

Exploring psychotic experiences in the context of multidimensional psychopathology

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CHAPTER 8

Impact

Main objectives, results and conclusions

The assessment of the different dimensions of psychosis in a graded fashion is progressively replacing the classification of threshold phenotypes in the form of distinct categories. Examples are the release of the National Institute of Mental Health, Research Domain Criteria and Clinician-Rated Dimensions of Psychosis Symptom Severity in the Emerging Measures and Models section of the DSM-5. This paradigm shift is supported by 'grey areas' between illness and normality, lack of zones of relative rarity, high rates of comorbidity, shared etiopathogenesis, heterogeneity within disorders, and diagnostic instability. Longitudinal assessment of the extended and transdiagnostic psychosis phenotype in general populations is a productive way to generate evidence for the expression of psychosis as multidimensional psychopathology. In this thesis, psychosis was assessed along a spectrum of severity including both helpseeking and non-helpseeking individuals in a representative community-based population of Izmir, which is one of the major cities in Europe and the Middle East, with around three million residents. Etiological and phenomenological associations (within the same domain and across different domains of psychopathology) over a six year follow-up period were the major focus of attention.

The summary of the main results described in different chapters of this thesis is as follows:

Results in chapter 2 showed that baseline characteristics of responders did not show large differences from characteristics of subjects who dropped out. In addition, socio-demographic characteristics were similar to studies with a similar design, but also had differences. Thus, results are sufficiently representative of the Izmir population. Furthermore, the spectrum of the positive psychosis domain showed a fluctuating phenotype over time. Chapter 3 demonstrated that affective psychopathology and the spectrum of the positive domain of psychosis were bi-directionally associated with each other over

time, in a sub-additive pattern. A remarkable number of socio-environmental and familial risk factors were shared across these domains. Similar cross-lagged correlations over time were demonstrated across these domains, suggesting mutually causal connections. In chapter 4, the prospective diagnostic evaluation of clinically relevant subthreshold psychosis showed that subsequent psychotic disorder diagnoses represented only a minority of outcomes whereas the majority had diagnoses of common non-psychotic disorders at follow-up. Furthermore, baseline characteristics of individuals (e.g. age range, sex, familial risk, socioeconomic status, comorbidity of symptoms, and persistence of subthreshold psychosis) were predictive of the longitudinal diagnostic outcome (i.e. any mental disorder and psychotic vs. non-psychotic disorder). The results of chapter 5 showed that an SNP (rs6265), hypothesized a priori, was significantly associated with the longitudinally assessed spectrum of the positive domain, including subthreshold and threshold phenotypes, adjusting for socio-environmental factors. The associations were in a dose-response but extra-linear fashion with stronger associations at the threshold level.

RELEVANCE

Scientific Impact

To date, few longitudinal community-based studies on the extended psychosis phenotypes have been performed, and they were conducted predominantly in western populations. Cultural and socio-economic characteristics of populations across geographical regions may lead to differences in findings. The TurkSch study is a unique example of a longitudinal community-based study conducted at the cross-border between Europe and the Middle-East. Hence, the design of the TurkSch study has the potential to stimulate similar studies in other regions in this part of the world. Furthermore, the sociodemographic correlates of attrition may guide future studies to make special efforts to include these particular groups.

There are a number of terms/definitions used in research in the area of subthreshold psychosis (i.e. schizotypy, schizotypal traits, schizotaxia, psychotic (like) experiences, psychotic symptomatology, attenuated psychotic symptoms, prodromal psychotic symptoms, high risk for psychosis) and associated outcomes (i.e. psychotic impairment, transition, clinical psychosis, psychotic disorders, first episode psychosis, affective psychosis, non-affective psychosis, schizophrenia spectrum). These terms usually differ based on aspects of the particular sample (i.e. general population-based, early intervention centre-based, help seeking, non-help seeking, presence of co-occurring distress and common mental disorder), and the outcome measures used (DSM diagnoses, questions on help seeking and dysfunction, Comprehensive Assessment of At-risk Mental State-CAARMS, Scale of Psychosis-Risk Symptoms-SOPS). These definitions indicate different positions within the psychosis spectrum. Standardized terms/definitions are necessary for the area to progress, for example in an international consortium testing the reliability and validity of these operational definitions. This thesis and the previous results of the TurkSch study demonstrated that clinical and general-population phenotypes in this research area have important similarities with regard to risk factors and longitudinal outcomes. Given the fact that the TurkSch study covered the full spectrum of psychosis from subclinical phenotypes gradually blending into clinically-relevant subthreshold phenotypes, threshold psychosis outside schizophrenia spectrum disorders and finally schizophrenia spectrum disorders, as well as associated risk factors, co-occurring dimensions and longitudinal outcomes, it may be used as an initial step towards the standardization efforts of psychosis spectrum terminology.

