



Reinventing schizophrenia – Embracing complexity and complication

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1. Introduction

The theme of this special issue is to ask individuals doing research relevant to schizophrenia to answer one or more of the following questions: a) Is the current schizophrenia construct viable or salvageable?, b) What alternative construct would you propose to supplant the current conceptualization of schizophrenia and what are the scientific underpinnings for the new construct?, and c) What strategies and methods are necessary to identify and/or validate a new construct in place of schizophrenia?

We posit that the answer to the first question from many investigators in the field will not be a clear yes or no, but instead a response of “in some ways and not in other ways.” There is substance to the construct of schizophrenia in many ways. If we harken back to the writings of Kendell on the clinical validity of a psychiatric syndrome (Kendell, 1989), we can illustrate this mixed response. The first criterion is whether one can identify a syndrome of “schizophrenia” by clinical intuition or cluster analyses or structural equation modeling. To some extent the answer is yes to this, in that there are certainly symptoms (i.e., hallucinations and delusions) that are on average more characteristic of schizophrenia than at least some other forms of mental illness (e.g., anxiety). However, the construct of schizophrenia does rather poorly on the second clinical validity criteria of demonstrating boundaries of “points of rarity” from other syndromes (Kendell and Jablensky, 2003). There are certainly no pathognomonic symptoms of schizophrenia, different people can have dramatically different symptom presentations,

and some symptoms we think of as characteristic of schizophrenia can be present in other disorders (hallucinations in Bipolar I Disorder, Major Depression with Psychotic Features, Personality Disorders). In terms of the third criterion, the construct of schizophrenia as defined in the DSM 5 does reasonably well on distinctive course or outcome, in that many people with DSM 5 defined schizophrenia end up having a relatively chronic course that is often functionally debilitating. However, this is in large part because the DSM 5 criteria, like the DSM-IV and III before it, requires a significant level of chronicity to obtain the diagnoses. As has been shown by Jim Van Os and others, if the diagnosis does not require such a level of chronicity, then there is a much more variable outcome among individuals who develop psychotic symptoms, which some recovering and doing quite well (van Os et al., 2009).

For the fourth criterion, the evidence that there is a distinctive treatment response is quite limited, with some individuals with schizophrenia responding well to antipsychotic treatments, but many not, and antipsychotics end up being useful at least to some extent in many syndromes other than schizophrenia (e.g., bipolar disorders). For the fifth criterion, showing that the syndrome runs in families (which can be read as having a genetic basis), the evidence is again mixed. There is certainly very strong evidence that genetics contribute to risk for schizophrenia, and a number of genetic “loci” have been identified for schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics, 2014). However, some individuals with a very high genetic loading for schizophrenia, as assessed either via polygenic risk or family saturation, do not develop schizophrenia (though they may still have

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elected psychosis spectrum symptoms), and some individuals who appear to have little genetic risk for schizophrenia can develop this illness. Lastly, for the sixth criterion, the evidence that there is a shared “more fundamental” abnormality associated with schizophrenia is quite variable. There are many impairments that are relatively commonly found in schizophrenia, perhaps more so than in other syndromes in some cases, such as altered pre-synaptic dopamine availability (Fusar-Poli and Meyer-Lindenberg, 2013), reductions in the volumes or thinner cortex of certain brain regions (e.g., hippocampus, frontal and temporal regions) (van Erp et al., 2016; van Erp et al., 2018), and disruptions in the activity of certain brain regions such as the prefrontal cortex (Minzenberg et al., 2009). However, none of these impairments are present in every individual with schizophrenia, nor are they always absent in individuals with other disorders.

Given this evidence of quite mixed clinical validity of the construct of schizophrenia, what should we do? Should we abandon it and replace it with a new construct? There are at least two responses one can have to this question. The first is to say that perhaps it is not the construct of schizophrenia that is the problem, but rather the criteria that we have used to determine clinical validity. It is not clear that any form of mental illness would do well across all six of these criteria – or even three or four of these criteria – and thus we need to rethink what it means to have clinical validity given the accumulation of evidence indicating that mental illness simply does not follow the somewhat simplistic approach to clinical validity developed decades ago. The second response is that even if we felt that these clinical validity criteria were the right ones, we would argue that the construct should not be fully abandoned, as it still does have strong clinical utility in that it facilitates communication among researchers and clinicians within and across cultures, is a way to retrieve a body of information relevant to understanding course, outcome, and treatment of individuals with the diagnosis and can be informative – at least to some extent – about potential associated factors including genetics, neurobiology, and neurotransmitter function. However, our adherence to the specific extreme chronicity definition (6+ months) embraced in most diagnostic schemes, while aiding with reliability and psychometrics, artificially separates out the tip of an iceberg from what is becoming increasingly clear as a spectrum of psychotic disorders and symptoms, both across diagnostic boundaries and across the boundaries of health and disease. We are not saying something new in making this argument – this argument has been made before by many individuals, including most notably Jim Van Os (Guloksuz and van Os, 2018). However, despite the growing recognition of this spectrum, the vast majority of our research designs continue to rely on traditional case-control studies that pit individuals with a specific diagnosis against some “control” population or some other diagnosis. Thus, we would argue that we need to both expand our recognition and study of psychosis across the spectrum and significantly modify the types of study designs that we use in order to better capture the complexity and complication of the psychosis spectrum.

