experimental grouping) is the same across the different categories (ie, NMI, NMI-ST, OPDs, SPD), given the diagnostic heterogeneity of the subjects.

In a second step—with the binary logistic regression—we estimated the effect of schizotypal class allocation on the risk of experiencing SDs, adjusting for sociodemographics and concomitant psychopathology as covariates.

### Results

Descriptive, sociodemographic, and psychopathological features of the sample are presented in table 1. The experimental subgroups differ with respect to age—which is higher in NMI—and psychopathological dimensions; post hoc analysis confirms the expected increase in SDs, NSs, and FTD from NMI to SPD (specific patterns are detailed in table 1).

The multinomial logistic regression analysis (table 2) shows that SDs are significantly associated with all the experimental schizotypy groups compared with the base category, NMI. The relative risk ratio increases from NMI-ST to OPDs to SPD. Similarly, NSs and FTD model the schizotypal class allocation. Specifically, SDs and NSs contribute to predict NMI-ST, OPDs, and SPD. FTD contributes to OPDs and SPD. Among the sociodemographic variables, age shows a significant association with OPDs; however, the effect size is clinically marginal (ie, the chance of belonging to OPDs vs NMI group decreases of 3% for each year of difference in age).

The overall model explained a substantial part of the variance (Nagelkerke pseudo-$R^2 = 0.58$).

Table 3 presents the results of binary logistic regression: all the schizotypy classes have a significant effect on the odds of experiencing SDs. The effect of age is statistically significant yet, as in the previous analysis, of modest size (ie, 2–3 orders of magnitude below NMI-ST, OPDs, SPD). Gender and contextual psychopathology (ie, NSs and FTD) do not influence SDs odds. The overall model explained almost 40% of the variance (Nagelkerke $R^2 = 0.397$).

### Discussion

In this study, we examined the hypothesis that SDs are a core phenotypic manifestation of that “latent personality organization” (ie, schizotypy) that Meehl postulated as “a necessary but variable phenotypic embodiment of...
schizotypic vulnerability.” Specifically, our purpose was to test the capacity of SDs to detect subclinical configurations of schizotypy (graded as NMI, NMI-ST, OPDs, and SPD) in the nonpsychotic part of the SzSp.

Overall, the results are consistent with our research hypothesis. SDs are associated with increasing schizotypal phenotypic expressivity in nonpsychotic genetically high-risk populations. They display an increasing quantitative pattern from NMI to SPD, and the level of SDs increases the relative risk of displaying psychopathological features of schizotypy. Such pattern is mirrored by NSs and, partly, by FTD (which increases the odds of belonging to OPDs and SPD group), 2 symptom dimensions consistently reported as indicative of the constellation of traits that mark genetic vulnerability for schizophrenia.41–44 Also, as shown by the binary logistic regression, the odds of experiencing SDs are primarily associated with the degree of schizotypal expressivity, independent of concomitant psychopathology (ie, NSs and FTD).

The study corroborates the concept of SDs as a valuable, quantitatively tractable, trait phenotype for indexing genetic liability to SzSp. Indeed, although in previous studies we demonstrated that SDs are a distinguishing psychopathological feature of the SzSp disorders both in clinical28,34 and in genetically high-risk populations,36 this is the first study that shows their classificatory power with respect to subclinical configurations of the SzSp. Concretely, the “resolution power” of SDs as a liability marker extends beyond the clinical side of SzSp (ie, diagnosable SPD and Schizophrenia) to reach subthreshold manifestations in subjects with no personality disorder but detectable schizotypal traits.

This has certain (nontrivial) conceptual, empirical, and clinical implications. Briefly:

1. With respect to genetic research, it provides a possible delineation of specific quantitative traits—indicative of clinically unexpressed SzSp vulnerability—that

| Table 2. Multinomial Logistic Regression Analysis: Schizotypal Class Allocation as Outcome Variable |
|---------------------------------------------------------------------------------------------------------------|
| **Sociodemographic**                                                                                                                                 |
| Gendera                                                                                                                                   | 1.080 |
| Age (y)                                                                                                                                  | 0.975 |
| **Psychopathological**                                                                                                                  |       |
| Self-disorders                                                                                                                             | 1.646* |
| Negative symptoms                                                                                                                         | 1.207* |
| Formal thought disorder                                                                                                                 | 1.056 |

| Table 3. Binary Logistic Regression: Presence/Absence of Self-disorders as Outcome Variable |
|-----------------------------------------------|
| **Sociodemographic**                                                                 |
| Gendera                                                                                     | 0.84  |
| Age (y)                                                                                     | 0.97  |
| **Schizotypal class**                                                                         |       |
| NMI-ST                                                                                      | 3.76  |
| OPD                                                                                          | 5.24  |
| SPD                                                                                          | 25.06 |

| **Psychopathological**                                                                 |
| Negative symptoms                                                                            | 0.94  |
| Formal thought disorder                                                                      | 1.08  |

Note: NMI-ST, no mental illness with schizotypal traits; NMI, no mental illness; OPDs, other personality disorders; SPD, schizotypal personality disorder. Model fit: $\chi^2 = 167.27, df = 15, P < .0001$.

