Published in final edited form as:
Curr Psychos Ther Rep. 2005 December 1; 3(4): 169–174. doi:10.1007/BF02629450.

Progress in the Prospective Study of the Schizophrenia Prodrome

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Abstract

Further understanding of the schizophrenia spectrum has helped to define the prodrome of the illness, leading to hopes of earlier identification and intervention in susceptible, at-risk individuals. Given the heterogeneity and comorbidity observed in the clinically and demographically identified prodromal sample, it is essential that neurobiological markers that are more closely linked to brain function, and perhaps the ability to predict evolution of psychosis, be identified. Ultimately, it may be possible to identify an algorithm of risk factors that will combine clinical and demographic risk factors with vulnerability markers associated with later development of schizophrenia to better target at-risk individuals or preventative treatment.

Introduction

Schizophrenia can be a devastating chronic psychotic illness that is one of the leading causes of disability in young people. Typically affecting young people in their teens or early 20s, schizophrenia not only affects the individual, but the entire social and psychologic structure surrounding them. Like any chronic illness, schizophrenia reduces an individual's work and earning potential, incurring healthcare costs that often must be absorbed by society in general. In recent years, the schizophrenia spectrum has been re-evaluated, redefined, and recategorized as new research attempts to delineate between what may be possibly separable pathophysiologic processes and what may be a broader continuum of psychotic illness than previously realized [1]. Recent schizophrenia spectrum studies have contributed to efforts to identify and characterize a "prodrome" of schizophrenia (a period of warning signs and symptoms of possible impending psychotic illness), with some success at identifying high-risk individuals who may convert to frank psychosis [2,3]. There is heightened interest in attempting to identify brain-based vulnerability markers for schizophrenia with the hopes of earlier identification and treatment of afflicted individuals and the potential for reduced disability, improved outcome, and perhaps prevention. This exciting area of research raises several important questions, ranging from the lack of specificity of the individual prodromal risk factors, leading to many false positives, to ethical concerns including the possible stigmatization of individuals and the premature or unnecessary exposure of patients to treatments with inherent risks and side effects [3,4•]. This article reviews the recent schizophrenia spectrum literature as it applies to the study of the prodrome of schizophrenia, detailing the progress and new insights and current limitations and suggestions for future research.

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The Schizophrenia Spectrum

The schizophrenia spectrum of disorders typically is thought to include not only individuals who meet the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for schizophrenia but subsyndromal forms of the illness including schizotypal personality disorder (SPD), "unaffected" first degree relatives who may have a genetic vulnerability, and individuals in the prodromal phase of the illness who may have a family history of the illness and/or the new onset of attenuated psychotic symptoms. The prodromal symptoms also overlap to some extent with the criteria for atypical psychosis, psychosis not otherwise specified, and brief reactive psychosis.

Schizotypal personality disorder

The study of SPD provides a means of studying individuals who do not manifest the full syndrome of schizophrenia, but share many of the clinical, phenomenologic, and neurobiological characteristics of the illness without the confounding effects of medication exposure or chronic illness [1]. SPD was defined, in part, based on the symptoms observed in unaffected first-degree relatives of people with schizophrenia, and is characterized by a pervasive pattern of social and interpersonal deficits with reduced capacity for close relationships in addition to attenuated psychotic symptoms. SPD is not without costs in terms of disability to the afflicted individual. Dickey *et al*. [5] reported that 104 neuroleptic-naïve subjects with SPD generally had lower socioeconomic status, poorer relationships and social skills, and lower estimated intelligence consistent with findings in schizophrenia.

Schizophrenia prodrome

Schizophrenia and SPD share phenomenologic and genetic similarities that have been vital in the development of prospective criteria for identifying the "prodrome" of schizophrenia, a period of warning signs and symptoms (including deterioration in functioning) which eventually converts to a clear presentation of a psychotic illness such as schizophrenia [6]. By definition, the prodrome is a retrospective diagnosis but great effort has been made to identify demographic and clinical criteria which can then be used to identify "putatively prodromal," "high-risk," "ultra-high risk," or "at-risk" individuals who may progress to a psychotic illness. Several clinical interviews have been developed to assess prodromal symptoms, including the Comprehensive Assessment of At-Risk Mental State (CAARMS) [7], the Structured Interview of Prodromal Symptoms (SIPS) [8], and the Bonn Scale of Basic Symptoms [9] (for a review see [10]). The prodromal criteria defined by CAARMS and SIPS identify three prodromal subgroups: a Genetic Risk and Deterioration subgroup (defined as having a first-degree relative with schizophrenia or meeting criteria for SPD plus a recent deterioration in functioning); an Attenuated Positive Symptoms group (having had a new onset of subsyndromal psychotic symptoms); and a Brief Intermittent (or Limited) Psychosis group (having had transient symptoms meeting a psychotic level of severity before resolution). Hawkins *et al*. [11] did an exploratory factor analysis of individual symptom ratings from the SIPS in 94 putatively prodromal patients that showed loading on positive and negative symptom factors, whereas the symptom of conceptual disorganization did not load with either of these factors, consistent with the three-factor symptom model of schizophrenia. Lencz *et al*. [12] reported that in 82 high-risk patients, social isolation and/or withdrawal were the most commonly reported symptom at initial presentation, and found that disorganized (*eg*, odd behavior and/or appearance) and negative symptoms also were prevalent, highlighting the likely importance of these symptoms in addition to functional deterioration as risk factors for schizophrenia.

