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Introduction: The Extended Psychosis Phenotype—Relationship With Schizophrenia and With Ultrahigh Risk Status for Psychosis

Jim van Os[1,2,*] and Richard J. Linscott[1,3]

[1]Department of Psychiatry and Psychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University Medical Center, Maastricht, The Netherlands; [2]Department of Psychosis Studies, Institute of Psychiatry, King's College London, King's Health Partners, London, UK; [3]Department of Psychology, University of Otago, Dunedin, New Zealand

*To whom correspondence should be addressed; Department of Psychiatry and Psychology, Maastricht University Medical Center, PO BOX 616 (location DOT12), 6200 MD Maastricht, The Netherlands; tel: +31-43-3875443, fax: +31- 43-3875444, e-mail: j.vanos@maastrichtuniversity.nl

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The Extended Psychosis Phenotype as Behavioral Expression of Vulnerability for Psychotic Disorder in Populations—Particularly if Persistent Over Time

In clinical practice, psychotic disorders naturally come as diagnosable "things," categories, the carriers of which form a diagnostic boundary below which reside the healthy noncarriers who do not display the mental phenomena observed in patients. In research, however, the focus is on scientific exploration of the distribution of experiences at all levels of severity in populations and its genetic and nongenetic causes. Population research has shown high rates of psychotic experiences in people who are not readily diagnosable according to ICD/DSM/RDC criteria—suggesting an "extended psychosis phenotype," which shares demographic, etiological, familial, and psychopathological factors with clinical psychotic disorder. In fact, affective dysregulation, psychotic experiences, motivational impairments, and cognitive alterations appear to be distributed and coexpressed to a degree in nonill individuals and have been shown to index risk for later onset of disorder, particularly if they tend to persist over time.[1] (also, R. J. L & J. v. O., unpublished data, 2011) In other words, the extended psychosis phenotype can be considered as the behavioral expression of vulnerability for psychotic disorder in populations. However, research on psychotic experiences in the general population is in its early stages. A systematic review of 285 rates of prevalence or incidence of psychotic experiences showed that method, cohort, and design variables accounted for more variance than meaningful variables (exposure variables). The biggest contributor among the method variables (self report) accounted for 2.7 times the amount of variance explained by the biggest exposure variable (drug use). Thus, rates were found to be higher in studies using smaller *n*, convenience sampling, and self-report assessment.[2] Furthermore, systematic review of the literature shows that there is evidence not only for a psychometric "continuum" (in the sense of an extended psychosis phenotype blending gradually into clinical syndromes)[3] but also for an underlying latent categorical structure of the population (in the sense that regardless of the presence of a psychometric continuum, the population may still be composed of 2 different types of people).[2] In addition, research suggests that onset of psychotic disorder can be understood in part as different types of subclinical experiences causally impacting on each other over time, for example negative symptoms predicting psychotic experiences,[4] affective dysregulation impacting on onset of psychotic symptoms,[5,6] or hallucinations giving rise to delusions,[7,8] suggesting a network model of onset of psychotic disorder. These reciprocally influencing symptoms, in turn, can be traced to "microphenotypes" of subtle responses of aberrant salience or negative affect to small variations in the environment that possibly constitute the core vulnerability in the way cerebral processing gives rise to subtle alterations in the representation of the social environment in the form of, for example, paranoia[9,10] or hallucinatory experiences (fig. 1).[11]

Relationship With Nonpsychotic Disorders of Anxiety and Depression

From the earliest reports on psychotic experiences in general populations, a high level of coexpression of anxiety and depression was noted.[12,13] In fact, research has demonstrated high rates of psychotic experiences in individuals with nonpsychotic illness,[14,15] which may have