2. Study the whole elephant, not just parts

It is definitely the case that the last 20 years have seen an increasing emphasis on studying less traditional aspects of psychosis, including the rise in research on Clinical High Risk (CHR) syndromes (Brewer et al., 2006; Cannon, 2005; McGorry et al., 2003; Yung et al., 2004) as well as what has been referred to as “Psychotic-Like Experiences” (PLEs) (Erment et al., 2019; Karcher et al., 2018a, 2020a; Loewy et al., 2005, 2011). However, the vast majority of these studies still focus on one segment of the spectrum of psychosis, typically studying either PLEs or CHR individuals, or individuals with clinically diagnosable psychotic disorders (and often further segmenting such studies across first/early episode versus more chronic individuals). This means that the same methods and questions are typically not brought to bear in the same study with individuals across a fuller spectrum of psychotic disorders. This makes it much more difficult to understand what factors may be centrally

associated with different facets of psychosis across the spectrum, which are more associated with greater chronicity or severity, and which may be more reflective of the experience of having a serious mental illness versus a predictor of onset. Thus, we would advocate for including a broader spectrum of individuals in any one study, such as including individuals with PLEs, those meeting CHR criteria, and early course of diagnosed schizophrenia/schizophreniform in the same study. This will require different types of collaborations among scientists, bringing together those who have historically studied different parts of the elephant to come together and develop protocols and research questions that apply across the spectrum of psychosis. This may also require different approaches to sample recruitment, deliberately recruiting individuals who do not meet full clinical thresholds for disorders and developing approaches that ensure sampling across the spectrum of symptom type and symptom severity. At minimum it would help to be more intentional about including true common data elements (e.g., exact same assessments and tasks) across studies that may be examining different segments of the spectrum of psychosis to be able to better integrate findings across studies.

One might ask how moving to a more spectrum approach from a solely case-control approach will help us understand the etiology and treatment of psychosis. At least hypothetically, there are at least two ways in which this approach might help us move forward. First, because we often ignore non-clinical manifestations of psychosis or psychotic-like experiences (or negative symptoms), it is possible that our “control” populations actually contain individuals who are having some of these experiences, which may in turn reduce effect sizes and also lead to heterogeneity in the results across studies if there is variability in the degree to which control populations are screened for such experiences. Second, case-control approaches typically conflate symptom type, symptom severity, and functional impairment in ways that can be difficult to disentangle when you only recruit “cases” that are on the most severe end of the spectrum. More dimensional designs that better cover the spectrum of type, severity, and impairment may allow us to disentangle the facets of mental illness and their relations to etiology and treatment response.

3. Population-based assessments of psychosis or PLEs

We would also argue that all population-based studies need to include metrics of the psychosis spectrum, something that has been done in many studies, but not all. The perception exists that psychosis is such a low base rate experience in the general population that is not cost-effective or feasible to add measures of psychosis in more general population studies. However, this concern primarily arises if you are focused on studying the most extreme components of psychosis, and becomes at least somewhat less of a concern if you wish to study the fuller range of psychosis, such as PLEs. For example, the Adolescent Brain and Cognitive Development Study, which recruited 11,800+ children across the U. S., included a version of the Psychosis Questionnaire Brief validated for use with children, and is generating important findings in regards to the similarities and differences in the correlates of PLEs in this more general population sample compared to data acquired in more clinically ascertained samples (Fine et al., 2019; Karcher et al., 2018a; O'Brien et al., 2020; Paul et al., 2020). Similarly, the original Human Connectome Project included a brief assessment of PLEs that provided useful information (Karcher et al., 2018b; Sheffield et al., 2016). The UK Biobank, a massive population-based study with rich genetic and imaging data also included a brief measure of psychotic experiences (Davis et al., 2018) that is starting to be mined for intriguing findings (Alloza et al., 2020; Garcia-Gonzalez et al., 2020; Legge et al., 2019; Lim et al., 2020; Roelfs et al., 2021; Schoorl et al., 2021; Vaissiere et al., 2020; Wainberg et al., 2021).

