



Editorial

The psychosis threshold in Ultra High Risk (prodromal) research: Is it valid?

Alison R. Yung^{a,*}, Barnaby Nelson^a, Andrew Thompson^a, Stephen J. Wood^b^a Orygen Youth Health Research Centre, University of Melbourne, Parkville, Australia^b Melbourne Neuropsychiatry Centre, University of Melbourne, Parkville, Australia

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ABSTRACT

“Transition to psychosis” has been the outcome of interest in Ultra High Risk (UHR) and “prodromal” studies. However, the point at which an individual crosses the line from high risk or prodromal state to psychosis threshold is arbitrary. There have been few attempts to examine whether this threshold has any validity in terms of biological markers or course and outcome. More research is needed to determine if the current point at which a person is declared “psychotic” is valid. Indeed some persons labeled as having developed psychosis may quickly recover. In such a situation their transition could be seen as “trivial”. Others who do not make “transition” may have worse outcomes. Validation of the transition point is an important issue as “risk syndrome for psychosis” (psychosis prodrome) is being considered for inclusion in the DSMV. Further, much research attempts to distinguish markers for psychotic disorders by examining the differences between UHR individuals who do and do not develop psychosis. Thus it behooves us not just to have this risk syndrome validated, but to have the hypothetical endpoint of psychosis validated as well.

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1. Introduction

Psychotic disorders such as schizophrenia are usually characterized by a prodromal period which precedes the onset of full-blown psychotic symptoms (Beiser et al., 1993; Olsen and Rosenbaum, 2006; Yung and McGorry, 1996). This phase is potentially a target for intervention. Treatment of the prodrome could prevent onset of fully-fledged disorder or at least may ameliorate or delay the onset phase. However, a major challenge has been to prospectively identify the prodrome, particularly given the non-specific nature of prodromal symptoms (Hafner et al., 2005; Lieberman et al., 2001). Over the last 15 years, criteria for the prospective identification of individuals at heightened risk of developing a first episode of psychosis (FEP) within a brief time period — that is, as possibly being in the prodromal phase of illness

(Yung et al., 2003) — have been developed. These criteria have been variably termed the “Ultra High Risk” (UHR) (Yung et al., 2003), “Clinical High Risk” (CHR) (Cornblatt et al., 2002), At Risk Mental State (ARMS) (Broome et al., 2005; Yung et al., 1996) or “prodromal” criteria (Cannon et al., 2008; Miller et al., 2002), and are based on a combination of trait and state risk factors for psychosis. These include attenuated positive psychotic symptoms (into which category the vast majority of UHR individuals fall; Cannon et al., 2008; Yung et al., 2003, 2004), brief self-limited psychotic symptoms, and family history of psychotic disorder. Several longitudinal follow-up studies have assessed the predictive validity of the criteria (Cannon et al., 2008; Yung et al., 2003, 2004), with rates of UHR patients developing FEP within one year between 10 and 50% (Olsen and Rosenbaum, 2006), with an average across multiple studies of 36.7% (Ruhrmann et al., 2003).

The discovery that it is possible to identify an individual before the onset of a first episode of psychosis, and the subsequent findings that prevention or delay of psychotic disorder may be possible with treatment (Amminger et al.,

* Corresponding author. Orygen Youth Health Research Centre, University of Melbourne, 35 Poplar Rd, Parkville 3052, Victoria, Australia.
Tel.: +61 3 93422800; fax: +61 3 93422921.

E-mail address: aryung@unimelb.edu.au (A.R. Yung).

2007; Bechdolf et al., 2005; McGlashan et al., 2006; McGorry et al., 2002; Morrison et al., 2004; Ruhrmann, 2007), have led to some excitement in the field. This has reached such an extent that there is now a proposal to include the attenuated symptoms group of the UHR/CHR/prodromal criteria in the next iteration of the Diagnostic and Statistical Manual of Mental Disorders (the DSMV) as a category called “Risk Syndrome for First Psychosis” (Carpenter, 2009; Woods et al., 2009; www.schizophreniaforum.org, 2009).

