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Developing Psychosis and Its Risk States Through the Lens of Schizotypy

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Starting from the early descriptions of Kraepelin and Bleuler, the construct of schizotypy was developed from observations of aberrations in nonpsychotic family members of schizophrenia patients. In contemporary diagnostic manuals, the positive symptoms of schizotypal personality disorder were included in the ultra high-risk (UHR) criteria 20 years ago, and nowadays are broadly employed in clinical early detection of psychosis. The schizotypy construct, now dissociated from strict familial risk, also informed research on the liability to develop any psychotic disorder, and in particular schizophrenia-spectrum disorders, even outside clinical settings. Against the historical background of schizotypy it is surprising that evidence from longitudinal studies linking schizotypy, UHR, and conversion to psychosis has only recently emerged; and it still remains unclear how schizotypy may be positioned in high-risk research. Following a comprehensive literature search, we review 18 prospective studies on 15 samples examining the evidence for a link between trait schizotypy and conversion to psychosis in 4 different types of samples: general population, clinical risk samples according to UHR and/or basic symptom criteria, genetic (familial) risk, and clinical samples at-risk for a nonpsychotic schizophrenia-spectrum diagnosis. These prospective studies underline the value of schizotypy in high-risk research, but also point to the lack of evidence needed to better define the position of the construct of schizotypy within a developmental psychopathology perspective of emerging psychosis and schizophrenia-spectrum disorders.

Key words: schizophrenia/prodrome/adolescence/basic symptoms/development

Introduction

Schizophrenia and other psychoses continue to be a significant cause of disability-adjusted life years (DALYs). Moreover, despite the fact that only a small proportion of cases emerge during childhood and early adolescence,[1] they belong to the 10 main causes for DALYs already in 10–14-year-old boys.[2] The full-blown clinical picture typically emerges during late adolescence and young adulthood. Increasingly conceptualized as a neurodevelopmental "brain disorder," psychoses represent the third most costly brain vulnerability in Europe.[3] Thus, for the last 2 decades, increasing efforts have been put into developing early detection methods and preventive interventions before the development of a first episode of psychosis.[4]

Historically, the inherently *developmental* nature of psychosis has already been suggested in the definitions put forward by pioneers such as Emil Kreapelin and Eugen Bleuler who described latent forms of schizophrenia in relatives of schizophrenia patients.[5,6] Rado[7] and Meehl[8] took up such observations in their development of a construct that they named *schizotypy* as a shorthand expression for the psychodynamic expression of the genetic vulnerability to develop schizophrenia. Taking on a dimensional perspective, these observations and theories suggested a *spectrum* of schizophrenic disorders, which, in some extreme cases and/or under unfavorable conditions, unfold into a clinically significant illness. In other words, efforts were taken to chart the developmental trajectories to illness hoping to perhaps deviate these trajectories onto less pathogenic paths at an early stage.

Today, this dimensional nature of schizophrenia-spectrum disorders is explicitly formulated in developmental terms, most notably by the dominant "neurodevelopmental" hypothesis.[9]

Surprisingly perhaps from this historical perspective, schizotypy research, with some notable exceptions,[10–12] has devoted little attention to examining developmental trajectories. Nevertheless, research on the clinical high risk (CHR) and emergence of psychotic disorders, including the "ultra-high risk" (UHR) approach[13] in help-seeking samples and the psychometric approach to "Psychotic-Like Experiences" (PLEs)[14] in the general population, clearly relate to schizotypy. In fact, assessment instruments developed in these approaches, and particularly those developed to assess UHR criteria, include phenomena typically assessed as traits in schizotypy, in particular positive symptoms of Diagnostic and Statistical Manual of Mental Disorders (DSM) schizotypal personality disorder such as unusual thought contents or magical thinking.[15] The appointed trait-state characteristic of similar phenomena is the most important difference between UHR and schizotypy assessments as the former, particularly in its American operationalization by the "Structured Interview of Psychosis-Risk Syndromes, SIPS"[16] a(table 1), requires a state characteristic and therefore necessitates to fulfill an "onset/worsening" requirement.[15] Therefore cases where subclinical psychotic or schizotypal manifestations have "trait" character (stability during the past) are excluded from the symptomatic UHR criteria. This "state" requirement is also inherent to the Attenuated Psychosis Syndrome[17] newly included as a self-contained disorder in the research section of DSM-5.[18]

For these close phenomenological links between trait-schizotypy and state-CHR, the current review critically assesses the value of the schizotypy construct for the prediction of psychosis in different population segments: the general population, genetic high risk samples, nonpsychotic patient samples with schizophrenia-spectrum disorder, and nonpsychotic patient samples meeting current CHR criteria.

