SUB-THRESHOLD STATES OF PSYCHOSIS – A CHALLENGE TO DIAGNOSIS AND TREATMENT

Stephan Ruhrmann, Frauke Schultze-Lutter, Joachim Klosterkötter

Abstract

In preventive research on psychoses, promising results of the first decade of early detection and intervention studies have led to the discussion of whether or not, in DSM-V, a *Prodromal Risk Syndrome* of some sorts should be considered. Yet, conversion rates predominantly are reported at rates well below 50%, thereby, for their limited follow-ups, possessing a considerable degree of uncertainty attached to the true status of non-converters. Further, across and within centres, they vary considerably, and are unsure to be maintained outside specialized services. These facts, amongst others, have raised serious doubts about the clinical and ethical appropriateness of including a risk syndrome at this time. With the discussion almost exclusively focusing on the predictive validity of at-risk criteria, the consistently reported main finding of this field of research is widely disregarded: Persons meeting at-risk criteria already suffer from multiple other mental and functional disturbances for those they seek help. In addition, they exhibit manifold psychological and cognitive deficits along with morphological and functional cerebral changes. Thereby, almost the entirety of these persons meets DSM-IV's general criteria for a mental disorder that is defined as a clinically significant behavioural or psychological syndrome associated with disability and/or severe distress. For this reason, the average help-seeking at-risk person clearly has to be considered as *ill*, i.e., as a *patient* with a need and right for treatment of *current* symptoms. Hence, it is argued that the clinical picture defined by current at-risk criteria should not be perceived exclusively as an as yet wanting attempt to define a prodromal or risk mental state but rather as a psychosis spectrum disorder in its own right – akin to ICD-10's Schizotypal Disorder – with conversion to psychosis just being one of several outcomes. It would introduce a conceptually consistent option for staging along the assumed underlying dimension of psychosis that includes mental states below the current threshold of psychotic disorders and may thus constitute a useful compromise between dimensional and categorical approaches to mental illness. Such a disorder, whose criteria are proposed and discussed, would initially best be part of the DSM-V research criteria. As a consequence from this shift in the perception of current at-risk criteria and quite probably meeting patients' needs best, access to standard medical care would have to be granted, and diagnosis- or symptom- rather than only conversion-related interventions would have to be developed.

Key Words: psychosis, psychosis spectrum disorder, DSM-V, Psychototypal Disorder, at-risk criteria, risk syndrome

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Introduction

Numerous retrospective studies on the prodrome of psychotic disorders have shown that the vast majority of patients develop negative and affective symptoms as well as precursors of positive symptoms and a significant loss of functioning already during this phase of illness (Yung and McGorry 1996a, Tan and Ang 2001, Gourzis et al. 2002, Häfner et al. 2003, Norman et al. 2005, Iyer et al. 2008). These findings and, despite all progress, the still limited success of treatment of manifest psychosis have stimulated an intensive research on prevention. The idea of preventing psychosis and particularly schizophrenia, however, has a long history in psychiatry (e.g., Sullivan 1927, Mayer-Gross 1932, Cameron 1938). Yet contrary to other medical disciplines, it took decades until it has been translated into research programs. In 1932, the wide-spread concerns of psychiatrists were summarized by the German psychiatrist Mayer-Gross, who had adopted a much more optimistic position himself: "The detection of the illness in its precursor state, which often spans a prolonged period of time, causes the greatest difficulties. … Furthermore, it has to be agreed to the general experience that these only gradually emerging changes in mental habitus often escape the observation of others and of self or remain unattended for their pettiness." (p. 295f., translated by FSL). Meanwhile,

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these concerns have gradually been overcome by findings from retrospective studies of the prodromal phase and of the negative effects of the duration of untreated psychosis (Marshall et al. 2005), and, since the mid 1990s, increasing efforts to predict and prevent psychosis have been made (McGlashan and Johannessen 1996, Yung et al. 1996, Klosterkötter et al. 1997); and, today, prevention of mental disorders is included into national and international health care policies (CDHAC 2000, EC 2005, BMG 2007): "Given the current limitations in effectiveness of treatment modalities for decreasing disability due to mental and behavioral disorders, the only sustainable method for reducing the burden caused by these disorders is prevention" (p. 14, WHO 2004). A *conditio sine qua non* for prevention is a valid prediction. For long, the predominant research strategy dedicated to this aim was the investigation of the offspring of families with diseased relatives (Erlenmeyer-Kimling et al. 2000). Conceptual advancements in prevention research (Gordon 1983, Bell 1992, Mrazek and Haggerty 1994, Yung and McGorry 1996b), however, allowed the development of new prediction strategies based on clinical variables (McGlashan and Johannessen 1996, Yung et al. 1996, Klosterkötter et al. 1997). Nowadays, basic symptom (Huber 1966, Schultze-Lutter 2009) and UHR criteria (Miller et al. 2003, Yung et al. 2005) constitute the major prediction approaches. Basic symptoms are disturbances of drive, affect, thought, attention and speech processes, (bodily) perception, motor action and central-vegetative functions that primarily remain in the subjective experience of the affected person. Of them, certain cognitive and perceptive symptoms form two alternative at-risk criteria (Schultze-Lutter et al. 2006, Schultze-Lutter et al. 2007b) (for the basic symptom criterion 'Cognitive Disturbances (COGDIS)' see **Box 2**: Criterion A.1). Notwithstanding their differences across and – over time - within centres, UHR criteria generally comprise of three alternative risk syndromes (see **Table 2**, second column): (1) attenuated positive symptoms (APS), (2) brief limited intermittent psychotic symptoms (BLIPS) and (3) a combination of one or more risk factors (always including genetic risk) and functional decline within a certain recent period whose length and degree differ across studies.

The clinical status of at-risk samples

As illustrated in the case vignette (see **Box 1**) and rather as a by-product of research on the predictive value of these criteria, studies of the last years have consistently revealed that a considerable portion of people fulfilling the characteristics of an at-risk state suffered not only from symptoms defining the criteria

Box 1. *Representative case vignette from the help-seeking population of the Cologne Early Recognition and Intervention Centre for mental crises (FETZ)*

A.Z., male, 19 years of age, still at school

Since the age of 13, he would suffer from **low mood**, **less intense feelings** (particularly a decrease in positive emotional responsiveness towards and empathy with others), **lack of energy and drive** as well as **feelings of physical weakness**. In addition, he reported **difficulties in persistence**, resulting in him frequently failing to carry things through to an end. These symptoms had **increased slowly but steadily** over the last six years with **feelings of worthlessness and inferiority** complementing the clinical picture since approximately two years. All of these problems would be present almost every day and **interfere with his social contacts**.

Four years ago, he had been under the **impression that he was part of a movie**, in which all other persons played a role according to a script that only he had not been informed about. At this time, he had also feared that the „movie" would actually be recorded by hidden cameras. This whole episode had lasted for about a month, yet throughout he had wondered if „I do not simply imagine the whole thing".

At present, he would mainly suffer from **concentration and memory problems** that, particularly at school, he would experience as handicapping. Further, he would frequently **forget what he was about to say** and would have to take a short mental break in order to remember his train of thought. On a nearly daily basis, he would experience difficulties in adequately expressing himself as he would **even fail to recall simple words**. He would then have to switch to another word and, for his own reassurance, would have taken to preparing his sentences in advance. Additionally, he would repeatedly encounter **difficulties in discriminating between fantasy and true memories** (e.g., if a friend had really been recently visiting). Sometimes, he would have to **mentally replay insignificant events of the day**; this would be extremely annoying. Further, **noises would sometimes maintain** in his mind and disturb his concentration. At times, he would be so **hypersensitive to stimuli** that he could not drive a car through the city centre when even the most slow chill-out music would play, because this already would be to **distractive**.