Recent debates about whether or not the Risk Syndrome should be included in the DSMV have focused on the validity, reliability and utility of the syndrome (Carpenter, 2009; Heckers, 2009; www.schizophreniaforum.org, 2009). Discussions have included the dangers of diagnosing those who meet Risk Syndrome criteria but who do not go on to develop psychotic disorder (or “make transition/convert to psychosis”). These so-called “false positives” face the danger of mislabeling, unnecessary medication and stigma. These people are contrasted with the “true positives” who go on to develop a psychotic disorder days to years after meeting Risk Syndrome criteria.

Although the field has rightly focused on the Risk Syndrome criteria, there has been no discussion on the validity of the outcome – the threshold for first episode psychosis. Data used to evaluate the predictive validity of the UHR/CHR/prodromal criteria do not use DSM-IV psychotic diagnoses as their outcome of interest, but instead define a syndrome of “psychosis” (Cannon et al., 2008; Miller et al., 2002; Yung et al., 2003, 2004). The definition of “psychosis” is arbitrary – a line drawn that makes categories (psychosis and non-psychosis) of what are actually continuous phenomena (the intensity, frequency and duration of psychotic experiences). Two structured instruments have been developed to assess UHR or prodromal symptoms and to determine if a person is psychotic or UHR/prodromal. These are the Comprehensive Assessment of Mental States (CAARMS) (Yung et al., 2005) and the Structured Interview for Prodromal Symptoms/Scale of Prodromal Symptoms (SIPS/SOPS) (Miller et al., 2002).

The CAARMS criteria for psychosis require that the person experience at least one fully (positive) psychotic symptom several times a week for over one week. The arbitrary nature of this “psychosis threshold” can be seen if one examines in detail the CAARMS definitions of UHR or “prodromal” status and the definition of full-threshold psychosis. Essentially, a change of one point – from a score of 5 to a score of 6 on, for example, the Unusual Thought Content scale – accompanied by a one point increase in frequency in these phenomena, sustained for one week, is sufficient to redefine an individual from UHR to psychotic. Although clearly a subjective definition, the rationale for choosing this threshold was that it is about the point at which antipsychotic medication would be prescribed and thus represents a change in treatment from ‘watchful waiting’ to pharmaceutical intervention. The definition was reached by a consensus between clinicians working in the early psychosis field in the early 1990s (Yung et al., 1996).

The SIPS/SOPS definitions of “schizophrenic psychosis” are also arbitrary. The definition requires the person to experience at least one fully (positive) psychotic symptom 4 times per week for at least one month, or to experience at least one

fully psychotic symptom for at least one day if this symptom is seriously disorganizing or dangerous (Miller et al., 2003). Thus on the one hand the former definition of psychosis according to SIPS/SOPS criteria seems to be at a higher threshold than the CAARMS psychosis criteria, while the latter definition seems to be at a lower threshold but requires a value judgment about how disorganizing or dangerous the symptom or symptoms are, rather than relying solely on intensity and frequency of the reported experience.

As the first group to operationalise criteria for a UHR/“prodromal” state and the one-week threshold for psychosis, definitions empirically created over a decade ago, we believe it is appropriate for us now to examine the validity of the arbitrary psychosis definition. In other words, is the current definition of “psychosis” meaningful? Do people who transition from the UHR state to psychosis differ from those who do not transition? Does the fact of their transition have implications for treatment and outcome? Are their brains different from the non-converters? This opinion piece seeks to examine the evidence for the validity of the psychosis threshold.

2. Examination of validators of the psychosis threshold

In seeking to validate such a “diagnosis” it is necessary to assess external validators, such as the presence or absence of aetiopathological markers and differences in course and outcome. In this brief paper we aim to summarize the evidence for the CAARMS threshold of psychosis, and to highlight the gaps in evidence. We will also report some case studies that illustrate an important point: that some individuals can cross the “psychosis threshold” and yet be well over time, while others who have not crossed the threshold can continue to be symptomatic and disabled.