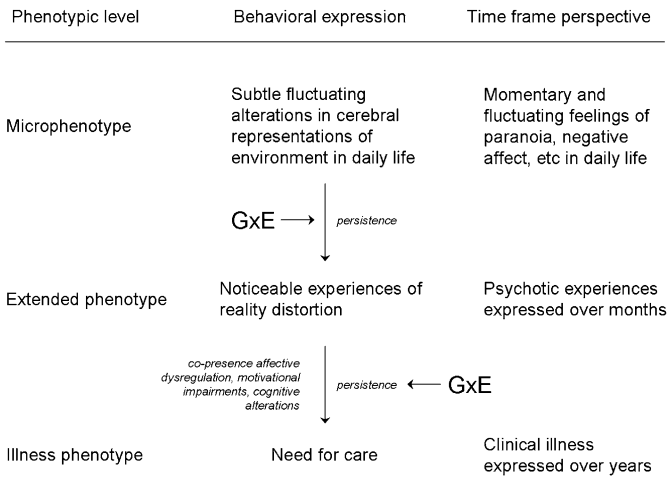

Fig. 1. Onset of psychotic disorder. The core vulnerability underlying psychosis is portrayed as subtle alterations in the way individuals process environmental stimuli from moment to moment in the flow of daily life, giving rise to altered representations of the environment in the form of, for example, fluctuating paranoid feelings, negative affective states, or reduced incentive for environmental interactions (microphenotype). In some individuals, these states tend to persist from moment to moment, under the influence of interacting genetic and environmental factors (G × E), at some stage giving rise to noticeable psychotic experiences, for example in the form of habitual paranoid ideation (extended phenotype). Persistence of these psychotic experiences over months or even years, under the influences of interacting genetic and environmental factors (G ×E), and depending on the degree of copresence of affective dysregulation, motivational impairment, and cognitive alterations, increases the risk for onset of psychotic disorder (illness macrophenotype) with a high likelihood of disease expression over a period of many years.

important clinical consequences for the outcome of these disorders,[16] reinforcing the view that psychopathology is represented by a network of overlapping and reciprocally impacting dimensional liabilities. Thus, a diagnosis of schizophrenia is highly predictive of virtually all other Axis I and Axis II psychiatric disorders in the same person,[17] and this relative nonspecificity extends to the level of familial aggregation. For example, the nonaffected siblings of patients with psychotic disorder display cognitive alterations compared with well controls, one of the reasons why cognitive alterations are considered a "core" marker of genetic risk for schizophrenia. However, siblings of patients with common mental disorders also display cognitive alterations, albeit to a lesser degree.[18] Similarly, nearly 30% of schizophrenia in the population can be attributed to psychiatric family history in general, compared with only 6% that is attributable to a family history of schizophrenia specifically.[19]

Relationship to Ultrahigh Risk Status and Psychotic Disorder

A recent meta-analysis of prospective population–based studies provided evidence that psychotic experiences in nonill people in the general population predict psychotic disorder.[20] In this meta-analysis, the yearly risk of conversion to a clinical psychotic outcome in exposed individuals (0.56%) was 3.5 times higher than for individuals without psychotic experiences (0.16%), and there was meta-analytic evidence of dose-response with severity/persistence of psychotic experiences, as well as evidence for a role of motivational impairment, social dysfunction, affective dysregulation, and level of active coping. In addition, although the evidence for conversion to nonpsychotic outcome was somewhat weaker, findings were directionally similar. Therefore, subclinical self-reported psychotic experiences in epidemiological non–help-seeking samples index psychometric risk for psychotic disorder, with strong modifier effects of persistence, a trait that appears to be under substantial genetic as well as environmental influence.[21,22] These data can serve as the population reference for selected and variable samples of help-seeking individuals at ultrahigh risk (UHR), for whom very much higher yearly transition rates have been suggested, in the order of 20% after 1 year,[23] although the largest and most recent studies suggest a more modest yearly transition rate of around 10%.[24,25] Given that the great majority of individuals meeting UHR criteria in fact have attenuated psychotic symptoms, which are similar to interview-based psychotic experiences assessed in general population research, the differences in yearly transition rates (0.56% in general population vs 20% in UHR samples) cannot be explained by differences in UHR criteria. Rather, an important difference between UHR samples and general population samples of the extended phenotype research is that the former is actively selected, typically by specialized researchers, for presence of help seeking and likelihood of imminent transition to psychotic disorder. Also, around 90% is diagnosed with an anxiety disorder or depression at baseline[26,27] which is important, given that these common mental disorders have a high prevalence of psychotic experiences,[14,15] which significantly impact on prognosis.[16] In other words, of the total pool of individuals with psychotic experiences in the general population, those that become help seeking and develop need for care, most often in the context of anxiety disorder and depression, can be selected for imminent risk for poor outcome (considered as transition to psychotic disorder). Depending at which point along the extended psychosis phenotype help-seeking individuals are selected, subsequent transition rates may be higher or lower (fig. 2). However, transition rates in UHR samples may not be absolute. For example, the suggestion of lower transition rates over time may reflect better and earlier treatments in the form of stress reduction, psychosocial support, pharmacological treatment for anxiety/depression, decreases in substance abuse, reduction of expressed emotion in families, and other treatment approaches for help-seeking individuals with early expression of psychosis.