In all, he would have the feeling that **thinking has become difficult and slow** and that his **social contacts and school performance** would be **impaired by this**.

and already constituting a disordered mental state, but from various additional mental and functional problems. In line with results of retrospective studies on first-episode patients, studies demonstrated significant decline in psychosocial functioning and in quality of life and, moreover, cognitive deficits as well as morphological and functional cerebral changes (Woods 2001, Addington et al. 2004, Ruhrmann et al. 2004b, Brockhaus-Dumke et al. 2005, Pukrop et al. 2006, Borgwardt et al. 2007, Fusar-Poli et al. 2007, Pantelis et al. 2007, Pukrop et al. 2007, Schultze-Lutter et al. 2007e, Brockhaus-Dumke et al. 2008, Koutsouleris et al. 2008, Ruhrmann et al. 2008, Buehlmann et al. 2009, Riecher-Rössler et al. 2009, Witthaus et al. 2009, Ruhrmann et al. 2010). For the variety of affected domains, it is therefore not surprising that affected persons seek help for their *current* problems. For being granted access to health care in institutionalized health care systems, however, it is generally required to suffer from a formally acknowledged disorder, i.e., to fulfil the criteria of a diagnosis according to either ICD or DSM in its currently valid versions. Yet, at-risk criteria related clinically relevant changes, i.e., the constituting at-risk symptoms (APS, BLIPS or cognitive and/or perceptive basic symptoms), are not captured by current diagnostic categories. In DSM-IV-TR, a mental disorder is "conceptualized as a clinically significant behavioural or psychological syndrome or pattern that occurs in an individual and that is associated with present distress (…) or disability (i.e., impairment in one or more important areas of functioning) or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom" (p. xxi, APA 2000). Although these criteria are met by the majority of persons fulfilling at-risk criteria for developing psychosis, they are only granted regular access to the health care system, when they suffer from additional mental disorders, mainly of depression or social anxiety (Lencz et al. 2004, Svirskis et al. 2005, Simon et al. 2006, Schultze-Lutter et al. 2009). Consequently, at least from a formal, insurance-related point of view, at-risk patients without current (co-)morbidity fall through the cracks of health care systems for lack of an established diagnosis. As a result, no evidence-based standard care will be developed and provided to these patients. However, if access to medical care is regarded as a basic right, this situation needs to be changed (Smith et al. 1999, Berwick et al. 2001). For this purpose, two solutions can be considered with regard to the upcoming revision of DSM-IV: inclusion of at-risk criteria directly translating into a risk syndrome or inclusion of a new psychosis-spectrum diagnostic category relating to the distress and impairment condition of mental disorder. In the following part, we will show, why the perception of the clinical picture delineated by current at-risk criteria not as a risk syndrome but as an independent disorder in its own right (Ruhrmann et al. 2004a) is the preferrable solution.

Advantages of the introduction of a new psychosis spectrum category

By definition, the term 'at-risk' implies that the expected outcome, in our context psychosis, is currently not manifest and, in fact, may never be. This probabilistic definition is also the core of the concept of *indicated prevention*, originally introduced into somatic medicine (Gordon 1983), because the earlier deterministic approach of primary prevention failed to adjust to modern pathogenic models of complex diseases. As a further adaption to mental disorders, the definition of indicated prevention was subsequently broadened to enable the development of criteria that can include clinically significant signs and early symptoms of pathological mental changes, as long as the clinical picture does not meet diagnostic criteria for the manifest disorder (Mrazek and Haggerty 1994). Currently, neither in DSM-IV-TR nor in Chapter V (F) of the ICD-10, diagnostic categories or syndromes are considered solely for their predictive value (WHO 1992, APA 2000), while other chapters of the ICD-10 have already included risk related diagnostic entities, which do not represent diseases. Thereby, it has to be differentiated between states representing risk factors and states representing just risk indicators. For example, hypertension and hypercholesterolemia - unless severe - remain clinically asymptomatic, thus their pathologic denotation primarily relates to their contribution to the development of cardio- and cerebrovascular disorders (WHO 1992, De Backer et al. 2003). Yet hypertension and hypercholesterolemia are certainly pathogenic risk *factors* and, unlike the clinical at-risk criteria for psychosis, not only risk *indicators* that, currently, are perceived as epiphenomena of pathophysiological processes resulting from as yet poorly understood gene-environment interactions (van Os et al. 2008). Another risk related diagnostic entity is given by cervical dysplasia with its different grades. Like the current at-risk criteria for psychosis, cervical dysplasia is also exclusively considered a risk indicator or a "scientific surrogate for cancer risk" (Schiffman et al. 2007)) that may or may not proceed to carcinoma (ibid.). Nevertheless, each grade of cervical dysplasia is included into the classification system (ICD-10 N87.0–N87.2, D06) as a diagnostic category - without even explicitly mentioning the associated increased risk of cancer. Instead, the accompanying text refers to the grading of 'cervical intraepithelial neoplasia (CIN)', and thus puts the respective diagnosis (!) into a staging scheme ranging from 'mild cervical dysplasia (N87.0)' as equivalent of CIN I to the – still reversible – 'carcinoma in situ of cervix uteri (D06.-)' as equivalent to CIN III. Hence, cervical dysplasia may provide a conceptual framework for the inclusion of a diagnostic category below the threshold of psychosis and based on current at-risk criteria.

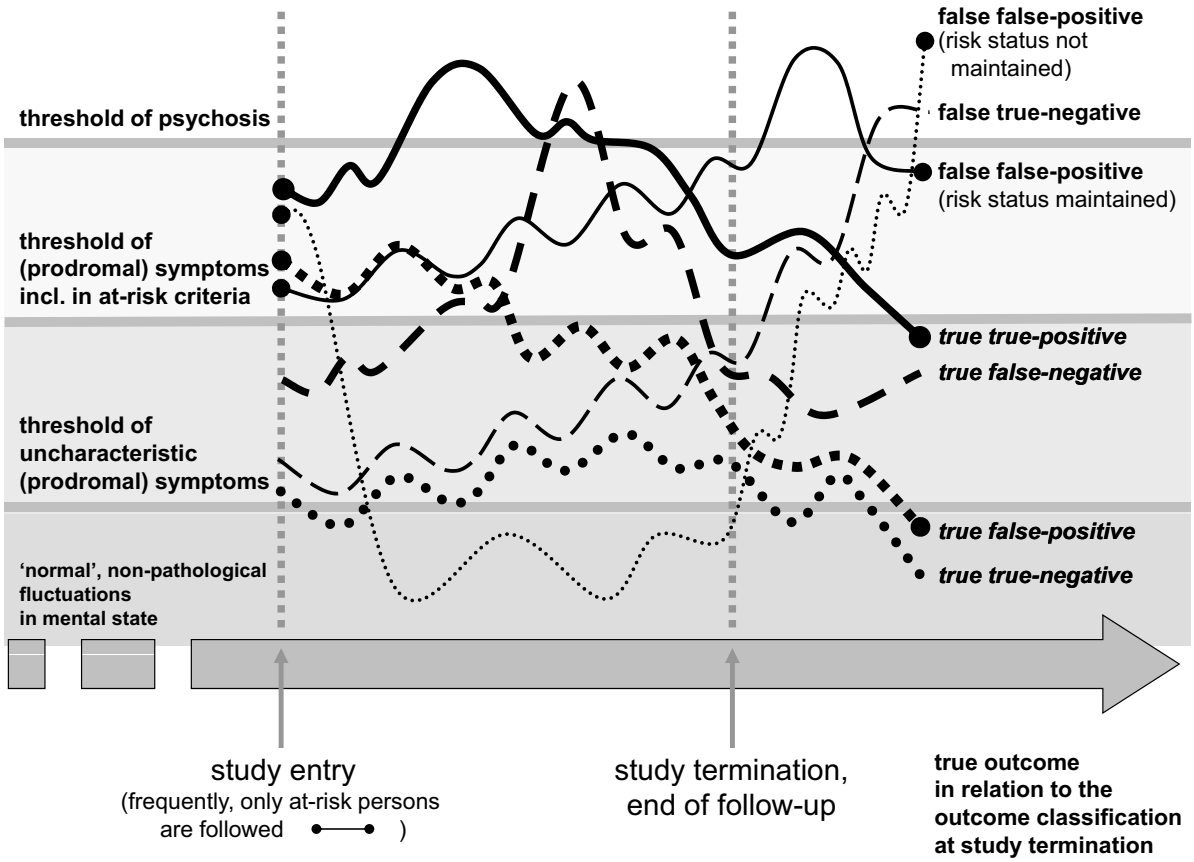
A *first* advantage of a new diagnostic category will be its consistency with the current, disorder-focussed, categorical classification of mental disorders in DSM. Consequently, within the decision-making process, the pros and cons of an introduction and, in case of a positive decision, the diagnostic criteria themselves could be focused without the necessity to decide about fundamental structural renewals of the diagnostic system itself. Such structural changes would be a prerequisite to introducing a risk syndrome in terms of a future-directed, probability-based state. By definition such future, probabilistic states cannot constitute a diagnosis, which requires clear-cut clinical statements