State of the Art in Early Detection of Clinical High-Risk States of Psychosis

Psychoses are etiologically heterogeneous disorders, associated to a variety of known risk factors. These include genetic factors that are among the strongest risk factors but still lack sufficient explanatory power for the emergence of psychosis.[19] Psychotic disorders are generally preceded by a prodromal phase of several years on average[20] that might already lead to help seeking for mental problems.[21] CHR research has therefore favored an indicated prevention approach on symptomatic individuals experiencing the first signs of the emerging disorder, rather than a selective or universal prevention approach, focusing on symptom-free individuals with specific risk factors or on general population samples.[22] With this focus on help-seeking clinical samples, early detection research clearly differs from the main focus of schizotypy research, ie on (genetic) risk samples or general population samples.

From the perspective of indicated prevention of psychoses, 2 main concepts are usually applied when identifying individuals in an CHR state:[4] the UHR criteria that focus on detecting an imminent risk of psychosis[23] and the basic symptom criteria that focus on the detection of the earliest possible specific symptom.[24] The 2 partially overlapping basic symptom criteria, "cognitive-perceptive basic symptoms" (COPER) and "cognitive disturbances" (COGDIS), include subtle self-experienced disturbances in thought, speech, and visual and acoustic perception processes. These are often not observable to others and are self-reported as phenomenologically different from mental states considered the "normal" premorbid self. As such, basic symptoms are clearly distinguishable from subtle disturbances described as traits in those at genetic high-risk[25,26] and also from the observable odd speech and the unusual perceptual experiences as described in schizotypy. Irrespective of differences in their assessment, UHR criteria generally allow the identification of 3 subgroups of CHR patients:[15] (1) attenuated positive psychotic symptoms (APS), (2) brief limited intermittent psychotic symptoms below DSM-IV's duration criteria for a brief psychotic episode,[27] and (3) genetic risk, ie, familial risk or patient with schizotypal personality disorder (SPD), plus recent significant functional decline. Patients with APS consistently account for the majority of UHR patients.[17] APS were modeled both on "psychotic-like experiences" defined by Chapman and Chapman[28] as delusional and hallucinatory phenomena in that some insight is still maintained, and on the 5 positive DSM-III-R prodromal symptoms of schizophrenia[29] that are phenomenologically equal to the positive symptoms in the definitions of the clinical manifestation of schizotypy, ie, DSM-IV's SPD and ICD-10's schizotypal disorder (SD)[30] (table 1). Thus the main differences between the APS UHR criterion in its definition by the SIPS,[16] SPD, SD, and the recent Attenuated Psychosis Syndrome, are (1) the inclusion of additional, mainly negative and disorganized symptoms in the criteria for SPD and SD; (2) the number of symptoms required; and (3) the onset and frequency criteria and, related to these, the differential emphasis put on the state and trait character of defining symptoms (table 1).

Irrespective of the applied CHR criteria, the conversion rate in CHR samples to first-episode psychosis, mainly of the schizophrenia spectrum, was estimated to range from 18% at 6 months, 22% at 1 year, 29% at 2 years, to reach 36% at 3 years;[4] as such, it shows a several 100-fold increase compared to the 0.035% 12-month incidence of psychosis in the community[31]

Table 1. Comparison of the Attenuated Psychotic Symptoms (APS) UHR Criterion According to the "Structured Interview of Psychosis-Risk Syndromes" (SIPS)[16] With the Diagnostic Criteria of SPD, Schizotypal Disorder, and Attenuated Psychosis Syndrome