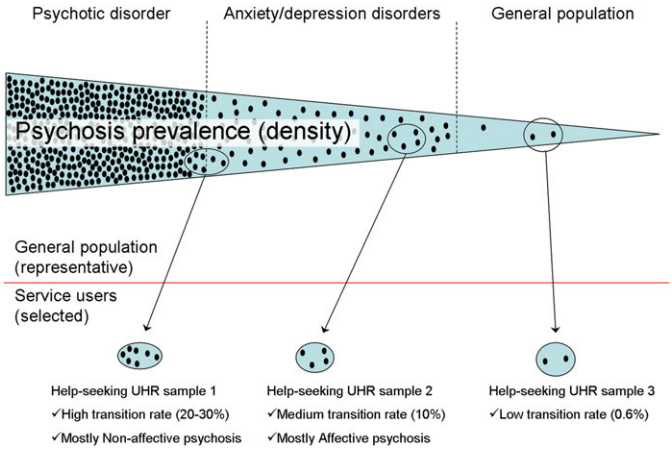

Fig. 2. Relationship between extended psychosis phenotype (general population) and ultrahigh risk (UHR) status (selected samples of help-seeking individuals). In the general population (level above the horizontal line), psychotic symptoms and experiences are common in (1) psychotic disorder (highest density), (2) disorders of anxiety and depression (medium density), and (3) nonill people in the general population (low density). At all levels of the extended psychosis phenotype, individuals may become help-seeking (level below the horizontal line) which is a requirement for UHR status. UHR samples of help-seeking individuals may be selected at any level of density along the extended psychosis phenotype, which will cause differences in the degree of inherent enrichment in risk for transition to psychotic disorder.

Box 1. Extended Psychosis Phenotype: Meta-Analytic Findings[2–4,21] to Date

- Prevalence around 7.5%, incidence around 2.5%; however, a substantial amount of the considerable heterogeneity in rates of psychotic experiences across studies is due to study method, cohort, and design factors
- Associated with family history psychotic disorder, childhood trauma, cannabis use, minority status, unemployment, low income, and younger age
- Prevalent in disorders of anxiety and depression predicting worse outcome and a more psychotic disorder risk as well as demographic profile
- The 2- to 5-year persistence rate is around 20%–30%
- Persistence is influenced by genetic and environmental factors
- Psychotic experiences predict onset of later psychotic disorder (at a rate of 0.6% per year), particularly if persistent
- Other factors associated with transition to psychotic disorder are baseline severity of psychotic experiences, level of admixture with affective dysregulation and motivational impairment, social functioning, and coping level.

Articles in This Issue

The main findings in the area of the extended psychosis phenotype are summarized in box 1. In the current issues, 3 issues are examined in more detail. First, van Nierop and colleagues[28] tackle the issue of self-reported psychotic experiences that are rated ''false positive'' at follow-up clinical interview. Are false-positives more subtle expressions of aberrant salience below the clinical threshold or do they merely represent epiphenomena? Kelleher and colleagues[29] examine the distribution of the criterion of attenuated psychotic symptoms, representing the defining criteria for UHR status in help-seeking samples in a non–help-seeking general population sample. Finally, Wigman and colleagues[21,22] examine how prevalent psychotic experiences are in a representative general population sample of individuals with disorders of anxiety and depression and show that copresence of psychotic symptomatology in disorders of anxiety and depression not only is common but also represents a functionally and etiologically highly relevant feature.

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