about presence or absence of a certain disorder, followed by clear-cut decisions about treatment - not prevention. Moreover, in light of the ICD following the same classification approach, the intended convergence of both systems would be facilitated by the decision for a diagnostic category.

With regard to the structure of current classification systems, a *second* advantage of the proposed spectrum diagnosis will be the resulting possibility to introduce a staging along the assumed underlying dimension of psychosis that includes mental states below the current threshold of psychotic disorders. This, in fact, may also constitute a useful compromise between dimensional approaches to mental disorders (Regier 2007, Demjaha et al. 2009, Krueger and Bezdjian 2009) and the categorical approach, which is deeply rooted not only in the clinicians' daily work but also – and probably even more resistant to conceptual changes – in the reimbursement procedures of health care systems around the world.

Suggestions to include at-risk states of psychosis into staging models have already been made earlier (Ruhrmann et al. 2003, McGorry et al. 2006). However, relating to the risk of a certain disorder by definition implies that the manifest disorder has not yet developed and may never develop. Hence, a syndrome exclusively conceptualized by a *risk* state cannot define an early *stage of the disorder.* Therefore, it is of outmost importance to clearly differentiate between at-risk states (including Huber's outpost syndromes) and prodromal states, which, by definition, inevitably and continuously progress into the manifest disorder. Yet as long as both at-risk and prodromal states are completely captured by clinical variables, they will not be distinguishable in cross-section but only in retrospect once frank psychosis had developed; on cross-sectional inspection, however, the observed syndrome may as well be a self-restricting, non-progressing episode (Simon and Umbricht 2010). But also such episodes cannot easily be classified right away, since, despite their spontaneous remission, they may still signify a first sub-threshold manifestation of the subsequent disorder for that Huber and colleagues (1979) coined the term 'outpost-syndrome' (Schultze-Lutter 2009). Alike prodromal states, outpost syndromes can unequivocally be classified only retrospectively, i.e., after the onset of frank psychosis. They were reported to last between three days and four years (mean: 5.3 months) with a mean interval to the onset of prodrome or first-episode of 10.2 years (Huber et al. 1979). The prevalence of single or multiple self-restricting at-risk-like episodes not heralding the subsequent development of psychosis

Figure 1. *Consequences of limited follow-ups on outcome classification in light of true final outcome (acc. to Schultze-Lutter and Ruhrmann 2008). For example, a 'false false-positive' assessment means that a person had been classified as false-positive at the end of a study's observation period, but developed a psychosis afterwards.*



is unknown. In light of retrospective data reporting intervals between the occurrence of first signs of mental illness and of first psychotic symptoms of up to decades (Huber et al. 1979, Häfner et al. 1993, Schultze-Lutter et al. 2010), current prospective studies cannot give reliable estimates of the frequency of such self-restricting episodes, because follow-ups are generally still much shorter than would be required to reliably rule out the development of psychosis (see **Figure 1**). A very rough approximation can only be derived from data of the Cologne Early Recognition (CER) study (Klosterkötter et al. 2001). With a follow-up of 9.6 years on average (SD=7.6, Median=7.8), the CER study is the only prospective study hitherto with an almost adequate follow-up in light of the duration of precursor states reported in retrospective studies. Therein, 30% of the initial criterion-positive cases (one of 66 basic symptoms) did not convert to schizophrenia (Klosterkötter et al. 2001).

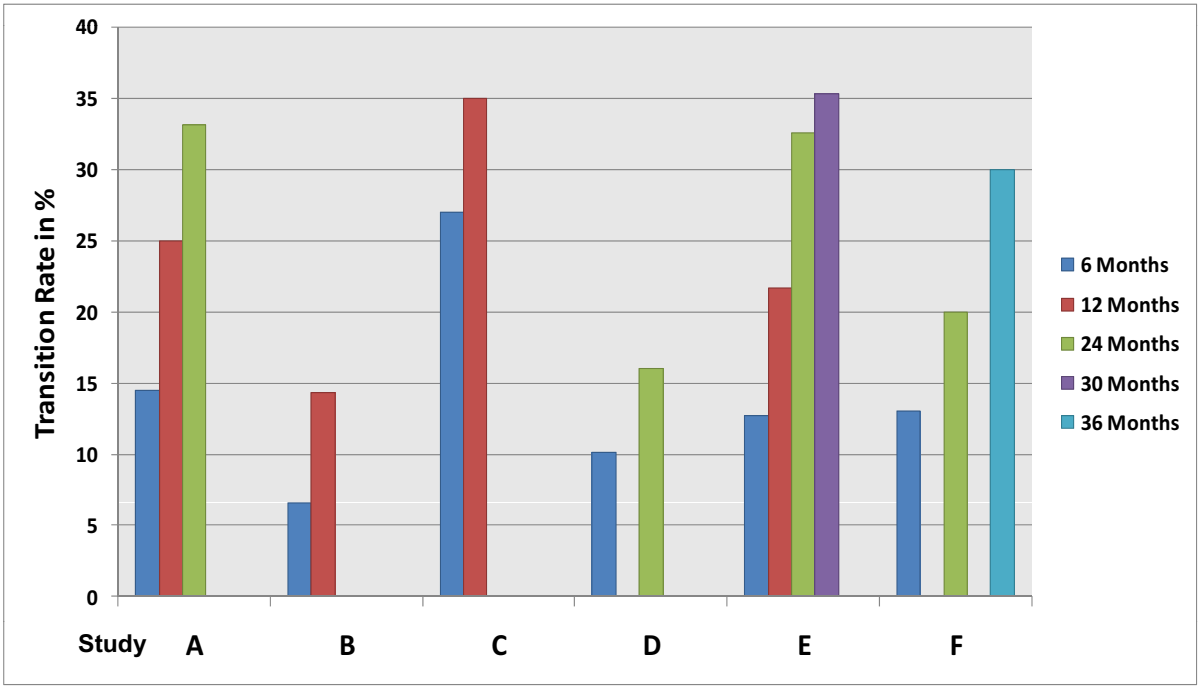
Such uncertainties of course and outcome would not affect the proposed psychosis-spectrum diagnosis that, like cervical dysplasia, could therefore be included into a staging model without causing logical inconsistency. In future and if need be, such a spectrum diagnosis may even be further stratified with regard to severity – as done with cervical dysplasia or with depressive episodes in ICD-10, thereby converging further towards a dimensional approach.