APS Psychosis-Risk Criterion (SIPS 5.0)	Schizotypal Personality Disorder (SPD) (DSM-IV-TR: 301.22)	Schizotypal Disorder (SD) (ICD-10: F21.0)	Attenuated Psychosis Syndrome (DSM-5, Section III)
Number of symptoms required: one or more SIPS item P1–P5 with a score of 3–5 (see below)	*Number of symptoms required*: 5 or more of the criteria-relevant symptoms detailed below	*Number of symptoms required*: 4 or more of the criteria-relevant symptoms detailed below	*Number of symptoms required*: one or more of the criteria-relevant symptoms detailed below
Onset: first appearance within the past year or current rating one or more scale points higher compared to 12 mo ago	*Onset*: symptoms form an enduring pattern of long duration and its onset can be traced back at least to adolescence or early adulthood	*Onset*: symptoms must have manifested over a period of at least 2 y	*Onset*: first appearance within the past year or current rating one or more scale points higher compared to 12 mo ago
Frequency: symptoms have occurred at an average frequency of at least once per week in the past month	*Frequency*: pattern is stable, inflexible, and pervasive across a broad range of personal and social situations	*Frequency*: symptoms must have manifested over this period either continuously or repeatedly	*Frequency*: symptoms have occurred at an average frequency of at least once per week in the past month
	Disability: the enduring pattern leads to clinically significant distress or impairment in social, occupational, or other important areas of functioning		*Disability*: symptom(s) is sufficiently distressing or disabling to the individual to warrant clinical attention
Exclusion: symptom(s) is not due to the direct physiological effects of a substance or a general medical condition; and not better explained by another DSM-5 diagnosis and has never been severe enough to meet diagnostic criteria for a psychotic disorder	*Exclusion*: not due to the direct physiological effects of a substance or a general medical condition; does not occur exclusively during the course of Schizophrenia, a Mood Disorder With Psychotic Features, another Psychotic Disorder, or a Pervasive Developmental Disorder	*Exclusion*: The subject must never have met the criteria for any disorder in F20 (Schizophrenia)	*Exclusion*: symptom(s) is not due to the direct physiological effects of a substance or a general medical condition; and not better explained by another DSM-5 diagnosis and has never been severe enough to meet diagnostic criteria for a psychotic disorder
Criteria-relevant symptoms			
P1 Unusual Thought Content/delusional Ideas (includes odd beliefs, magical thinking, and delusions not held with absolute conviction)	Odd beliefs or magical thinking that influences behavior and is inconsistent with subcultural norms (eg superstitiousness, belief in clairvoyance, telepathy, or "sixth sense"; in children and adolescents, bizarre fantasies or preoccupations); ideas of reference—nonparanoid	Odd beliefs or magical thinking influencing behavior and inconsistent with subcultural norms	Delusion in an attenuated form
P3 grandiose ideas			
P2 suspiciousness/ persecutory ideas	Suspiciousness or paranoid ideation; ideas of reference—paranoid	Suspiciousness or paranoid ideas	
P4 Perceptual abnormalities/hallucinations (derealization is part of P1, depersonalization is part of one negative symptoms item, N4)	Unusual perceptual experiences, including bodily illusions	Unusual perceptual experiences including somatosensory (bodily) or other illusions, depersonalization, or derealization	Hallucination in an attenuated form
P5 disorganized communication	Odd thinking and speech (eg vague, circumstantial, metaphorical, over-elaborate, or stereotyped)	Vague, circumstantial, metaphorical, over-elaborate, or often stereotyped thinking, manifested by odd speech or in other ways, without gross incoherence	Disorganized speech in an attenuated form

Table 1. *Continued*

APS Psychosis-Risk Criterion (SIPS 5.0)	Schizotypal Personality Disorder (SPD) (DSM-IV-TR: 301.22)	Schizotypal Disorder (SD) (ICD-10: F21.0)	Attenuated Psychosis Syndrome (DSM-5, Section III)
	Additional symptoms: inappropriate or constricted affect; behavior or appearance that is odd, eccentric, or peculiar; lack of close friends or confidants other than first-degree relatives; excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgments about self	*Additional symptoms*: inappropriate or constricted affect, subject appears cold and aloof; behavior or appearance which is odd, eccentric, or peculiar; poor rapport with others and a tendency to social withdrawal; ruminations without inner resistance, often with dysmorphophobic, sexual, or aggressive contents; occasional transient quasi-psychotic episodes with intense illusions, auditory, or other hallucinations and delusion–like ideas, usually occurring without external provocation	

Note: DSM, Diagnostic and Statistical Manual of Mental Disorders.

and significantly higher conversion rates than CHR-negative help-seekers in specialized early detection services.[32] More recent studies combining UHR and basic symptom criteria reported a conversion rate of patients meeting both basic symptom (especially COGDIS) and UHR criteria (especially APS) that was roughly 3 times higher than that of patients meeting one but not the other criterion.[33,34] However, real long-term conversion data is only slowly accumulating, and from one UHR sample (N = 311; mean follow-up: 7.5 ± 3.2 years), an overall conversion rate of transition was estimated to reach 35% over a 10-year period,[35] while from one basic symptom sample (N = 160; mean follow-up: 9.6 ± 7.6 years), an overall conversion rate across the follow-up of 65% for COPER and 79% for COGDIS was reported.[36,37] Thus, in order to improve prediction and reduce the rate of nonconverters, the search for additional predictors continues on all possible levels—from psychopathology to genetic factors including schizotypy as a possible expression of a genetic liability.[4]

Yet, nonconverters of CHR samples do not generally have a favorable outcome: a recent study showed that in 34%–82% nonconverters, UHR symptoms persisted over 1–3 years;[13] 40% had poor social or role outcomes after 3 years;[38] and 75% were diagnosed with anxiety, affective or substance use disorder after 1 year.[39] Thus, it was concluded that APS in particular predict more severe mental conditions and not only psychoses.[38,39] Along this line of argument, an Attenuated Psychosis Syndrome (table 1) was tentatively included in DSM-5[18] as a self-contained disorder with treatment focus on current symptoms but not a risk syndrome with treatment focus on prevention of assumed future psychotic symptoms.[40]

