Psychosis as a transdiagnostic and extended phenotype in the general population

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A large body of research indicates that weak expressions of positive psychotic symptoms (“psychotic experiences”) can be measured in the general population, and likely represent the behavioural manifestation of distributed multifactorial (genetic and non-genetic) risk for psychosis. Psychotic experiences are a transdiagnostic phenomenon: the majority of individuals with these experiences have a diagnosis of non-psychotic disorder, particularly common mental disorder, in which psychotic experiences predict greater illness severity and poorer treatment response. Some of the people with common mental disorder and psychotic experiences will present to mental health services meeting criteria for “clinical high risk”. Treatment of the transdiagnostic dimension of psychosis in individuals with common mental disorder who meet “clinical high risk” criteria thus may improve outcome (which cannot be interpreted as prevention of “schizophrenia”). Subthreshold psychotic experiences are transient in about 80% of individuals, while around 20% go on to develop persistent psychotic experiences and 7% a psychotic disorder, with an annual transition rate of 0.5-1%. Persistence is associated, on the one hand, with environmental exposures, particularly childhood trauma, and, on the other, with network-type dynamic interactions between psychotic experiences themselves (e.g., interactions between hallucinatory experiences and delusional ideation) and between symptom dimensions (e.g., interactions between affective symptoms and psychotic experiences, or interactions between subthreshold negative symptoms and psychotic experiences). The study of psychotic experiences is helping to elucidate the mechanisms by which environmental and genetic influences shape the transdiagnostic expression of psychosis proneness, that is mostly transitory but may first become persistent over time and eventually give rise to transition to a psychotic disorder.

Key words: Psychotic experiences, extended psychosis phenotype, ultra-high-risk states, genetic risk, socio-environmental factors, neurocognition, aberrant salience, network models of severity

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While there has been no universal consensus on the concept of “psychosis”, since the term was introduced by Canstatt into the psychiatric literature1, one of the most common uses has been to refer to phenomena such as delusions and hallucinations2.

These phenomena have been thought of as key characteristics of psychotic disorders such as schizophrenia for a long time and, somewhat more recently, also referred to as the positive symptom dimension3. However, in recent years, it has become increasingly evident that psychotic experiences are common not only in individuals with psychotic disorder, but also in the general population (i.e., prevalence of ~7%)4. In addition, while subclinical psychotic experiences are transitory in about 80% of individuals, around 20% go on to develop persistent psychotic experiences and 7% a psychotic disorder, with an annual transition rate below 1%.1,6

These findings have been taken to suggest an “extended psychosis phenotype”7, i.e. a phenotype that shares demographic, environmental, familial and psychopathological features7 and is both phenomenologically and temporally continuous with clinical psychotic disorder. In other words, while psychotic experiences are not exclusive to, and can occur independently of, psychotic disorder (“phenomenological continuity”), these experiences can endure over time in some individuals, and may be followed by a psychotic disorder (“temporal continuity”).8

This continuity of psychotic experiences and psychotic disorder implies that, at all phenomenological and temporal stages of the “extended psychosis phenotype”, individuals may become help-seeking and classified as meeting criteria for an ultra-high-risk (UHR) state7. In UHR individuals, much higher annual transition rates have been reported, which may be explained primarily by selection for the presence of help-seeking behaviour rather than by differences between measures for determining UHR status and presence of psychotic experiences per se8.

There is evidence that the prevalence of psychotic experiences varies according to place and ethnicity. Nuevo et al9, for example, reported considerable variation in the prevalence of psychotic experiences across countries using data from the World Health Organization (WHO) World Health Survey. Also, in a more recent analysis of data from the WHO World Mental Health Surveys, McGrath et al9 found higher lifetime prevalence estimates in middle- and high-income countries than in low-income ones. Furthermore, psychotic experiences have been found to be more common in ethnic minority groups4,10,11.

The method for assessing psychotic experiences does seem to affect prevalence estimates. A recent meta-analysis4 reported markedly higher prevalence estimates of psychotic experiences in studies based on self-report compared with those using interview-based measures. However, no correlation was found between prevalence estimates and the number of items used4.

A TRANSDIAGNOSTIC PHENOTYPE OF PSYCHOTIC SPECTRUM DISORDER

Most individuals with psychotic experiences have a current diagnosis, primarily
one of mood or anxiety disorder\textsuperscript{12-18}, accounting for the association between psychotic experiences and suicidal ideation and behaviour\textsuperscript{19}. Wigman et al\textsuperscript{17} reported a more than two times greater prevalence of psychotic experiences in individuals with depression or anxiety disorder than in people without these disorders. The presence of psychotic experiences in individuals with depression or anxiety disorder is commonly associated with a poorer prognosis and, therefore, early treatment of these experiences (rather than mislabelling as UHR status) requires attention and may be beneficial for the course of psychosis expression\textsuperscript{2}.