Subthreshold psychosis is represented in current classification systems as categorical entity, based on positive psychosis phenomena. For instance, the attenuated psychosis syndrome, classified under subheadings of both 'other specified schizophrenia spectrum and other psychotic disorder' and 'conditions for further study' in DSM 5, is characterized by clinically relevant

subthreshold delusions, hallucinations and disorganized speech. Results in this thesis and previous results in the TurkSch study question the validity of this type of classification and demonstrates the need for multidimensional assessments and dynamic interplay between affective and psychosis domains.

The results on dynamic transitions over time in the extended psychosis phenotype in this thesis showed that a high proportion of clinically relevant subthreshold psychosis does not persist over time. These results demonstrate the need to reconsider the view that psychosis itself is ‘toxic’ for the brain and/or part of a phenotype that progresses through stages. Research in the area of high-risk for psychosis predominantly leans on unidimensional assessment strategies with a reliance on positive phenotypes. However, this strategy unintentionally may set a self-limiting barrier for research in this area. Results described in this thesis clearly show that the subthreshold positive domain usually co-occurs with symptoms from other domains. The outcomes are also heterogeneous and dependent on the degree of interplay between dimensions. Through unidimensional assessment strategies, the associations between emerging outcomes and prior symptom domains outside the positive domain (or the interconnectivity between domains) are missed. Furthermore, various outcomes outside the positive domain are overlooked. Therefore, this thesis may contribute to the methodology of future prospective research to include broader phenotypes of psychopathology in order to evaluate different pathways to psychotic impairment.

Studies designed to investigate etiological associations predominantly compare ‘cases’ that have distinct categories of mental disorders with ‘healthy’ controls. However, this methodology has some limitations. Different domains of psychopathology, even as they are co-occurring in the same disorder, may be associated with different pathways, thus with different genetic and environmental risk factors, which may cause much heterogeneity from sample to sample. Furthermore, controls may share some

phenotypes with cases, in particular subthreshold phenotypes, which could cause loss of power and precision. Additionally, data is usually collected on a single factor (e.g. molecular data only, socioenvironmental exposure only etc.) which hampers insight into confounding, moderation, mediation and moderated mediation for many other influences. Finally, the descriptions of ‘caseness’ are mostly based on a single assessment, not taking into account fluctuating manifestations over time. However, case-control studies have advantages of getting more rapid results and being cheaper. Therefore, integrating dimensional assessments of psychopathology as well as cumulative measures of different risk factors can add extra value. The design of risk assessment in this thesis is dimensional and longitudinal, providing opportunity to adjust for other factors. This design may stimulate further research on risk assessment in the future.

Socioeconomic Impact

Meta-analyses have reported that dimensional measures have increased validity, explaining more variance in risk factors, neurophysiological markers, and functioning in comparison with categorical measures. The perspective of research on dimensional assessments and the interconnectivity between dimensions in this thesis, along with other studies with similar research questions, can accelerate the rise of personalised medicine in psychiatry with enhanced diagnostic and prognostic accuracy. Furthermore, this framework may improve the search for biomarkers in psychiatry.

Screening psychosis risk in the community through a unidimensional assessment strategy has two major limitations. First, most of the individuals with this ‘risk state’ do not develop a psychotic disorder, but rather develop a common non-psychotic disorder. Furthermore, some individuals even do not develop any mental disorder over time. Second, a high proportion of individuals who develop psychotic disorders does not meet the criteria of risk categories. Along with other studies with similar research questions, the results of this thesis showed that early expres-

sions of psychotic psychopathology comprise multiple signs and symptoms from multiple domains. The results on the characteristics of individuals with subthreshold psychosis (e.g. age range, sex, familial risk, socioeconomic status, comorbidity of symptoms, persistence of subthreshold psychosis) who develop psychotic disorders as well as common-non psychotic disorders over time may help to plan personalized early intervention strategies. Therefore, these results contribute to the growing evidence for ways to improve screening strategies.