Thus, while current CHR criteria already provide good starting-points to detect emerging psychotic disorders, the predictive and discriminative power to parse nonconverters from converters should be further improved to identify a target group for specific preventive interventions.[4] To date, it is not yet clear how the trait construct of schizotypy could complement CHR state assessment beyond the minor role it currently plays as a risk factor in the UHR GRDF criterion. Further, it remains to be shown how schizotypy could be conceptualized with regards to emerging schizophrenia-spectrum disorders. Critically, the relationship between schizotypy and clinical outcome needs to be evaluated if researchers are to refer to schizotypy as a potent object of clinical research. In order to evaluate the link between schizotypy and clinical outcome, in particular psychosis, the following section provides an overview of longitudinal studies on the role of schizotypy as a potential predictor of psychotic disorders that might also act as an amplifier in CHR samples (figure 1).

Schizotypy in Emerging Psychosis

In the following selection of studies, the potential links between the multidimensional schizotypy construct and emerging psychosis as defined by positive symptoms are examined. In our conceptualization of schizotypy, we followed the broad description provided by Nelson and colleagues in their recent review.[41] Despite some disagreement regarding the underlying factor structure of schizotypy, they concluded that the prevailing current understanding of schizotypy is that it is comprised of 3 factors, which broadly correspond to the positive,

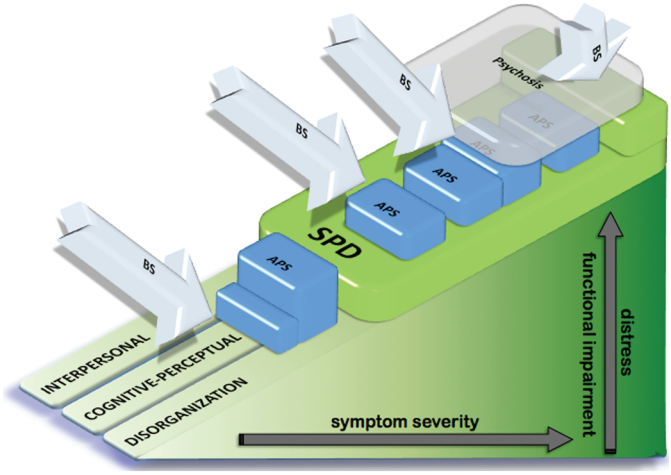

Fig. 1. Model of the assumed relationship and interactions between dimensions of schizotypy, clinical expressions of schizotypy, symptomatic CHR criteria, and overt psychosis. In line with Rado's and Meehl's description, this dimensional model assumes a distribution of schizotypal characteristics in the general population from absence via clinically significant expressions in terms of schizotypal (personality) disorder (SPD) to the most extreme, ie, psychotic expression, with increasing severity of schizotypy being associated with higher levels of distress and/or functional impairment. Attenuated psychotic symptoms (APS) might appear at as a clinical manifestation or as an exacerbation of the underlying schizotypy, in particular of features of the cognitive-perceptual and, though to a lesser degree, the disorganization dimension. The occurrence of APS might be triggered by aberrations in information processing at neurobiological level that are perceived and expressed as basic symptoms, in particular of cognitive-perceptive basic symptoms and cognitive disturbances. Neurobiological aberrations have been consistently described in multitude for patients with psychosis, while physiological correlates of schizotypy in terms of a trait or biomarker are yet to be discovered.

negative and disorganized dimensions of schizophrenia (figure 1). The first "positive" factor is the "cognitive-perceptual factor," which includes magical thinking, unusual perceptual experiences, ideas of reference and paranoia. Another "disorganized factor" includes odd behavior and odd speech. The third is the "interpersonal factor," which resembles the negative dimension of schizophrenia and includes constricted affect, social anxiety, lack of close personal relationships, and suspiciousness. Consequently, we did not include studies that only assessed the dimensions of hypomania or impulsiveness/nonconformity (or Eysenck's psychoticism scale that had informed the initial definition of impulsiveness/nonconformity) that are currently related to and primarily examined in emerging affective disorders.[42,43]

Literature Search

About 219 potential studies of interest were retrieved from PubMed for the search: schizotypy AND (psychosis OR schizophrenia) NOT (neurocognitive OR psychological OR genetic OR imaging OR EEG OR psychometric); these were complimented by a subsequent screening of the qualifying articles' references. For the selection of qualifying articles, we employed the following criteria:

1. Study had a prospective longitudinal design with a minimum of 2 assessment points.
2. Outcome assessments included a clinical measure of psychosis (either a categorical diagnosis or a dimensional scale for the assessment of frank positive psychotic symptoms).
3. Baseline assessments included a measure of at least 2 dimensions of the triad of schizotypy: positive schizotypy (cognitive-perceptual phenomena), negative schizotypy (interpersonal/affective phenomena) and/or disorganization schizotypy (cognitive-behavioral phenomena). In effect, the third criterion excluded a number of epidemiological studies measuring PLEs that heavily rely on the positive dimensions of subclinical expression.
4. Longitudinal analyses assessed the relationship between the baseline schizotypy assessment(s) and the clinical outcome measure(s).