2.1. Aetiopathological markers

If the current psychosis threshold represents a valid discontinuity then people who have crossed the threshold should have different neurobiological characteristics from those who have not (given the acceptance of the current paradigm that schizophrenia and other psychotic illnesses are brain diseases). To date there are some preliminary data indicating progressive brain differences between individuals around the point of transition from UHR state to psychosis and those who did not make such a transition. For example, our longitudinal structural brain imaging studies of UHR patients during the period of transition to psychosis found significant neuroanatomical changes in both grey and white matter. These regions include cingulate, medial temporal and orbitofrontal cortices (Pantelis et al., 2003), prefrontal cortex (Sun et al., 2009), superior temporal gyrus (Takahashi et al., 2009) and left parietal and occipital white matter (Walterfang et al., 2008). Recent work has largely replicated these findings in a separate sample suggesting that the psychosis threshold has some validity. However, all the cited studies have limitations, in particular small numbers and a reliance on largely the same sample, so replication with larger sample sizes is needed. Additionally some of the individuals who made transition were rescanned after they had started on antipsychotic medication (although they commenced this

treatment after onset of psychosis rather than while UHR). Thus, differences between the groups may be due to medication effects. There is evidence, however, that similar changes occur in the absence of antipsychotic treatment. A study from the Edinburgh High Risk group (Job et al., 2005) found progression of grey matter changes in young people who developed schizophrenia, and these occurred prior to the onset of the disorder and before commencing antipsychotic treatment.

Another method of assessing brain integrity is neuropsychological function. To our knowledge, only two studies have examined progressive neurocognitive changes around the time of psychosis onset (Hawkins et al., 2008; Wood et al., 2007). In the earlier study, we found that UHR patients who made the transition to psychosis displayed significant decline in visuospatial memory, verbal fluency and attentional switching, while these changes were not found in UHR patients who did not transition. Again this study suffers from a small sample size (16 UHR patients, 7 of whom made transition), and replication with larger numbers is required. The more recent study by Hawkins and colleagues, which does not show significant cognitive decline over the transition, does have a larger sample, but is confounded by being nested within a multi-site intervention trial, and because the neuropsychological battery is reported as a global score.

Other areas not yet examined longitudinally in UHR patients include neurotransmitter levels and receptor function, brain metabolites such as the neuronal marker n-acetyl aspartate, psychophysiological measures such as mismatch negativity and gene expression. These areas are gaps in our current knowledge base and have the potential to shed light on the validity (or otherwise) of the psychosis threshold.

2.2. Course and outcome

If we have the cut-off for psychosis approximately correct, then individuals who make transition should have a worse course and outcome than those who do not make transition (assuming that psychotic disorder has worse course and outcome than sub-threshold positive psychotic symptoms). Long term follow-up data are needed to test this hypothesis. To date, nothing has been published about this, with the only medium- to longer-term studies of UHR/prodromal patients focusing on rates of psychosis, rather than symptomatic or functional outcome of those who developed psychosis and those who did not (Cannon et al., 2008; Morrison et al., 2007; Phillips et al., 2007). Currently we are following a cohort of over 400 people who presented to the PACE Clinic between 1995 and 2005 to investigate this, amongst other issues. If there are a substantial number of people who cross the “psychosis threshold” and then revert to UHR status or even achieve remission and continue to function well then this may indicate that the psychosis cut-off is not meaningful and does not represent a valid diagnosis. Nevertheless, these cases will have been deemed to have become “psychotic” and attracted a DSM-IV psychotic diagnosis of some kind. This disorder may even be schizophrenia, since this diagnosis can be made on the basis of one week of psychotic symptoms, given that they have been treated, and six months of prodrome. Yet they will in fact have had a “trivial transition”.

In contrast, another person may never have crossed the arbitrary psychosis threshold, yet have deteriorated or failed to make age-appropriate gains in social and cognitive functioning and had intermittent positive psychotic symptoms. This person would be viewed as a non-transitioned case, yet in fact seems to resemble the traditional central concept of schizophrenia more than the first.

An additional complicating factor is the issue of treatment. It is likely that those who “transition” to psychosis receive more treatment than UHR patients who do not transition (e.g., will be linked in with first episode psychosis services, who generally provide longer, and possibly more intensive, episodes of care than UHR services). This additional treatment will of course influence the “natural progression” of disorder in transitioned cases, possibly contaminating our perspective on the validity of the transition threshold. One would hypothesize that the direction of this contamination would be towards a more favorable outcome for UHR patients who transition than would be the case if these patients had transitioned without receiving the extra treatment this “transition” attracts. Although clinically and ethically questionable, a more rigorous test of the validity of the transition threshold in terms of clinical course and outcome would be for UHR patients who transition and those who do not transition to receive the same type and amount of treatment.