The traditional consideration of psychosis as a dichotomous event, in some degree, may add to the stigmatization of individuals with psychosis. The TurkSch study evaluated psychosis as a common phenomenon lying on a spectrum from illness to normal mentation, and showed substantial shared aspects across these ends. Furthermore, the longitudinal results show that the majority of individuals with baseline clinically relevant subthreshold psychosis do not develop ‘schizophrenia’. Therefore, psychosis over time does not concur with the social image of schizophrenia as a ‘devastating progressive and desperate mental illness’. These results might be an important basis for the fight against stigmatization of psychosis in society.

Target Groups

Academic community in other disciplines

This thesis provides an advanced design to meet the challenges of longitudinal data collections in representative-community-based populations. Furthermore, genetic analyses within a general population-based sample were performed. Therefore, the results may be of interest not only for psychiatrists and psychologists, but also for geneticists, physicians from various disciplines working in the area of epidemiology as well as social scientists. A multidisciplinary perspective within an epidemiological framework can productively bring together different areas of research that sometimes have difficulties finding each other.

Patients and their relatives

For patients with psychosis, the results of the TurkSch study demonstrate that the condition they experience has shared aspects, or connectedness, with experiences of a substantial part of the general population. For any person with psychotic experiences, and particularly for relatives of individuals with subthreshold psychosis, it is a vital question if a psychotic disorder may arise in the future. The answer is that the majority is not going to be diagnosed with a psychotic disorder, although there is an apparent risk for mental disorders in general, with an increasing risk if they have persistent psychotic experiences, co-occurring mental distress, low socioeconomic status, substance use, and family history of mental disorders. Therefore, a devastating worry for a future psychotic disorder is not useful. However, the modifiable risk factors among these, such as substance use, may be targeted to reduce the risk of impairment.

Society at large

Stigmatization of psychosis is common in society. The results of the TurkSch study have shown that psychosis is a much more common phenomenon than is generally assumed, lying on a spectrum from normal mentation to need for care. Furthermore, psychotic experiences are generally transient, and not antecedents of ‘devastating’ mental illness, so these experiences may be considered as part of human variation with deep roots in evolution of mind.

Policy makers

The findings in this thesis support the view that psychotic experiences may be a useful marker for mental distress that has transdiagnostic value. Furthermore, psychotic experiences have close associations with socio-environmental exposures, which are therefore associated with the longitudinal outcomes of individuals’ mental states. Community-based prevention strategies should be organised taking into account a multidimensional perspective, prioritizing the impact of socio-environmental expo-

sures in order to reduce the burden of mental problems. Furthermore, efforts to fight against stigmatization of psychosis in society are of value.

Mental health care providers

The results of this thesis provide an important base for physicians and other professionals working in the area of mental health. Subthreshold psychosis should not be considered merely as the 'pre-psychotic' phase. However, considering frequency and distress associated with the experiences, socio-environmental and genetic risk of individuals, and interactions with other dimensions of psychopathology, may result in more precise predictions of transdiagnostic outcomes over time. Therefore, avoiding 'schizo'-discourse when considering psychosis phenotypes is required. Rather, follow-up of these individuals in a supportive environment, treatment of co-occurring disorders leading to impairment in social, occupational, or other important areas of functioning, and psychoeducation on plausible socio-environmental risk may be of value.

Network Product

The TurkSch study was based on interdepartmental and international collaborations. Results of the study have been presented in many national and international conferences. A new assessment of the cohort (T_3) is being planned. Furthermore, a PhD thesis at Maastricht University, focussing on the longitudinal neighbourhood-contextual measures of the TurkSch study is in progress.

Summary and Conclusion

The results of this thesis have several scientific and social impacts. First, the assessments covered the full spectrum of psychosis, as well as the dynamic interplay between symptom domains. Therefore, results may contribute to the efforts to achieve a consistent terminology for multidimensional psychotic pheno-

types as well as more comprehensive and precise classification of psychosis. Second, the results on longitudinal outcomes of subthreshold psychosis as well as the moderating factors were presented. These results may have impact on clinical practice when considering individuals with subthreshold psychosis. Furthermore, these results may help to improve screening strategies in order to provide more comprehensive community-based prevention strategies. Third, the methodology may stimulate further research on assessment of risk factors with more accurate results. Finally, the consideration of psychosis as a common phenomenon lying on a spectrum from illness to normal mentation as well as the longitudinal outcomes of these phenotypes may be an important basis for the fight against stigmatization of psychosis in society.