There was no restriction related to sample characteristics, and 4 types of samples were identified: general population samples, CHR samples (as defined in the previous section), genetic risk samples (familial risk; first- and second-degree relatives), and clinical samples with a nonpsychotic schizophrenia-spectrum disorder, ie, schizotypal or schizoid personality disorders. A total of 18 studies (15 independent longitudinal samples) qualified for our review. A summary of their main characteristics and findings is provided in table 2.

General Population Samples

Four independent samples encompassing a total of 7282 participants were included in studies spanning from 5 to 50 year study intervals (table 2). All studies suggested that ratings of schizotypal dimensions significantly relate to later development of either psychotic disorders or schizophrenia spectrum disorders.[44–49] More specifically, they suggest that the positive dimension is mainly associated to the later emergence of psychotic disorders, while the negative dimension (especially anhedonia) is rather selectively associated with the emergence of nonpsychotic schizophrenic-spectrum disorders. Information on the disorganization dimension was completely missing as none of these general population studies had assessed this dimension (table 2).

These results may inform large-scale screening and primary prevention strategies in the general population. Further, they suggest that in psychosis high-risk research schizotypy should not be reduced to its positive dimension but assessed multidimensionally (both

Table 2. Outline of the Reviewed Longitudinal Studies Linking Schizotypy to Clinical Outcome in 4 Different Types of Studies: General Population Studies, Clinical Studies of ARMS Samples, Genetic Risk Studies, and Clinical Studies of Patients Diagnosed With SPD, SD, or Schizoid PD

Study	Sample	Age (*n*)	Study Interval	Schizotypy Assessment	Conversion to Psychosis
General population studies					
Kwapil et al[44]	General pop. (College students)	Mean age 19.3 y (*n* = 534)	10 y	SADS-L; Wisconsin manual for assessing psychotic–like experiences; positive and negative schizotypy	Positive and negative schizotypy predict Schizophrenia spectrum disorders (*n* = 5); only positive schizotypy predicts psychotic disorders (*n* = 14)
Kwapil[45]	Same sample as Kwapil et al[44]			Same assessment as Kwapil et al[44]	24% of high scorers on the Revised Social Anhedonia Scale develop Schizophrenia spectrum by age 30
Chapman et al[46]	Same sample as Kwapil et al[44]			Same assessment as Kwapil et al[44]	5% of high scorers on the Perceptual Aberration or Magical Ideation Scales developed Schizophrenia over 10 y; 40% if identified with criteria combining Magical Ideation and the Revised Social Anhedonia Scale
Miettunen et al[47]	General pop (Northern Finland 1966 Birth cohort)	31 y (*n* = 4871; assessed in 1997; excluding *n* = 55 with previous psychotic diagnosis)	11 y (hospitalizations between 1998 | and 2008)	Perceptual Aberration, Physical and Social Anhedonia scales (Chapman Scales); Hypomanic Personality scale; Bipolar II scale; Schizoidia Scale; and Temperament and Character Inventory	Social Anhedonia and the Hypomanic Personality scale showed consistently higher scores in persons developing any psychotic disorder after the age of 31 (*n* = 30) than those not developing a mental disorder (*n* = 4734). Physical anhedonia was significantly lower in those developing psychosis than in those developing another mental disorder (*n* = 107)
Bogren et al[48]	General pop.	0–92 y, median age 33 y (*n* = 1797)	40–50 y	Semistructured clinical interview of schizoid and schizophrenia-related personality features	"Paranoid-schizotypal" rating as one of 4 predictors of psychosis (*n* = 61), but not schizophrenia (*n* = 17).
Gooding et al[49]	General pop. (College students)	Mean age 23.8 y (*n* = 135)	5 y	Same assessment as Kwapil et al[44]	PerMag risk group double % of schizophrenia spectrum disorders (all SPD) than controls (*n* =8)
Studies in clinical samples with clinical high risk (CHR) state of psychosis					
Salokangas et al[50]	CHR sample; UHR & COGDIS	16–35 y, mean age 22.4 y (*n* = 245)	18 mo	Schizotypal Personality Questionnaire (SPQ)	Subscales "Ideas of reference" and "no close friends" were predictors of conversion to psychosis (*n* = 39)
Ruhrmann et al[33]	same CHR sample as in Salokangas et al. 2013			SIPS-defined SPD (presence of only at least 1 y required)	SIPS-defined SPD was one of 6 predictors of psychosis included in the predictor model
Schultze-Lutter et al[51]	CHR sample; UHR and COPER	16–38 y (*n* = 100) converters (*n*= 50) and risk-, age- and gender-matched nonconverters (*n* = 50)	1–5.5 y (46 ± 17 mo)	Selbstbeurteilung nach der Aachener Merkmalsliste für Persönlichkeits-störungen (SAMPS); (Self-assessment according tot he Aachen symptom list for personality disorders)	Only schizoid subscale score was a significant though weak predictor of conversion; in particular items "lack of close friends or confidants other than first-degree relatives" and "emotional detachment observed by others"