3. Are all psychotic symptoms the same?

We have previously posited that psychotic symptoms are heterogeneous in origin (Nelson and Yung, 2009; Yung et al., 2009), and may be indicators of three different underlying processes: (a) an expression of an underlying fundamental disturbance suggesting vulnerability to a psychotic disorder such as schizophrenia; (b) clinical “noise” around a non-psychotic syndrome and not necessarily associated with distress, disability, or risk of schizophrenia. These symptoms might be expected to remit with treatment of the non-psychotic illness (Yung et al., 2007). We have previously called these “incidental” psychotic-like experiences (Yung et al., 2006); and (c) normal variants, present in non-clinical individuals, and not associated with distress or disability or increased vulnerability to psychotic disorder (Claridge, 1972; van Os et al., 2002; Yung et al., 2009). It is possible that UHR services such as the PACE Clinic are seeing individuals with category (b) attenuated psychotic experiences, especially since the service is becoming more well-known and the presence of psychotic experiences may be asked more frequently of young people presenting with a range of mental health problems. It may also be possible that people with category (c) experiences are also being referred. For example, if they present with another complaint but happen to volunteer that they experience psychotic-like phenomena. The outcome is likely to be better even if these category (b) or (c) experiences cross the arbitrary psychosis threshold than the outcome of someone with a vulnerability to schizophrenia.

4. Case histories

The following case histories from the PACE Clinic long term follow-up study highlight that outcome is not entirely

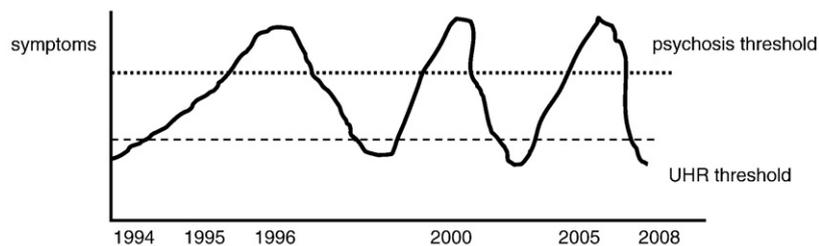


Fig. 1. Representation of course of symptoms over time: Case 1: Peter.

dependent on crossing the psychosis threshold. They also illustrate the heterogeneity of the UHR “syndrome”.

4.1. Case with good outcome but who crossed the psychosis threshold

4.1.1. Case 1: “Peter”¹

In 1996, at the age of 27, Peter was referred to the PACE Clinic by his local doctor. He presented with a 2 year history of depressed mood, social withdrawal and 10 years of heavy cannabis use. He reported about one year of attenuated psychotic symptoms, including the intermittent feeling that the television and radio may broadcast messages just for him, a feeling of being watched, and feeling that his parents were talking in riddles. While being seen at PACE, he was encouraged to cease cannabis use, and within 4 months had stopped. Within one week of ceasing cannabis his attenuated psychotic symptoms worsened and became held with delusional conviction. He had therefore crossed the arbitrary psychosis threshold and was referred for treatment to a psychiatric service and started on antipsychotics. However he was non-compliant and dropped out of treatment after a few weeks.

In 2008, Peter, now 39, was seen for follow up 11 years after discharge from PACE. He reported that he had had two other periods (in 2000 and 2005) during which similar delusions, and also auditory hallucinations reached the psychosis threshold. However he was free of symptoms between these periods. Both episodes were in the context of heavy alcohol and cannabis use and stopped shortly after ceasing these substances. At the time of assessment in 2008 Peter reported feeling well. Since the last episode his life had improved: he was recently married and had a 2 year old daughter. He had been employed as a delivery driver for the last two years. He felt satisfied with life. His Social and Occupational Functioning Assessment Scale (SOFAS) was rated as 80, indicating good functioning.

The time course of Peter’s symptoms in relation to the UHR and psychosis thresholds can be graphically represented, as shown in Fig. 1.

4.2. Case with poor outcome who did not cross the psychosis threshold

4.2.1. Case 3: “Stewart”

Stewart was referred to the PACE Clinic at the age of 19 in 1997 by a community mental health clinic (CMHC). He had

been taken to the CMHC by his mother who was concerned about him ruminating about past events, such as being taunted and bullied at school. On assessment at PACE he was irritable with low mood and displayed attenuated psychotic symptoms, including the belief that others thought they were better and smarter than he was, and that they may have been trying to hurt him or give him a hard time.