A *third* advantage of the introduction of an independent diagnosis rather than a risk syndrome for psychosis lies within the avoidance of stigmatization that might be triggered by explicitly linking the current mental state to a threatening and negatively labelled outcome (Corcoran et al. 2005). Although an increased risk of psychosis would maintain to be a characteristic of such a diagnosis – as is risk of cancer in the diagnosis of cervical dysplasia, the psychological and medical focus would be shifted from an uncertain future outcome to current psychopathology and needs.

Excursus to the fourth advantage: prediction of psychosis

A short initial side note on the current state of the art of prediction shall now be made to support understanding of the fourth advantage: As figure 2 demonstrates, so far published time-related transition rates differ significantly, thus giving way to concerns about the *predictive* validity of the criteria. In part, this is due to the use of different criteria as well as to the fact that even allegedly equal criteria using the same label, i.e. 'UHR' criteria, differ in definitions and symptom operationalization across and, over time, even within centres (Phillips et al. 2000, Miller et al. 2003, Yung et al. 2005). Similarly, another source of variance are the diverging definitions of transition (e.g. Miller et al. 2003, Yung et al. 2008, Woods et al. 2009) that do not, however, differ in predicting certain subtypes of affective or non-affective psychosis. Yet a main source

Figure 2. *Transition rates for different observation periods across and within centres.*
A: Schultze-Lutter et al. 2007 (subgroup positive for basic symptom criterion 'cognitive disturbances, COGDIS'); B: Ruhrmann et al. 2010 (COGDIS and ultra-high risk (UHR) criteria as alternative intake criteria); C: Yung et al. 2003, 2004 (UHR) ; D: Yung et al. 2006, 2008 (UHR, revised version of the former study); E: Cannon et al. 2008 (UHR; 30-months transition rate in reanalysis of revised data base 40% [Woods et al. 2009]); F: Haroun et al. 2006.



of varying transition rates is quite possibly the composition of help-seeking populations across and within centres, with centres differing in terms of their location and/or, within same centres, in terms of time or level of implementation into the local health care system (see **Figure 2**).

In this regard, it has been argued that lower conversion rates could be related to service utilization changes occurring in the wake of a growing acceptance and popularity of the early detection approach that supposably resulted in earlier help-seeking and, consequently, in more patients in earlier prodromal states less likely to convert within limited follow-ups (see **Figure 1**). This argument is supported by the rise in conversion rates over longer observation periods (Klosterkötter et al. 2001, Miller et al. 2003, Haroun et al. 2006, Schultze-Lutter et al. 2007b, Yung et al. 2008, Woods et al. 2009, Ruhrmann et al. 2010). Alike the classification of any outcome, also the dependence of transition rates on the duration of observation periods introduces a severe problem in current data: The investigated periods (see **Figure 2**) are rather too short in light of the range of years that pre-psychotic phases were shown to last on average (Huber et al. 1979, Häfner et al. 1993, Schultze-Lutter et al. 2010). And although a recent retrospective study found that symptoms included in at-risk criteria appeared only at a later state of the prodrome, on average 2.7 (SD=5.1; range 0-33) years before the first positive symptom (Schultze-Lutter et al. 2010), as outlined above (see **Figure 1**), for all but the converted subjects, the true outcome is not known but remains a probability in all available prospective studies but the CER study (Klosterkötter et al. 2001). Moreover, in general population and birth cohort studies, persistence of psychosis-like experiences was linked to the subsequent development of clinical psychosis (van Os et al. 2009), and a re-analysis of CER data indicated that prodrome duration might be related to different predictive accuracy of potentially predictive symptoms (Schultze-Lutter et al. 2007d). In summary, observation periods in most current prospective prediction studies allow a valid determination of outcome only for those transiting during the study; a valid determination of true transition rates and with that of non-transition would require decades of observation (see **Figure 1**).

Yet, these considerations are related to phenomena arising in samples of highly specialized centres and, hence, have occurred in samples highly preselected for their risk of psychosis - a selection bias well intended with regard to the studies' aims (McGorry et al. 2003). If the same criteria were now to be included into DSM, the stability of their predictive accuracy across different clinical settings would first require proof, e.g., their accuracy should be as high within primary health care settings as within specialized centres. Outside specialized centres, however, the prevalence of at-risk patients presumably will be much lower and lowest in the non-help-seeking general population. This fact will have significant impact on the frequently employed 'positive predictive value' (PPV) that, other than sensitivity and specificity, is highly dependent on prevalence rates (Hennekens and Buring 1987, Guyatt et al. 2008): For example, even at fixed sample size, sensitivity and specificity (both assumed at 90%), the PPV drops from 50.0% to 8.3% when the prevalence drops from 10% to 1%. Prevalence-independent measures are the positive and negative likelihood-ratios, which therefore are favoured in the literature on evidence-based medicine (Sackett et al. 2000, Guyatt et al. 2008). As is demonstrated in **Table 1**, conclusions about the predictive validity based on the PPV are not supported by the LRs in most studies and thus, the generalizability of results even across populations of specialized centres is uncertain, at least as long as inferences on the immediate risk are drawn.

As **table 1** further demonstrates, the number of studies allowing conclusions about sensitivity of criteria is rather small; only three studies (see **Table 1**, rows 1-4) included criteria-negative control groups from their help-seeking populations (Klosterkötter et al. 2001, Yung et al. 2006, Yung et al. 2008, Woods et al. 2010). Despite promising reports on sensitivities and specificities, the positive LRs across studies are rather small, whereas the negative LRs are within a moderate to high range (Guyatt et al. 2008) (Note: contrary to positive LR, negative LRs are the better, the lower their value). Thus some current at-risk criteria appear well able to rule out an increased risk of psychosis - an important finding with regard to the reduction of false-negative predictions. With regard to the positive LRs, however, risk probability only seems slightly increased by positive at-risk criteria – at least at the given observation times. This is mainly due to an unfavourable ratio of a high sensitivity to a lower specificity (see **Table 1**). Yet, so far attempts to increase specificity by different variable selections have mainly resulted in a loss of sensitivity even in the subsamples fulfilling at-risk criteria (see **Table 1**, rows 5-8) (McGorry et al. 2008). An exception is the model of Mason et al. (2004) that showed favourable values for both parameters, although it would still have excluded 16% of UHR subjects later converting to psychosis (1-sensitivity) from preventive measures, and it must be assumed that the sensitivity would have dropped further, if the model was applied to the complete sample of the centre. A main reason of the observed pattern of sensitivity declining with growing specificity and vice versa lies within the dichotomous nature of the suggested predictor models, discriminating between 'risk' and 'no risk' by means of a certain cut-off point. A recently proposed approach to overcome this problem has yet to be further validated (Ruhrmann et al. 2010). In conclusion, current at-risk criteria are clearly associated with an increased risk of developing psychosis when compared to the incidence of psychoses in the general population (annual rate of 0.035%, (Kirkbride et al. 2006)) or other clinical samples, even within institutions serving a broader spectrum of disorders (Yung et al. 2008, Woods et al. 2009). Yet with regard to the non-conversion rate that, except for the CER study, generally by far exceeds 50% in larger samples, the prediction of psychosis still involves a considerable degree of uncertainty.