Table 2. *Continued*

Study	Sample	Age (*n*)	Study Interval	Schizotypy Assessment	Conversion to Psychosis
Mason et al[52]	CHR sample; UHR	13–28 y, mean age 17.3 y (*n* = 74)	1–2 y (26 ± 9 months)	SPD subscale of the International Personality Disorder Examination (IPDE) and Assessment of Prodromal and Schizotypal Symptoms (APSS)	Only schizotypal personality characteristics led to a significant increase in predictive power of UHR criteria for conversion to psychosis (*n* = 37), but considered as of low clinical utility
Klosterkötter et al[36]	Clinical sample suspected to develop psychosis	Mean age 29.3 y (*n* = 160)	≥5 y (9.6 ± 7.8 y)	Clinical diagnosis of personality disorders (DSM-III-R criteria)	Irrespective of the presence of CHR criteria, only SPD of all baseline diagnoses was significantly related to the subsequent development of schizophrenia (*n* = 79) in the total sample
Genetic risk studies					
Shah et al[53]	Genetic-high risk	8–25 y, mean age 15.9 y (*n* = 96)	2.4 ± 1 y	Perceptual Aberration, Magical Ideation and Social Anhedonia scales (Chapman Scales)	The 3 scales were significant predictors within the multivariate risk algorithm for psychosis (*n* = 12)
Johnstone et al[54]	Genetic high risk and "well" controls	16–25 y, mean age 21.2 y (*n* = 173)	5 y	Structural Interview for Schizotypy (SIS) and Rust Inventory of Schizotypal Cognitions (RISC)	SIS total score and subscales "Oddness" and "Social withdrawal factor" as well as RISC total score constituted 4 of 5 predictors of conversion to schizophrenia (*n* = 20)
Carter et al[55]	Genetic high risk	9–22 y, mean age 15.1 y (*n* = 207)	25 y	Minnesota Multiphasic Personality Inventory (MMPI)	Wiggin's Psychoticism scale of MMPI as a predictor of schizophrenia (*n* = 31)
Erlenmeyer-Kimling et al[56]	Genetic high risk and clinical and normal controls	7–12 y, mean age 9.5 y (*n* = 161)	9–11 y	Physical Anhedonia Scale (PhyA)	Physical anhedonia as a direct precursor of psychosis (*n* = 13) in females but not males
Clinical studies of patients diagnosed with SPD, SD or schizoid PD					
Nordentoft et al[57]	Patients with SD	18–45 y mean age 24.9 y (*n* = 79)	2 y	ICD-10 diagnosis	Rate of conversion to psychotic disorder: 25% in specialized treatment group and 48% in standard care group (total diagnosed with psychotic disorder = 23)
Wolff et al[58]	Children clinically diagnosed as "schizoid"	4.3–14.6 y, mean age at first referral 9.83 y (*n* = 32)	≥20 y	Clinical semistructured interview	Three quarters if clinical sample developed SPD during adults, while 6.25% (*n* = 2) were diagnosed with a schizophrenia-spectrum psychotic disorder
Fenton and McGlashan[59]	Inpatients; DSM-III borderline or SPD	Mean age 29 y (*n* = 105)	Mean 15 y after discharge	DSM-III-SPD	"magical thinking," "social isolation," suspiciousness/ paranoid ideation" as predictors of psychosis (*n* = 18)

Note: DSM, Diagnostic and Statistical Manual of Mental Disorders; SD, schizotypal disorder according to ICD; SPD, schizotypal personality disorder (PD) according to DSM.

the positive and negative dimensions) to enable a differential risk assessment for psychotic disorders on the one hand, and nonpsychotic personality-related disorders on the other.