Stewart did not transition to psychosis during his 12 months at the PACE Clinic. He was followed up in 2008, 10 years after discharge. At this time, aged 29, he was found to be functioning poorly: he had not worked since leaving PACE, spent most of his time alone at home and had no friends. He continued to ruminate constantly about past grievances, and continued to feel that others, even strangers, looked down on him and may wish him harm. He denied other psychotic symptoms. He reported feeling frustrated that his life was passing him by, but seemed to make little attempt to change his circumstances. Stewart still fulfilled CAARMS criteria for UHR status, and met DSM-IV criteria for Social Phobia and Dysthymia at follow up. He had a SOFAS score of 35, indicating very low functioning (Fig. 2).

5. Conclusion

UHR research has focused on the general category of “psychosis” as an outcome. This has been useful from a practical point of view, and has clinical implications regarding the need for early intervention, including the need to commence antipsychotic treatment. It has also provided a “neat” outcome variable in research studies. However, the “transition to psychosis” should be recognized as an arbitrary cut-off point that may or may not be particularly useful diagnostically or prognostically. That is, it may not have implications for response to treatment, outcome and the presence of underlying biomarkers. At present there are some neuroimaging data suggesting that the cut-off may approximately correspond to some brain changes. These findings need to be replicated in larger, preferably unmedicated, samples. Other measures of possible underlying factors, such as genetic markers, are also needed, as well as further information regarding psychopathology and outcome.

We also argue in this paper that there may be some UHR cases who do not make the transition to first episode psychosis yet nevertheless may manifest the underlying schizophrenic substrate, just as there will be people who make the transition to psychosis who do not manifest it. In some, this “transition” will have no implications for their underlying neurobiology, cognition, genetics or any other marker, and no implication for long term outcome. That is it

¹ All names of cases have been changed.

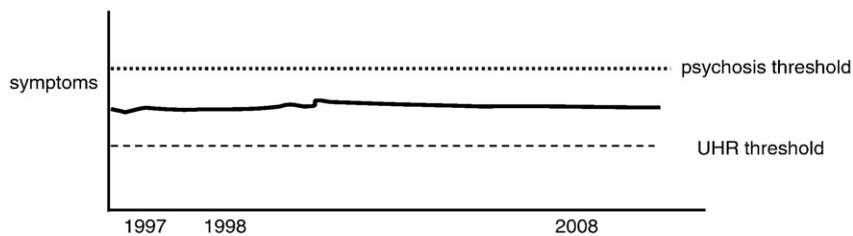


Fig. 2. Representation of course of symptoms over time: Case 3: Stewart.

may have been a “trivial transition”. Researchers cannot assume that this person will have the same biomarkers as a person who makes “transition” and develops a chronic course typical of severe schizophrenia. On the other hand, it is important to examine functional outcome, and assess predictors of this within the UHR group (Cornblatt et al., 2003; Niendam et al., 2009).

As representatives from the PACE Clinic, the original UHR (prodromal) service (Yung et al., 1996), we feel it is our responsibility to highlight the limitations of the concept, and to remind other researchers and clinicians that it was only ever an empirically defined cut-off in what are continuous symptoms. It has been a useful starting point, but ongoing thinking and research are needed.

These are more than just esoteric issues. The danger is the reification and codification of both the transition threshold and the UHR criteria as if they have implications for need for care and prognosis. This is evident already in the widespread use of the term “prodromal” (e.g. Cannon et al., 2008; McGlashan et al., 2006; Miller et al., 2002; Olsen and Rosenbaum, 2006), which implies inevitable transition to psychotic disorder. It is particularly timely to highlight these issues given the impending drafting of the DSM-V, in which the possibility of including a “prodromal risk” criterion for schizophrenia has been raised (Woods et al., 2009). It is critical not just to have this “risk syndrome” validated, but to have the hypothetical endpoint of psychosis validated as well.

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Contributors

All authors contributed to the conceptualization of the paper. Yung wrote the first draft, Wood Nelson and Thompson wrote sections of the paper and all authors reviewed and revised subsequent drafts.

Conflict of interest

The authors declare no conflicts of interest.

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