As this excursus demonstrates, at the current state of the art, risk prediction most certainly requires further research to solve even the most important problem of the *true* predictive validity of at-risk criteria. To this, long-term transition rates and sensitivity in different

Table 1. *Prognostic accuracy of different predictors of psychosis*

Study	At-risk criteria	N positive for (ARG/CG)	Age (years) mean ± SD	Follow-up (in months) mean ± SD	Variables considered as predictors	Predictors	Sensi-tivity	Speci-ficity	PPV	NPV	Pos. LR*	Neg. LR*
Klosterkötter et al., 2001; Schultze-Lutter et al., 2006[1]	basic symptoms (BS)	110/50	28.8 ± 9.8	9.6 ± 7.6 (in years)	BS	result 1: 1/66 BS positive result 2: 1/10 cognitive-perzeptive BS (COPER) result 3. 2/9 cognitive BS (COGDIS)	0.98 0.87 0.67	0.59 0.54 0.83	0.70 0.65 0.79	0.96 0.82 0.72	2.4 1.9 3.9	0.03 0.2 0.4
Yung et al., 2006	UHR	119/173	range 15 - 24	6	UHR (in total), GAF	UHR positive 50≤GAF>50	0.92 0.69	0.62 0.62	0.10 0.10	0.99 0.97	2.4 1.8	0.1 0.5
Yung et al., 2008 (follow-up of Yung et al., 2006)	UHR	119/173[1]	range 15 - 24	24	UHR (in total)	UHR positive (whole sample) UHR positive (PACE) UHR positive (Youthscope)	0.91 1.00 0.75	0.63 0.52 0.74	0.16 0.17 0.14	0.99 1.00 0.98	2.5 2.1 2.9	0.1 0.0 0.3
Woods et al., 2009[§]	UHR	see footnote 2	18.2 ± ?	30	UHR	UHR positive	0.89	0.60	?	?.	2.2	0.2
Lencz et al., 2003	APS	34	16.4 ± 2.3	24.7 ± 15.9	positive syndrome scale of SIPS	result 1: SIPS-positive syndrome scale ≥ 15 result 2: highest items score (SIPS P.1.-P.5.) = 5	0.67 0.78	1.00 0.76	1.00 0.54	0.89 0.90	*a*/0 3.3	0.3 0.3
Mason et al., 2004	UHR	74	17.3 ± 2.8	>12, 26.3 ± 9.2	various: demography, psychopathology	result 1:schizotypal personality disorder result 2: unusual thought content/magical ideation, marked impairment in role functioning, acoustic hallucinations, anhedonia / asociality	0.76 0.84	0.76 0.86	? ?	? ?	3.2 6.0	0.3 0.2
Yung et al., 2004	UHR	104	19.4 ± 3.5	12	various: demography, psychopathology	trait-state criterion positive plus APS positive duration of symptoms > 5 years GAF < 40 SANS attention > 2 model of '≥1 predictor positive'	0.31 0.08 0.17 0.14 0.60	0.93 1.00 1.00 1.00 0.93	0.69 1.00 1.00 1.00 0.81	0.72 0.69 0.70 0.89 0.82	4.4 *a*/0 *a*/0 *a*/0 8.1	0.7 0.9 0.8 0.9 0.4
Cannon et al., 2008	UHR	291	18.1. ± 4.6	30	various: demography, psychopathology, role functioning, antipsychotics, substance abuse	[1] genetic risk & GAF reduction ≥ 10%, [2] unusual thought content (SIPS item P.1. >2), [3] paranoid ideation (SIPS item P.2. > 2), [4] social functioning [< 7], [5] any substance abuse result 1: all of the 5 result 2: 1, 2, & 3 result 3: 1, 2, & 4	0.08 0.34 0.30	0.98 0.89 0.90	0.79 0.74 0.81	? ? ?	4.0 3.1 3.0	0.9 0.7 0.8
Ruhrmann et al., 2010	UHR COGDIS	179 [3]	23.0 ± 5.2	18	various: demography, psychopathology, role functioning, substance abuse	SIPS Positive score >16 Bizarre Thinking (SIPS item D.2.>2) Sleep Disturbances (SIPS item G.1. >2) Schizotypal personality disorder (SIPS definition)[4] GAF-M score , highest past year Years of education (incl. university, YE)	0.42	0.98	0.83	0.87	19.9	0.6

ARG: at-risk group; CG: control group; GAF: Global Assessment of Functioning Scale (-M: modified version, SIPS); SIPS: Structured Interview for Prodromal Syndromes; COGDIS: COGDIS: basic symptom criterion 'cognitive disturbances (table3)'; PPV: positive predictive value; NPV: negative predictive value; pos. LR: Likelihood Ratio when test result is positive [sensitivity / (1-specificity)]; neg. LR: Likelihood Ratio when test result is negative [(1 -sensitivity) / specificity]; ?: no data reported; *a*/0: division by zero; see also table 1 for abbreviations

* Calculated by author based on reported data (except for Klosterkötter et al., 2001, Schultze-Lutter et al., 2006, Ruhrmann et al., 2010); § analysis revised data base of Canon et al. 2008

[1] total sample; subgroups: AR-PACE = 76, CG-PACE = 67, AR-Youthscope = 43, CG-Youthscope = 106; [2] AR = 303-377, CG = 335-483 (sample sizes not clearly reported, range matches reported variance); [5] for sample size see table1; [3] total study sample including drop-outs n = 245; [4] minimum duration of symptoms only 1 year

Table 2. *Comparison of Psychototypal disorder, UHR criteria, ICD-10 schizotypal disorder and DSM-IV-TR schizotypal personality disorder*

	Psychototypal Disorder (see **Box 2** for details)	**UHR Criteria according to the SIPS** (McGlashan et al. 2001)	**Schizotypal Disorder** (ICD-10: F21.0)	**Schizotypal Personality Disorder** (DSM-IV-TR: 301.22)
Number of symptoms required / onset & duration	Criterion A.1. (Cognitive disturbances) At least 2 symptoms; minimal frequency of at least once a week during the last 3 months; Criterion A.2. (Attenuated positive symptoms) At least 1 symptom; average frequency of at least once per week in the past month or, if onset had been rather recent, at least 4 times in the past week	Criterion B. Attenuated Positive Symptom (APS) Prodromal Syndrome Any SIPS Positive Symptoms P1-P5[1] Scales scored 3-5; first appearance within the past year or current rating one or more scale points higher compared to 12 months ago; symptoms have occurred at an average frequency of at least once per week in the past month	Criterion A. The subject must have manifested, over a period of at least two years, at least three to four of the following, either continuously or repeatedly (see below (1)-(9))	Criterion A. A pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behavior, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following (see below (1)-(9))
Attenuated positive symptom	(2) odd beliefs or magical thinking influencing behaviour and inconsistent with subcultural norms (e.g., superstitiousness, belief in clairvoyance, telepathy or "sixth sense"; in children and adolescents, bizarre fantasies or preoccupations) including non-delusive, attenuated forms of experiences of alien control ('Ich-Störungen')	P1 Unusual Thought Content/ Delusional Ideas	(4) [3] odd beliefs or magical thinking influencing behaviour and inconsistent with subcultural norms	(2) [3]odd beliefs or magical thinking that influences behavior and is inconsistent with subcultural norms (e.g., superstitiousness, belief in clairvoyance, telepathy, or "sixth sense"; in children and adolescents, bizarre fantasies or preoccupations)
Attenuated positive symptom	(1) ideas of reference (excluding delusions of reference) (3) suspiciousness or paranoid ideas, unrelated or exceeding normal reaction to an adverse event and not restricted to fear of humiliation and embarrassment	P2 Suspiciousness / Persecutory Ideas	(5) suspiciousness or paranoid ideas	(1) ideas of reference (excluding delusions of reference) (5) suspiciousness or paranoid ideation
Attenuated positive symptom	(4) grandiose ideas including promotion of obviously unrealistic plans	P3 Grandiose Ideas	not included	not included
Attenuated positive symptom	(5) unusual perceptual experiences including somatosensory (bodily) illusions or derealisation (e.g., . repeated unformed images and pseudohallucinations such as shadows, trails, sounds incl. hearing own name called, felt presence of something/someone or frequent illusional misperceptions)	P4 Perceptual Abnormalities / Hallucinations (derealisation is part of P1, depersonalization part of N4 Decreased Experience of Emotions and Self)	(7) unusual perceptual experiences including somatosensory (bodily) or other illusions, depersonalization or derealization	(3) unusual perceptual experiences, including bodily illusions
Attenuated positive symptom	(6) odd thinking and speech, vague, circumstantial, metaphorical, over-elaborate or often stereotyped thinking, manifested by odd speech or in other ways, without gross incoherence	P5 Disorganized Communication	(8) vague, circumstantial, metaphorical, over-elaborate or often stereotyped thinking, manifested by odd speech or in other ways, without gross incoherence	(4) odd thinking and speech (e.g., vague, circumstantial, metaphorical, overelaborated, or stereotyped)
Transient psychotic symptoms	not included	Criterion A. Brief Intermittent Psychotic Symptom Prodromal Syndrome (BLIPS) Any SIPS P1-P5 Scales scored 6;	(9) occasional transient quasi-psychotic episodes with intense illusions, auditory or other hallucinations and delusion-like ideas, usually occurring without external provocation	not included