Studies in Clinical High-Risk Samples

We identified 5 CHR studies on 4 samples with a total of 369 patients and follow-ups ranging from 18 months to 5.5 years (table 2).[33,36,50–52] Irrespective of whether

self-report questionnaires or clinical semistructured interviews were used in the assessment of schizotypy, there was some though not consistent indication that schizotypal dimensions might play a role in the conversion to psychosis in patients already identified at CHR prior to and independently from schizotypy assessment. One of the key questions with regard to this particular clinical population is whether the addition of an assessment of schizotypy can significantly increase the predictive power of already-existing CHR criteria. In addressing this question, Mason et al.[52] argued that, from a statistical point of view, schizotypy might increase the predictive power of UHR criteria; however, from a clinical point of view, this contribution might be of limited actual value. Indeed, comparing the schizotypy scores between converters and nonconverters in this study did not yield a critical difference that could be meaningfully implemented in clinical practice (only a 2 scale-point increase in converters, representing a measure difference below 2 standard deviations). Furthermore, the study did not clearly distinguish trait manifestations (long lasting—2 to 5 years) from state manifestations (present within the past month), a distinction necessary to establish the role of schizotypy in the psychotic developmental process.

Overall, CHR studies suggest that, contrary to the findings in general population samples, the positive dimension of schizotypy was of little, if any value in terms of increasing the psychosis-predictive accuracy in samples already considered to be prone to psychosis for UHR and/or basic symptom criteria. Rather, when schizotypy was differentially assessed, the interpersonal, negative dimension seemed to explain additional variance and to assist the detection of converters to psychosis. With regard to the large phenomenological overlap between UHR criteria, in particular APS, and the positive and disorganized dimensions of schizotypy but not with its negative dimension (table 1), this finding is hardly surprising. However, all but one study on CHR patients[33] had rather short follow-ups that might not have been sufficient to detect an insidious development of psychosis in patients with more pronounced schizotypy (figure 1).

As early detection is moving increasingly into younger age groups, the need to distinguish between developing but stable schizotypal traits or SPD, and developing but novel psychotic symptoms or APS in children and adolescents becomes more imperative.[1,60] Further, CHR patients with high scores on schizotypy measures might in general require an adaptation in early intervention techniques; these should not only address positive symptoms of schizotypy or APS (such as unusual thought contents) as a—possibly neurobiological based—deviation from premorbid information processing but also the general aberrant information processing style and way to experience and interpret the world (figure 1). Moreover, standard care interventions might not be optimally suited to address the needs of patients with pronounced negative features of the interpersonal dimension not captured by CHR criteria (figure 1) whose personality traits and ensuing social environment are characterized by enduring social withdrawal and poverty of interpersonal relationships. Clinical research is only starting to address these questions.[61,62] Furthermore, from a neuropharmacological point of view, symptom profiles with more pronounced negative/interpersonal and disorganization dimensions are still not adequately addressed by current treatment guidelines of schizophrenia.[63] Thus, current evidence seems to be in favor of the inclusion of a multidimensional assessment of schizotypy in CHR studies, in particular as current and future clinical research move into the evaluation of early intervention strategies.[64]

Genetic High-Risk Samples

The 4 identified studies on samples at genetic risk for psychosis included a total of 637 offsprings (first- or second-degree relatives) of patients diagnosed with schizophrenia, and covered follow-ups between 8 and 25 years.[53–56] Similar to general population studies, schizotypy dimensions were found to be significantly associated with the later emergence of psychotic disorders in genetic high-risk samples. However, no clear pattern of associations between schizotypal dimension and either psychotic or schizophrenic-spectrum disorders emerged. Yet, substantially different assessment methods were employed over the 20-year span covered by these studies (1993 and 2012) that may have contributed to the heterogeneity of findings. The most recent study by Shah and colleagues,[53] underscored the pre-eminence of schizotypy amongst a variety of predictive risk factors from etiological (degree of relatedness to family member with schizophrenia: genetic risk), to environmental (cannabis use, obstetric complications, welfare), and cognitive (IQ, perseveration, verbal fluency) assessments. In a multivariate structural equation model, only baseline ratings on the Chapman scales (Magical Ideation, Perceptual Aberration, and Social Anhedonia Scales) were directly and positively related to conversion to psychotic disorders. Interestingly, many risk factors included in this analysis represent distal factors that might also be developmentally significant to schizotypy, as most of them significantly correlate with adolescent expression of trait schizotypy.[65] For this reason, it has been argued that schizotypal traits during adolescence could represent a developmental link between early risk factors and later development of psychotic disorders (Debbané & Barrantes-Vidal, this issue). However, more longitudinal research on the complex relationships between early and intermediate risk indicators for psychosis is needed to examine this assumption.

Clinical Studies of Patients Diagnosed With SPD, SD, or Schizoid PD

The 3 studies that examined the development of psychosis in patients characterized by a clinically relevant expression of schizotypy (ie, SPD, schizoid PD, or SD) but with no information on psychometric schizotypy and thus on the different dimensions involved 376 patients followed for 2–20 years.[57,58,66] Ever since introducing the diagnosis of SPD into the DSM, the actual rate of conversion from SPD to schizophrenia-spectrum psychosis has been an object of speculation.[67] In a recent study on adult in- and outpatients diagnosed with SPD, the conversion rates to a psychotic disorder varied between 25% and 48%.[57] Suspected SPD in children however seldom led to the later emergence of a schizophrenic-spectrum psychotic disorder (only 6.25%), although SPD will ensue in 3 quarters of the cases.[68] Thus, an association between SPD and psychosis is clearly indicated yet its details necessitate further validation. Future studies of this clinical group should therefore provide dimensional scores of schizotypy to clarify the possible patterns of associations between SPD and emerging psychotic disorders.