However, subclinical psychotic experiences are not only common in individuals with depression or anxiety disorder but may also be causally associated with affective disturbance, including anxiety, depressive and hypomaniac symptoms\textsuperscript{13,20-24}. In a German prospective cohort community study of 2,524 adolescents and young adults\textsuperscript{24}, a dose-response relationship, suggesting causality, was reported between levels of affective dysregulation (both depression and mania) and psychotic experiences.

There is further evidence that subclinical experiences of negative symptoms are (at least) as prevalent as subclinical experiences of positive symptoms\textsuperscript{25,26}. In addition, subclinical negative and disorganized symptoms have been found to be predictive of, and co-occur with, subclinical positive symptoms, and co-occurrence of subclinical positive, negative and disorganized symptoms seems to predict later functional impairment and help-seeking behaviour\textsuperscript{25}. The evidence therefore suggests that subclinical psychotic experiences represent two underlying constructs: a) a distribution of a specific phenotypic expression of attenuated psychotic phenomena (delusional ideation and hallucinatory experiences) and b) a set of transphenotypic fundamental associations between domains of psychopathology (positive, affective, negative, disorganization).

A similar bimodal set of general, transdiagnostic and specific phenotypic expressions is observed at the level of psychotic disorders. Thus, there is growing evidence for a transdiagnostic psychosis phenotype underlying schizophrenia spectrum and bipolar disorder, with overlapping affective and non-affective psychotic symptoms\textsuperscript{27-29} (Figure 1). This transdiagnostic psychosis phenotype has continuity across subclinical\textsuperscript{24,29,30} and clinical\textsuperscript{27,28} symptom levels and is further supported by the absence of consistent and clear “points of rarity” across psychosis spectrum disorders\textsuperscript{3,31,32}.

There is further evidence that a general, transdiagnostic psychosis dimension is complemented by five specific diagnostic constructs of psychosis (i.e., positive symptoms, negative symptoms, disorganization, mania, depression), which, when used in combination, allow for a
more accurate classification of individuals into categorical diagnoses based on dimensional scores. This approach draws on bifactor models for generating quantitative scores of a) a general, transdiagnostic psychosis factor and b) specific psychosis factors. Then, it adopts a strategy in which: first, quantitative scores on the general, transdiagnostic psychosis dimension may be used to determine whether to place individuals on the affective or non-affective end of the psychosis spectrum; and, in a second step, based on the profiles for specific symptom dimensions, patients may be classified into specific diagnoses.

What is more, this approach provides directly measurable general, transdiagnostic as well as specific phenotypes for cross-disorder investigations to identify transdiagnostically shared genetic and environmental contributions, as well as non-shared factors contributing to specific symptom dimensions. Given evidence for a general, transdiagnostic phenotype of psychosis at both the clinical and subclinical level of psychotic experiences, the existence of an “extended and transdiagnostic phenotype” in the general population can be suggested.

GENETIC AND SOCIOENVIRONMENTAL FACTORS ASSOCIATED WITH THE EXTENDED PSYCHOSIS PHENOTYPE

Several studies have examined the level of psychotic experiences as an indirect measure of expression of the distributed genetic risk for psychotic disorder. Findings from these studies suggest that subclinical psychotic experiences and schizotypal symptoms in twins from the general population and relatives of patients with psychosis are influenced by genetic effects. There is also evidence that subclinical psychotic experiences may reflect the transitory developmental expression of genetic risk for psychosis in the general population.

A Danish birth cohort study reported that subclinical psychotic experiences at age 11-12 years, assessed by clinical interview, were strongly associated with a family history of treated psychotic, but not common mental disorder, identified in an unmasked fashion through the national case register. Further, studies and meta-analyses have consistently reported that socio-environmental risk factors such as ethnicity, urbanicity, childhood adversity, stressful life events, and cannabis use are shared across subclinical psychotic experiences and psychotic disorders.

Wigman et al., in a general population sample of female twins, showed that childhood trauma and prospectively recorded stressful life events were associated with persistence of psychotic experiences. In addition, psychotic experiences were more likely to persist in monozygotic than in dizygotic twins when persistence occurred in the co-twin.

Overall, these findings suggest that both genetic and socio-environmental factors are associated with the “extended psychosis phenotype”. However, to date, molecular genetic studies have failed to generate replicated findings on similar associations with a priori selected single-nucleotide polymorphisms, a limited early version of the polygenic risk score, or genetic variants identified using a genome-wide association approach.

Cross-disorder investigations and studies using the more powerful recent version of the polygenic risk score are now required for identifying shared genetic and environmental factors (including G × E) of the “transdiagnostic and extended psychosis” phenotype as well as non-shared factors of specific psychosis constructs.