Table 2 *continued*

		first appearance in the past three months; present for at least several minutes per day at a frequency of at least once per month		
Cognition	Criterion A.1. 2 of 9 cognitive disturbances (basic symptoms; see **Box 2**)	not included	(6) ruminations without inner resistance, often with dysmorphophobic, sexual or aggressive contents	not included
Affect	not included	not included	(1) inappropriate or constricted affect, subject appears cold and aloof	(6) inappropriate or constricted affect
Behaviour & appearance	not included	not included	(2) behaviour or appearance which is odd, eccentric or peculiar	(7) behavior or appearance that is odd, eccentric, or peculiar
Psycho-social functioning	The disorder causes clinically significant distress or impairment in social, occupational, or other important areas of functioning Note: If psychosocial impairment is severe and persistent, the development of a Psychotic Disorder is more likely. Classification of subtype: see **Box 2**	not included as single aspect,but as a necessary part of Criterion C (see below, (3) in 'family history of schizophrenia/psychosis')	(3) poor rapport with others and a tendency to social withdrawal	(8) lack of close friends or confidants other than first-degree relatives (9) excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgments about self
Course & outcome	Does not occur exclusively during the course of Schizophrenia, a Schizophreniform Disorder, a Schizoaffective Disorder, a Mood Disorder With Psychotic Features, a Delusional Disorder, a Brief Psychotic or another Psychotic Disorder, a Personality Disorder (e.g., other than in Schizotypal PD, a pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships is not present) or a Pervasive Developmental Disorder and is not better accounted for by severe Obsessive-Compulsive or Anxiety Disorder. Classification of total duration of mental disturbances: • With recent onset (< 1 year) • With past onset (> 1 year) Classification of longitudinal course: see **Box 2**	Expected to develop into a frank psychotic disorder in a high proportion of individuals	The disorder runs a chronic course with fluctuations of intensity. Occasionally it evolves into overt schizophrenia. There is no definite onset and its evolution and course are usually those of a personality disorder	Pervasive pattern of deficits, i.e., personality disorder; a relatively stable course, with only a small proportion of individuals going on to develop Schizophrenia or another Psychotic Disorder
Family history of psychosis	not included	Criterion C. Genetic Risk and Deterioration Prodromal Syndrome (1) patient meets criteria for Schizotypal Personality Disorder [2] (2) patient has 1st degree relative with a psychotic disorder (3) patient has experienced at least 30% drop in GAF score over the last month compared to 12 months ago [1 and 3] or [2 and 3] or all are met.	It is more common in individuals related to schizophrenics and is believed to be part of the genetic "spectrum" of schizophrenia. A history of schizophrenia in a first-degree relative gives additional weight to the diagnosis but is not a prerequisite.	Appears to aggregate familiarly and is more prevalent among the first-degree biological relatives of individuals with Schizophrenia than among the general population

GAF: Global Assessment of Functioning Score; SIPS: Structured Interview for Prodromal Syndromes;
[1] SIPS Item indices; [2] SIPS definition: minimum duration of symptoms only 1 year; [3] numbers according to original listing

clinical settings are among the most essential questions to be answered. Yet, even if satisfying answers will be given in future, the probabilistic nature of the risk-related approach of prediction implicates that false-positive estimations will continue to occur. Also the addition of biological markers is unlikely to solve this problem, as even in studies demonstrating biological aberrations in manifest psychosis patients usually exhibit a wide range of overlap with healthy controls. Like in other fields of prevention, a decision will therefore have to be made: the hazards associated with the onset of psychosis, and particularly of schizophrenia, have to be weight against those associated with a false-positive prediction. This inevitably leads to a complex, mainly ethically driven debate that might not be concluded in the near future (Corcoran et al. 2005, Klosterkötter and Schultze-Lutter in press). However, as this debate over-emphasises aspects of prediction and prevention not in the least unique to psychosis, it runs the risk that those in need for help will continue to be excluded from being entitled to legitimately claiming health care services. In this lies the *fourth* advantage of an independent diagnostic category: it shifts the focus from an uncertain future to current, very real needs of patients without losing sight of potential future demands. It allows to acknowledge a person who suffers from at-risk related changes in thinking, affect, experience and functioning so much that they seek help for them, i.e., the typical member of at-risk samples reported in studies, as *ill* and, therefore, as a patient. The *fifth* advantage is an immediate consequence of these considerations. An at-risk syndrome based approach will always impose a restriction on intervention studies as the primary outcome criterion has inevitably to be the future preventive effect, implicating the significant difficulties discussed above. The introduction of a spectrum disorder would enable the formulation of a comparably immediate symptomatic and functional improvement as the primary outcome measure in intervention studies instead. Thereby, the main pre-requisite for the development of evidence-based clinical *treatment* options will be fulfilled. Further, instead of applying treatments off-label that are based on empirically barely proven conclusions of analogy to treatment of frank psychosis, research on alternative interventions tailored to this particular mental (and presumably biological) condition would be facilitated (Ruhrmann et al. 2009). Indeed, it has already been argued that treatment approaches that show no or only little effect in full-blown psychoses might be highly efficient in less severe but possibly biologically related mental states as characterised by at-risk criteria (Amminger et al. 2010, McGorry et al. 2009). As another result of such treatment related intervention research, in future, evidence-based guidelines for clinical practice could be provided to avoid under- as well as overtreatment. The focus on treatment will also contribute to the avoidance of stigma, as it emphasises the reversibility of the current state. Patients and their relatives and peers have thus the chance to perceive control over their mental state *hic et nunc*, thereby reducing stress, which should in turn also reduce the potential risk of psychosis (Nuechterlein 1987, Bak et al. 2009).

Psychototypal disorder: Advancing schizotypal disorder (ICD-10)

ICD-10 already includes an independent psychosis spectrum disorder that is diagnosed independently of any associated risk of psychosis and shares some similarities with the UHR criteria: the schizotypal disorder (StD; ICD-10, F21). In DSM-IV that, relating to Meehl's schizotypy model (Meehl 1962, Meehl 1990), had only included a presumed spectrum personality disorder, namely the schizotypal personality disorder (StPD, 301.22), no such disorder is as yet recognized. Thus in comparison to ICD-10's StD and UHR criteria (here defined in accordance with (McGlashan et al. 2001)), major differences of DSM-IV-TR's StPD result from its conceptualisation as an axis II disorder (which clearly separates StPD from a psychosis spectrum disorders like StD that would have to be placed on axis I), the related requirement of a stable course of symptoms and the perception of subsequent psychosis as the exceptional development of a co-morbid axis-I-disorder (see **Table 2**).