General Results and Limitations

Taken together, the above studies of schizotypy in general population, CHR, genetic risk and non-psychotic schizophrenia-spectrum disorder samples suggested a longitudinal associations between measurements of schizotypy and later development of a psychotic disorder. The literature search, however, was likely biased towards positive results, because studies that had included schizotypy as just one of many potential predictors but failed to find a significant schizotypy–related result (such as the NAPLS study)[69] unlikely mention schizotypy in title, key words, or abstract. Consequently, these negative findings would be undetected in our literature search.[69] Furthermore, while associations between schizotypy and schizophrenia-spectrum disorders were reported in some instances,[44,45] they necessitate further replication from independent samples in studies specifically designed to address this topic. Importantly, most studies lack a consistent evaluation of the disorganization dimension of schizotypy, a dimension associated with the developmental process of schizotypy during adolescence,[70,71] and with known endophenotypes of schizophrenia.[72]

Schizotypy in the Field of High-Risk for Psychosis Research

Longitudinal studies assessing the relationship between schizotypy and clinical outcome pointed towards the construct of schizotypy—in clinical as well as psychometric terms—as a significant though weak predictor of psychosis. Importantly, the results indicated the importance of the multidimensionality of the schizotypy construct, and the value of assessing at least both the positive (cognitive-perceptual) and negative (affective-interpersonal) dimensions of schizotypy. As the third, ie, the disorganized dimension was unconsidered by studies, their psychosis-predictive value remains to be investigated. Several other points, however, require further examination. Firstly, it is not clear whether dimensions of schizotypy preferentially predict the emergence of psychotic disorders in general, or more specifically schizophrenia-spectrum psychotic disorders. Studies do not always distinguish between different subclassifications of psychotic and schizophrenia-spectrum psychotic disorders, which would be necessary to gain better insight in this issue. Secondly, gender differences that are frequent in personality disorders and dimensions[73,74] have not been systematically investigated; only one study reported Physical Anhedonia as specifically related to risk in female participants.[56] Thirdly, age-related peculiarities in the assessment of schizotypy have not been studied. Yet, research on adolescents from the community suggested higher prevalence rates of, particularly perception–related APS in younger adolescents,[75] and a similar age bias was observed in adolescent positive schizotypy.[70] Such age-related characteristics may well lower the risk for psychosis by (attenuated) hallucinations and/or unusual thought contents in young age groups. Fourthly, cultural or *Zeitgeist* influences on the assessment of schizotypy have not been addressed to date in cross-cultural or longitudinal studies but might explain differences in findings across countries or time. For example, comparison of prevalence rates in DSM-SPD between German and North American high-risk and community samples consistently found 3- to 4-fold higher rates in American samples,[47] and statements such as "the government refuses to tell the truth about UFOs" (item of the Magical Ideation scale relating to speculations about area 51) might not possess general or lose timeliness.

With regards to an early clinical detection of psychosis, 3 of 4 studies examining the additive value of assessing schizotypy in CHR sample found merits in it.[31,46,52] Yet it was argued that while an assessment of schizotypy increased predictive value statistically, it might fail to carry substantial clinical meaning in terms of discriminating non-converters and converters.[52] Although further research is needed to confirm this appraisal, it appears that schizotypy may be more useful as a distal risk marker, and employed to select psychosis-prone persons early on to examine some of the initial interactions leading to CHR states and possibly psychosis. Indeed, in comparison to CHR state risk indicators, schizotypy measures might not be equally predictive of psychosis. However, beyond 3- to 5-year intervals, state markers may be traded for trait markers such as schizotypy, for which predictive value over intervals as lengthy as 25–50 years was reported. Further, schizotypy measures might be included as a lower risk predictor in

psychopathological risk stratification models and/or improve knowledge of the pretest illness probability so important for an adequate evaluation of the post-test illness probability, eg, after the assessment of CHR criteria.[76]

To conclude, the concept of schizotypy has already informed preventive research in psychoses to an important degree, particularly with regard to the definition of the UHR criteria. Yet, while it seems to have the ability to detect psychosis-prone subjects from the community, long-term prospective studies combining both trait and state markers, ie, including schizotypy-identified but otherwise mentally well persons and CHR patients, are still missing. As CHR patients must be assumed to represent already the more extreme end of the schizotypy-psychosis continuum, such studies would preferably be conducted in primary care settings or on large community samples.

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