*aMale as reference category for gender.

*p < .05; **p < .01; ***p < .001.

Table 2.

| Sociodemographic | NMI-ST Vs NMI | OPD Vs NMI | SPD Vs NMI |
|------------------|---------------|------------|------------|
| Gendera          | Estimated Relative Risk Ratio | 95% Confidence Intervals | Estimated Relative Risk Ratio | 95% Confidence Intervals | Estimated Relative Risk Ratio | 95% Confidence Intervals |
| Gendera          | 1.080 | 0.409–2.849 | 0.535 | 0.225–1.273 | 0.686 | 0.244–1.928 |
| Age (y)          | 0.975 | 0.946–1.005 | 0.972* | 0.946–0.998 | 0.986 | 0.955–1.019 |

Table 3.

| Sociodemographic | Adjusted Odds Ratio | 95% Confidence Intervals | P Value | Wald Statistic |
|------------------|---------------------|--------------------------|---------|----------------|
| Gendera          | 0.84                | 0.43–1.61                | .5915   | 0.29           |
| Age (y)          | 0.97                | 0.95–1.00                | .0171   | 5.69           |
| Schizotypal class |                    |                          |         |                |
| NMI-ST           | 3.76                | 1.27–11.16               | .0169   | 5.71           |
| OPD              | 5.24                | 2.05–13.39               | .0005   | 11.98          |
| SPD              | 25.06               | 7.86–79.88               | <.0001  | 29.67          |

Psychopathological

| Negative symptoms | 0.94 | 0.88–1.01 | .1016 | 2.68 |
| Formal thought disorder | 1.08 | 1.00–1.17 | .0585 | 3.58 |

Note: NMI-ST, no mental illness with schizotypal traits; OPDs, other personality disorders; SPD, schizotypal personality disorder. Model fit: $\chi^2 = 76.03, df = 7, P < .0001$.

*aMale as reference category.

*bNMI as reference category.
can empower linkage and association studies and help illuminate the genetic architecture of the underlying schizotaxic diathesis.\textsuperscript{15,53}

2. From the viewpoint of the construct validity of SzSp, it provides a core feature that could serve as a prototypical trait on a continuum of expressivity ranging from subtle personality deviations to full-fledged clinical configurations.

3. With respect to early recognition research intervention programs, it can help supplement current criteria to identify people at risk of psychosis, enriching current prodromal and ultrahigh risk models (which mostly rely on state-like symptoms\textsuperscript{21,22}), with a candidate quantitative trait phenotype associated with schizotaxic risk.

4. Similarly, from the viewpoint of translational impact on clinical practice, it provides the rationale for the inclusion of SDs in clinical assessment practices. SDs (eventually explored with newly available interview checklists, such as SPI-A\textsuperscript{31} and EASE\textsuperscript{30}) can help form differential diagnoses indicating subjects with SzSp vulnerability and hence support more comprehensive clinical decision making, particularly in situations where diagnostic allocation is not immediate.\textsuperscript{54,55}

Finally, the observed relationships between SDs, NSs, FTD, and different classes of schizotypal expressivity warrants a comment. The significance levels obtained for each of the 3 models in the multinomial logistic regression (table 1) indicate that the independent psychopathological variables (SDs, NSs, FTD) significantly contribute to discriminate NMI-ST, OPDs, SPD from the reference class (NMI). This coheres with a multidimensional construct of schizotypy and confirms that NSs and FTD constitute subclinical features of schizotaxic vulnerability.\textsuperscript{56,57} Thus, a composite phenotype (dimensionally mapping SDs, NSs, FTD) may be even more useful.

\textbf{Limitations}

These results should be interpreted in the context of 6 main methodological limitations. First, our stratification of schizotypy in 4 classes is a rough approximation of clinically plausible thresholds, mostly performed for the purpose of hypothesis testing. Therefore, a more refined heuristic stratification of Meehl’s schizotypy continuum model is warranted. Also, the sample characterization in terms of diagnostic assessment was based on \textit{DSM-III-R} operational criteria, which are not optimal to capture all possibly relevant signs and symptoms of schizotypy. Second, all participants were members of multiplex families; hence, the reference category we used for the analysis, NMI (ie, subjects with no personality deviations and no schizotypal traits), still belongs by definition to a genetically high-risk population and cannot be equated to a community sample. However, this feature should reduce, rather than amplify, the quantitative differences in SDs across the experimental subgroups. Third, the assessment of SDs was performed by means of a psychometric proxy: a dimensional score obtained aggregating available psychopathological items (Appendix) assessed on the basis of their lifetime prevalence as trait features (see “Methods” section). This offers only an approximation of the potential range of manifestations of SDs and does not allow more detailed analysis (eg, explore features like intrusiveness, pervasiveness, and temporal coaggregation) that would have required more sophisticated instruments (eg, EASE\textsuperscript{30}).