As further demonstrated in **table 2**, StD, UHR criteria and StPD likewise consider attenuated forms of positive symptoms according to the A criterion of Schizophrenia in DSM-IV, except for 'odd behaviour and appearance' that was not included in UHR criteria. Further, UHR and StD but not StPD incorporate transient psychotic symptoms. And negative and schizoid-like affective symptoms are part of both StD and StPD but, for specificity reasons, not of UHR criteria.

With regard to the debate about the inclusion of a risk syndrome for psychosis into DSM-V, StD could serve as an alternative model for an independent axis-I psychosis spectrum disorder associated with but not restricted to an increased risk of developing frank psychosis. While such a conceptualisation would avoid problems related to insufficient predictive accuracy and/or time-related uncertainties of long-term outcome including unnecessary early labelling and stigmatisation as 'psychosis-prone' (see above), it could still serve as a starting-point for further research on the prevention of psychosis. Moreover, such a step would further increase convergence between DSM and ICD. In modification of the term 'schizotypal disorder', such a spectrum disorder could be termed *Psychototypal Disorder* to delineate its association not only to schizophrenia but all non-affective and affective psychoses ('psychot-' from psychotic ; '-o-' = connective vowel, like in psychotomimetic; '-typal' = pertaining to a type [Webster's Dictionary], i.e., psychosis spectrum). Yet, whatever term would be chosen, 'at-risk' or 'prodrome' should be no part of it to avoid any premature statement about future outcome. For further evaluation, refinement and validation, especially in non-specialized settings, such a disorder should initially be included among the DSM-V research criteria.

Criteria of a Psychototypal Disorder

When relating to current at-risk criteria and to StD as an exemplary disorder concept, some difficulties in

the choice of symptoms for inclusion in a Psychototypal Disorder category and their operationalization occur (for an exemplary, preliminary definition see **Box 2**).

First, UHR criteria include three different risk syndromes that have rarely been evaluated separately. APS, however, were repeatedly reported to account for the vast majority of inclusions (about 80%), resemble four of the nine StD criteria (see **Table 2**) and, hence, would be first-choice. This, however, introduces a second difficulty as APS in early detection research are not assessed by presence of single symptoms but by certain severities of syndromally defined items of specifically designed scales (McGlashan et al. 2001, Yung et al. 2005); see **Table 2**). Thus sufficiently discriminating criteria of APS corresponding to the commonly dichotomous symptomatic criteria of ICD as well as DSM diagnoses would first have to be developed and validated from data of large samples (e.g., PACE, EPOS and NAPLS). These problems do not occur with the basic symptom criteria that have been studied separately and are based on the assessment of single symptoms (Klosterkötter et al. 2001, Schultze-Lutter et al. 2007a), thereby fully complying with the composition of ICD and DSM criteria. A third difficulty relates to the time criterion, which is a maximum five-year presence in the Australian (Yung et al. 2005), a maximum one-year presence at current severity level in the American UHR conceptualisation and a minimum two-year presence in StD (see **Table 2**). The minimum time should certainly be shorter than the two-year criterion of the StD, as a prolonged minimum symptom duration would again foreclose early access to help. In addition, a maximum duration of symptoms should not be defined, because this had mainly been introduced within research contexts for reasons of risk enrichment and sufficient conversion rates. To avoid potential confusion with personality disorders (in case of APS, especially with StPD), it should be explicitly noted that, in Psychototypal Disorder, symptoms delineate a change from premorbid functioning and personality and that therefore "a pervasive pattern" of deficits (APA 2000) is not observed, although social withdrawal, discomfort in social interactions and deficits in social skills, odd or eccentric behaviour as well as an inappropriate or constricted affect might develop in course of the disorder. To make allowance for the association between symptom duration and conversion to psychosis in at-risk patients (Ruhrmann et al., 2010, Yung et al., 2004) and to support further development of prediction and prevention efforts starting from such a Psychototypal Disorder, a classification of total duration of mental disturbances (e.g., 'with recent onset (< 1 year)' and ‚with past onset (> 1 year)') as well as of the longitudinal course (i.e., single episode, episodic or continuous) should be introduced. A fourth difficulty is with the consideration of psychosocial functioning. A decline in psychosocial functioning has repeatedly been demonstrated in at-risk samples (Addington et al. 2004, Yung et al. 2004, Yung et al. 2006, Cornblatt et al. 2007, Riecher-Rössler et al. 2007, Ruhrmann et al. 2007, Cannon et al. 2008, Ruhrmann et al. 2010) and was a predictor of conversion to psychosis in these samples (see **Table 2**). Further, a persistent functional deterioration, already in 1923 termed "Knick in der Lebenslinie" [kink in the life line] by Kraepelin's pupil Eugen Kahn (1923) often precedes the manifestation of psychosis (Yung and McGorry 1996a, Tan and Ang 2001, Gourzis et al. 2002, Häfner et al. 2003, Norman et al. 2005, Iyer et al. 2008). In addition, impairment in one or more important areas of functioning is part of the DSM's conceptualisation of mental disorder (see above), although it is not mandatory for all syndromes (APA 2000): for example, functional impairment is mandatory for Schizophrenia, (non-psychotic) Mania and Schizoaffective Disorder with Hypomanic, Manic or Mixed Episode, but not for Schizophreniform and Brief Psychotic Disorder or, apart from the impact of delusion or its ramification, for Delusional Disorder. Furthermore, it is not required for the diagnosis of a Major Depression Disorder and Schizoaffective Disorder with Major Depressive Episode for that clinically significant distress caused by the symptoms is sufficient. Hence the question arises if functional impairment really has to be an obligatory criterion of the Psychototypal Disorder. The most obvious advantage of dropping this criterion lies in the opportunity to offer treatment as soon as symptoms cause significant distress but before functional impairments develop (Lehman et al. 2002). The potential psychosis-predictive but also presumably outcome-related role of severe impairment in psychosocial functioning could again be accounted for by a related classification of subtypes (see **Box 2**) to support further prevention research as well as the initiation of adequate supportive and interventive measures. These subtypes could be further specified in terms of the symptom-independent Social and Occupational Functioning Scale (SOFAS) in future studies (Goldman et al. 1992, APA 2000). A related fifth difficulty concerns (attenuated) negative symptoms. Negative symptoms were argued to be the core syndrome of schizophrenia (Stahl and Buckley 2007); and findings from retrospective and prospective studies support the important role of negative symptoms in the early course of psychotic disorders (Häfner et al. 1998, Cornblatt et al. 2003, Mason et al. 2004, Riecher-Rössler et al. 2007, Ruhrmann et al. 2007, Schultze-Lutter et al. 2007c, Perivoliotis et al. 2009). Though these findings demonstrate the presence of (attenuated) negative symptoms in at-risk samples, especially non-severe forms of negative symptoms are not specific to the psychotic spectrum but also occur with other disorders (Peralta and Cuesta 2004). Consequently, their inclusion into the diagnostic criteria of the suggested syndrome would compromise the symptomatic specificity thus rendering its separation from other diagnostic constructs more difficult. The same problem would occur, if BLIPS would be included into this new diagnostic syndrome, especially with regard to its separation from Brief Psychotic Disorder. Thus, contrary to UHR criteria and StD (see **Table 2**), BLIPS or 'occasional transient quasi-psychotic episodes' are not suggested as diagnostic criteria.