4. Capture the full spectrum of symptoms across the continuum

While the bulk of work taking a spectrum approach to schizophrenia has focused primarily on defining risk based on PLEs or psychosis, schizophrenia is associated with other symptom domains that have received relatively less attention. More specifically, both negative symptoms and cognitive impairments are core features of schizophrenia that have been shown to be significant predictors of functional outcomes (Alloza et al., 2020; Bowie et al., 2006; Fervaha et al., 2014). Moreover, there are limited treatments that target these symptoms; thus, they represent an enduring aspect of the disorder that remains an important target for research and treatment. Might it be that large distinctions in chronicity and severity when examining CHR and PLE samples are due in part to differences in negative symptoms or cognitive impairments? Indeed, work in CHR has suggested that persistent negative symptoms are associated with significant impairments in functioning at both baseline and longitudinally, whereas those without persistent negative symptoms improved over time (Devoe et al., 2021). In regards to cognitive impairments, deficits in cognition relative to controls have been shown to precede development of psychotic symptoms in CHR populations (Lencz et al., 2006). Further, these cognitive impairments in high risk samples are associated with poor functioning independent of psychotic symptoms (Carrion et al., 2011). While some of this work has been done, no studies to our knowledge have taken a broad symptom approach across the entire psychosis continuum, revealing a crucial gap in the literature that represents an important future direction. Thus, we argue that research adopting a continuum approach takes special care to examine the full spectrum of symptoms across the continuum to better understand symptom development, progression of symptoms, and functional outcomes across the full spectrum to better understand and identify the full complexity of illness. This may require the development of new clinical assessments that are designed to better capture variance in the lower and more intermediate levels of symptom severity, as many current clinical assessment tools have good sensitivity at the more severe levels of symptoms (e.g., Brief Psychiatric Rating Scale (Ventura et al., 1993)) but would not do well at capturing more subtle variance. Indeed, recent work has sought to develop negative symptom measures for CHR populations that reflect our current understanding of negative symptoms (Strauss et al., 2020). It will be important to examine whether these assessments show a similar or differential factor structure and presentation across the spectrum. Similarly, the types of questionnaires often used in more population-based studies to study the less severe end of the psychosis spectrum would likely not capture variance at the more severe end of the spectrum and many do not capture functional impairment, which may be critical to understanding transition to clinical disorder (Karcher et al., 2018a; Loewy et al., 2011).

5. Merge research approaches to capture complexity

We would also argue that researchers and the field would benefit from increased collaborative initiatives focused on different types of risk factors and correlates of psychosis across the spectrum, in order to capture and understand complexity of these factors. We will give one example of this. There is a massive amount of research on the genetic risk factors for psychosis, particularly with advances in methods and technology and the use of polygenic risk scores for psychosis and other mental health syndromes that can be applied across many different samples and populations. However, while we know that genetics is important for understanding the development of psychosis, we also know that it is only part of the story, and that the impact of genetics can vary widely across individuals, likely due to a host of environmental risk factors across the lifespan (Karcher et al., 2020b, 2021; van Os et al., 2010). However, the vast majority of genetic studies still take a “main effect” approach to examining the relationships of genetic to psychosis, and do not examine whether we can better understand how and why genetics contribute by examining interactions with various

environmental factors (Robinson and Bergen, 2021; van Os et al., 2008). For example, recent work using the UK Biobank has shown that cannabis use was associated with a much higher risk of experiencing PLEs for individuals with greater polygenic risk for schizophrenia (Wainberg et al., 2021). Further, other recent studies have begun to explore “exposome” scores in psychosis, showing important interactions between degree of environmental risk and polygenic risk in understanding the emergence of psychosis across the spectrum (Mas et al., 2020; Pries et al., 2020).

6. Summary

The time is ripe to ask questions about the utility of the current conceptualization of schizophrenia, but it is far too simplistic to expect that there are easy yes or no answers to whether the current construct is viable or salvageable. As with most important things in science, the answers need to be much more nuanced, and we need to be willing to embrace and tackle the complexity of psychosis, acknowledging its continuity across multiple spectra of health, disease, and diagnostic domain, and being willing to capture that complexity in our theoretical work, research designs, and statistical analyses. This will likely require the development of new measures that better capture variance across the spectrum of severity and which include functional impairment, the creation of new collaborations of scientists with converging expertise across the spectrum of psychosis, and likely new analytic approaches that allow us to grasp, understand, and replicate the complexity of the likely results that we will obtain with such data, including machine learning and other computational psychiatry methods.

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Deanna Barch wrote the original draft of the submission, and both Erin Moran and Nicole Karcher made additions and revisions.

Declaration of competing interest

The authors do not report any conflicts of interest.

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