NEUROCOGNITION, ABERRANT SALIENCE, REASONING BIASES AND THE EXTENDED PSYCHOSIS PHENOTYPE

Neurocognitive alterations, in particular in processing speed and working memory, have been reported to be more common in individuals with psychotic experiences than in those without these experiences. There is also some evidence of poorer functioning in individuals who report subclinical psychotic experiences, which may potentially in part be due to neurocognitive alterations.

However, to what degree any association between psychotic experiences and neurocognitive alterations is specific is difficult to examine, as psychotic experiences are strongly associated with a range of non-psychotic mental disorders which in turn are associated with cognitive alterations. The fact that neurocognitive alterations have been found in siblings of patients with psychotic disorder and, to a lesser extent, in siblings of patients with non-psychotic disorders, suggests transdiagnostic overlap even at the level of what is commonly considered a key marker of genetic risk of schizophrenia.
salience to subtle variations in the environment as well as reasoning biases reflect “microphenotypes” that potentially form part of the core vulnerability of the “extended psychosis phenotype.”

**TRANSDIAGNOSTIC AND NETWORK MODELS OF SEVERITY**

Several studies have reported that exposure to childhood trauma is associated with both occurrence and persistence of psychotic experiences. For example, in a recent study, individuals with childhood trauma reported higher levels of psychotic experiences both at baseline and at 3-year follow-up than those without childhood trauma, suggesting that childhood trauma creates a vulnerability for psychotic experiences to persist over time.

If, as van Os and Linscott proposed, psychotic experiences persist over a prolonged period of time under the influence of G×E, this may increase the risk for initial onset and sustained expression of psychotic disorder, as demonstrated by Dominguez et al. in a repeated measures study of psychotic experiences in the general population spanning more than 10 years.

In addition, van Nierop et al. reported that childhood trauma increases in particular the likelihood of co-occurrence of hallucinations and delusions (rather than either symptom alone), which has, in turn, been shown to be associated with greater symptom severity and familial risk of psychotic disorder. Since a similar pattern is evident for other socio-environmental factors, such as cannabis use and urbanicity, as well as for increased likelihood of co-occurrence of psychotic experiences with other symptoms, it has been proposed that a transdiagnostic model of severity may apply, in which coexistence of psychotic experiences, affective and anxiety symptoms reflects greater severity, socio-environmental risk and poorer functioning.

This may be complemented by, and combined with, a network model of severity (Figure 2), in which symptoms of the transdiagnostic psychosis phenotype do not vary independently, but impact on each other over time, and connectivity of symptoms increases as socio-environmental load increases.

In this model, as a result of elevated connectivity, more symptoms are recruited and severity of states increased further, which, in the event of exposure to further

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**Figure 2** Environmental impact on connectivity in the network, resulting in psychosis admixture. In A, there is a low level of environmental exposure, creating a minor disturbance that does not spread extensively through the network of symptoms and remains “contained” in the non-psychotic domain of psychopathology. In B, environmental exposure is moderate, resulting in a more extensive spread across the network, although not into the psychotic domain of psychopathology. In C, the degree of environmental exposure is high, creating a major disturbance that spreads through the network, also “recruiting” more severe psychotic symptoms.
CONCLUSIONS AND FUTURE PROSPECTS

In recent years, research has revealed a phenomenological and temporal continuity of psychotic experiences with psychotic disorder, as well as the co-occurrence and overlap of psychotic experiences with affective and anxiety symptoms and disorder, which, taken together, suggests an “extended and transdiagnostic psychosis phenotype” in the general population. Evidence suggests the existence of a general, transdiagnostic factor as well as five specific psychosis factors, which are measurable and best represented by a dimensional bifactor model of psychosis. A bifactor “general” and “specific” model of psychosis may substantially enhance classification accuracy of categorical diagnoses based on dimensional scores.

While there is evidence that subclinical psychotic experiences and psychotic disorder are associated with similar socio-environmental and genetic variables, cross-disorder investigations are now required for identifying shared genetic and socio-environmental variables (including $G \times E$) underlying the transdiagnostic psychosis factor, as well as non-shared variables underlying specific psychosis factors. Transdiagnostic overlap may be present even at the level of what are commonly considered core markers of genetic risk of schizophrenia such as neurocognitive alterations. Co-presence of neurocognitive alterations, alterations in salience attribution, and reasoning biases may be particularly relevant on the pathway from persistence of psychotic experiences to initial onset and, ultimately, sustained expression of psychotic disorder.

Initial evidence on transdiagnostic and network models of severity now needs to be strengthened further through prospective studies into the dynamic nature of the “extended psychosis phenotype” cutting across boundaries of diagnostic categories of current classification systems.

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REFERENCES

2. van Os J, Murray RM. Can we identify and treat “schizophrenia” as a single entity? Two studies to prevent true psychotic illness? BMJ 2013;346:f606.
29. Shevlin M, McElroy E, Murphy J. The psychosis continuum: testing a bifactor model of psy-

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