The main innovation of the Psychototypal Disorder in comparison to the UHR criteria and StD, however, is the introduction of subjective cognitive disturbances, i.e., COGDIS. COGDIS symptoms can also occur in biological relatives of patients with schizophrenia (Klosterkötter et al. 1997), but are rarely found in non-psychotic psychiatric disorders (e.g., Klosterkötter et

Box 2. *Psychototypal Disorder: Research Criteria*

A. Characteristic symptoms
Symptoms have not been present or have been significantly less frequent in what is considered the premorbid, healthy state. They do not exclusively occur in hypnagogic and hypnopompic states or other states of 'clouded' consciousness such as during intoxication by psychotropic substances. One (or both) of the following:

A.1. Cognitive disturbances
At least two of the following subjectively experienced and self-reported cognitive disturbances have occurred at a minimal frequency of at least once a week during the last three months:

(1) sudden disrupting interference of completely trivial thoughts that are unrelated to current thinking and mood/affect
(2) sudden blockage or gradual fading of thoughts including loss of thread/train of thoughts in terms of a self-experienced tendency to loosening associations
(3) pressure of unrelated thoughts not associated with each other or linked by a common underlying theme
(4) disturbance of receptive speech, either heard or read, experienced as difficulties or even inability to comprehend and recognize the meaning of rather common words, word sequences or sentences
(5) disturbance of expressive speech, reported as problems in verbal fluency, verbal precision and/or word availability due to difficulties in verbal expression with a particular problem producing adequate words
(6) unstable ideas of reference that are immediately rectified and perceived as an unfounded, faulty impression once the patient becomes aware of this experience
(7) disturbance of abstract thinking with a reduction of understanding towards the concrete, literal meaning, either self-recognized or showing in explanation of proverbs and/or fables
(8) inability to divide attention, self-experienced difficulties in integrating input from more than one sense and, thus, in dealing with two demands involving more than one sense at the time with at least one demand generally performed on a (semi-)automatic level, e.g., difficulty in preparing a sandwich and talking to someone at the same time
(9) captivation by details of the visual field so that the whole attention seems to be caught and captured by a single random aspect from that one's eyes can hardly be averted

A.1. cont'd:
Note: Except for (7), these symptoms will largely remain to the patient's experience and will not become obvious in the clinical interview.
Note: (2) and (7) might not be reliably assessable in children younger than 13 years of age. If reported by younger children, they should carefully be examined for their psychopathological character.

A.2. Attenuated positive symptoms
At least one of the following symptoms that do not reach psychotic intensity and are noted subjectively or by others. Insight is retained, such that the symptomatic distortions are ultimately not taken to be real; thought contents and perceptual experiences can be critically questioned by relating to own knowledge or by talking to others. They might temporarily impact on behaviour or, in case of odd thinking and speech, on communication with others.
Symptoms must occur at an average frequency of at least once per week in the past month or, if onset had been rather recent, at least four times in the past week.

(1) ideas of reference (excluding delusions of reference)
(2) odd beliefs or magical thinking influencing behaviour and inconsistent with subcultural norms (e.g., superstitious-ness, belief in clairvoyance, telepathy or "sixth sense"; in children and adolescents, bizarre fantasies or preoccupations) including non-delusive, attenuated forms of experiences of alien control ('Ich-Störungen')
(3) suspiciousness or paranoid ideas, unrelated or exceeding normal reaction to an adverse event and not restricted to fear of humiliation and embarrassment
(4) grandiose ideas including promotion of unrealistic ideas and plans
(5) unusual perceptual experiences including somatosensory (bodily) illusions or derealisation (e.g., . repeated unformed images and pseudohallucinations such as shadows, trails, sounds incl. hearing own name called, felt presence of something/someone or frequent illusional misperceptions)
(6) odd thinking and speech, vague, circumstantial, metaphorical, over-elaborate or often stereotyped thinking, manifested by odd speech or in other ways, without gross incoherence

Note: (1) to (5) might not be reliably assessable in children younger than 13 years of age. If APS are reported by younger children, they should carefully be examined for their psychopathological character.

B. The disorder causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Note: If psychosocial impairment is severe and persistent, the development of a Psychotic Disorder is more likely.

C. Does not occur exclusively during the course of Schizophrenia, a Schizophreniform Disorder, a Schizoaffective Disorder, a Mood Disorder With Psychotic Features, a Delusional Disorder, a Brief Psychotic or another Psychotic Disorder, a Personality Disorder (e.g., other than in Schizotypal PD, a pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships is not present) or a Pervasive Developmental Disorder and is not better accounted for by severe Obsessive-Compulsive or Anxiety Disorder.
Note: If criteria are met prior to the onset of Schizophrenia or any other Psychotic Disorder, add "Premorbid", e.g., "Psychototypal Disorder (Premorbid)".

D. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Classification of subtype:
- Without severe impairment in psychosocial functioning
- With severe and persistent impairment in psychosocial functioning

Classification of total duration of mental disturbances:
- With recent onset (< 1 year)
- With past onset (> 1 year)

Classification of longitudinal course:
- Episodic with inter-episode psychosocial functional impairment (episodes are defined by the re-emergence of symptoms listed in A.1 or A.2)
- Episodic with no inter-episode regaining premorbid level of psychosocial functioning for at least 1 month
- Continuous (symptoms listed in A.1 or A.2 are present throughout the period of observation)
- Single episode in partial remission (frequency criteria no longer fulfilled)
- Single episode in full remission (symptoms listed in A.1 or A.2 not present for at least three months)

al. 1996, Meng et al. 2009) and hardly ever in healthy adult control or adolescent general population samples (ibid.). Hence they seem to be well suited for the inclusion into a psychosis spectrum disorder beyond any consideration of their psychosis-predictive value. Furthermore, in light of the discussion of the inclusion of cognitive impairments into DSM-V criteria of schizophrenia – either assessed by neuropsychological testing or within a clinical interview (e.g., Keefe and Fenton 2007, Barch and Keefe 2010, Bora et al. 2010) - or even of the re-conceptualisation of psychotic disorders as a 'Salience Dysregulation Syndrome' (van Os 2009a, van Os 2009b, van Os and Kapur 2009) incorporating the dimension of cognitive impairment, the inclusion of a cognitive dimension into the proposed syndrome is much in line with current dimensional and aetiological concepts of psychoses. Moreover, the introduction of COGDIS will allow the diagnosis and treatment of persons suffering from subjective cognitive disturbances but lacking attenuated positive symptoms (Schultze-Lutter et al. 2007c, Ruhrmann et al. 2010). Thereby, the diagnostic scope would not only be broadened cross-sectionally but also gain temporal sensitivity, as cognitive basic symptoms are assumed to precede the appearance of APS (Klosterkötter 1992, Ruhrmann et al. 2003), which was supported by first retrospective results (Schultze-Lutter et al. 2010). Hence, the inclusion of COGDIS may enable an initiation of treatment for a larger group of distressed, help-seeking persons as well as an earlier diagnosis of the Psychototypal Disorder. Future research, however, will have to corroborate such a sequential development of symptoms that may lead to a further sub-staging and subsequent adaptation of treatment then.

Conclusion

The inclusion into DSM-V research criteria of a psychosis-spectrum disorder, which would help to avoid imponderabilities associated with the predictive character of a risk syndrome, could be conceptualized within the framework of the proposed heuristic staging model (McGorry et al. 2006), thereby defining a mild expression along the psychotic continuum with a potentially increased yet by no means obligatory risk of progressing to frank psychosis. The next step, however, would be the examination of its reliable assessment in specialized centres and in clinical practice as well as of its diagnostic (!) validity. Further, based on such a disorder, future research would have to examine neuropsychological and biological parameters for their ability to further improve diagnostic validity of the disorder as well as of risk assessments based on it. These future results would then have to guide the decision on transferring the disorder from research to diagnostic criteria in DSM-VI.

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