Fourth, given the circumscribed experimental aim of the current study (ie, to test if SDs detect subclinical configurations of schizotypy in unaffected genetically high-risk subjects), we did not perform any further analysis to address the individual genetic risk of the participants. Indeed, given the complexity of the pedigrees, this could have not been done by the simple stratification (first degree, second degree, etc) but would require a computation of each family member’s true genetic vulnerability (ie, taking into account his unique position in the genogram and hence all his affected relatives, close and distant\textsuperscript{36}). Fifth, our use of only 2 domains of concomitant subclinical psychopathology, ie, NSs and FTD, may be an oversimplification of the multifaceted variability of SzSp psychopathology in unaffected family members, but there is no consensus in the field about the number of dimensions that best represents the full clinical picture of SzSp diathesis. Hence, to qualify schizotaxia, we opted to use NSs and FTD because of their historical prominence and the consistent empirical evidence in the literature.\textsuperscript{41–44} Finally, it ought to be pointed out that the study is based on a population sample, which is mainly nonclinical and only diagnosed in the contexts of a genetic research protocol. Thus, the diagnoses are not dependent on contact with treatment facilities, and the clinical expressivity—even in the case of OPDs and SPD—is plausibly less flamboyant than in patient population. This not only reduces the generalizability of the results outside genetically high-risk samples but also minimizes the phenotypic background noise due to the confounding effect of hospitalization, psychotropic medications, marginalized social status, and cognitive and personality deterioration.

\textbf{Conclusion}

Despite the profusion of candidate phenotypic taxonomies, the delineation of informative SzSp vulnerability phenotypes is still a vexing issue in contemporary research. This study, informed by Meehl’s schizotaxia-schizotypy model, tested the validity of anomalous self-experiences (SDs) as a candidate vulnerability phenotype in a sample of nonpsychotic, genetically high-risk subjects.

Our results confirmed the experimental hypothesis, showing that SDs’ classificatory power—previously
demonstrated for clinical conditions—also reaches those infraclinical conditions that constitute the silent part of the SzSp. This discriminatory power is comparable to that of alleged markers of schizotypic diathesis, such as subclinical NSs and FTD, and independent from concomitant psychopathology. This capacity to detect subclinical manifestations of schizotypy suggests that SDs form a promising candidate for tracking disease susceptibility in asymptomatic (ie, nonclinical) genetic carriers.

Future research should test:

1. if SDs, besides covarying with the likelihood of expression of schizotypal configurations, are also proportional to the degree of genetic relatedness (taking into consideration the complex architecture of pedigrees) and follow the same transgenerational pattern of transmission;
2. the longitudinal stability and predictive value of SDs with respect to the lifetime development and expression of schizotypy.

Finally, the results indicate a multidimensional model of schizotypal vulnerability (including SDs, NSs, and FTD as composite descriptors) as an empirically grounded prototype to address the heritable SzSp predisposition.

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Appendix. Self-Disorder Scale, Item Composition

| Copenhagen Interview of Functional Illness (Section and Item Code) | Content |
|---------------------------------------------------------------|---------|
| Personality exploration—11                                  | Gender identity problems/anxiety of being homosexual (refers not to homosexuality but to pervasive lack of identity) |
| Personality exploration—12a                                  | Identity disturbance, does not know who he/she is (like a sense of being extraterrestrial) |

Appendix Table. Continued

| Copenhagen Interview of Functional Illness (Section and Item Code) | Content |
|---------------------------------------------------------------|---------|
| Subjective experience—12                                      | Often feels self is different at different times (as numerically different) |
| Subjective experience—25                                     | Frequent shifts in opinion about how he/she should live life (loss of natural engagement, hyperreflexivity) |
| Subjective experience—28                                     | Feels perplexed, confused, or has lost feelings of the world’s naturalness or meaning |
| Subjective experience—47                                     | Has lost leniency and needs to reflect on the simplest things (hyperreflexivity) |
| Subjective experience—48                                     | Feels he/she has no feelings for him/herself and/or the world |
| Subjective experience—51                                     | Feels that he/she is not really alive |
| Subjective experience—52                                     | Thought block |
| Subjective experience—54                                     | Thought emptiness |
| Subjective experience—55                                     | Feels that he/she is disappearing |
| Subjective experience—57                                     | Feels that there are no boundaries between him/herself and the surroundings |
| Subjective experience—71                                     | Feels he/she has lost all feelings of pleasure (anhedonia) |
| Subjective experience—87                                     | Feels like a stranger to him/herself |
| Subjective experience—89                                     | Loss of thought control |
| Subjective experience—98                                     | Thought pressure |
| Subjective experience—100                                    | Thoughts are felt strange and anonymous |
| Subjective experience—101                                    | Thought can be apprehended by others |
| Subjective experience—102                                    | Feels that his/her appearance changes when he/she looks in the mirror |
| Subjective experience—103                                    | Feels it is necessary to concentrate on body movements that normally are completed automatically and without reflection |
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