Prospective studies of the putatively prodromal subjects identified using the various prodromal criteria have reported a psychotic conversion rate ranging from 10% to 55% at an

interval of 1 to 5 years (see [3] for a review). Yung *et al*. [13] recently reported a psychotic conversion rate of 34.6% at 1 year in a sample of 104 "ultra high risk" (UHR) subjects identified using CAARMS, and showed long duration of prodromal symptoms, poor functioning at initial screening, the presence of low-grade psychotic symptoms, depressive symptoms, and disorganization were all risk factors for the later development of psychosis. We [3] have recently reported that of 50 subjects "at-risk" for schizophrenia, 15% converted to psychosis within 1 year, with 50% meeting criteria for schizophrenia and the other 50% meeting criteria for affective psychoses. Those individuals with greater severity of subsyndromal psychotic symptoms, primarily paranoia, referential thoughts, or thought disorder, were more likely to develop a psychotic illness.

Atypical psychosis, psychosis not otherwise specified, and brief psychotic disorder

The diagnoses of atypical psychosis, psychosis not otherwise specified, and brief psychotic disorder per DSM-IV all include having psychotic symptoms that do not meet criteria for schizophrenia or a psychotic mood disorder because of an insufficient number of symptoms or duration of illness. Hlastala *et al*. [14] followed adolescents with atypical psychosis (who showed many of the symptoms included in the brief intermittent psychosis prodromal group) and monitored them for the development of a more definitive diagnosis. "Atypical" symptoms were defined as those symptoms that were fleeting, atypical in nature (highly detailed, suggestible or correlated with past trauma), or situationally specific. The study compared the atypical psychosis group with groups meeting criteria for schizophrenia or bipolar affective disorder with psychotic features. None in the group with atypical psychosis developed frank psychosis after 2 years of follow-up, but were reported to be more likely to have comorbid posttraumatic stress disorder or depression. Another study by Correll *et al*. [15] followed adolescents with psychosis not otherwise specified or brief psychotic disorder (both including symptoms at a psychotic level of severity, but not meeting criteria for schizophrenia) for up to 2 years, and only a fraction (7/26, or 27%) developed schizophrenia or schizoaffective disorder, and only two had the same initial diagnosis at follow-up. The studies by Correll *et al*. and Hlastala *et al*. in addition to the growing prospective prodromal schizophrenia literature suggest that even symptoms at a psychotic level of severity show relatively poor predictive value for schizophrenia leading to the potential inaccurate identification of individuals as prodromal or at-risk. Other factors such as functional impairment, social isolation, depressive symptoms, or environmental risk factors are needed to develop an algorithm of risk for schizophrenia.

Environmental Risk Factors

Aside from the clinical and genetic risk factors, there are several known environmental risk factors for schizophrenia that have been further elucidated in recent reviews [16-18]. These risk factors could act as a second "hit" that contributes to the emergence of the illness in a genetically vulnerable individual. Obstetrical complications have long been associated with schizophrenia and likely represent a risk factor for the illness that is relevant in combination with other factors [18]. In a sample of 55 subjects at-risk for psychosis, we (unpublished data) found that 21 (41%) reported a history of definite obstetrical complications as per the Lewis Obstetric Complications Scale compared with six (14%) of 41 normal comparison subjects. Yun *et al*. [19] showed that in an "ultra-high risk" group of 74 patients, a history of obstetric complications was not associated with increased risk for psychotic conversion. This finding is not inconsistent with the literature on the association of obstetrical complications and schizophrenia that shows a consistent relationship with relatively small effect sizes that only reach a statistical level of significance with large populations [16].

Prenatal exposure to influenza epidemics and stressful life events also are thought to contribute to the manifestation of schizophrenia. Other factors, including urban dwelling and

immigration, have been found to increase risk for schizophrenia approximately 1.5 to almost three-fold, with speculation that poverty and poor nutrition and health may account for these effects [20]. Substance abuse, especially cannabis abuse in early adolescence, in addition to nicotine use, is associated with a twofold increase in risk [18,21]. Recently, we [3] have reported that at-risk subjects who later converted to psychosis at 1-year follow-up were more likely to have abused substances before the onset of psychosis. In unpublished data, we have found that 15 of 40 at-risk subjects or 37.5% met criteria for cannabis abuse or dependence history at initial assessment. Of those individuals who converted to psychosis, 83% met criteria for cannabis abuse or dependence, compared with 29% who did not convert ($P < 0.05$).

The incidence of schizophrenia is approximately 0.5 to one per 1000 individuals per year, and environmental factors seem to increase the risk only twofold or three-fold, making these factors relatively impractical for predicting future disease according to a recent review by Weiser *et al*. [22]. Therefore, a risk factor such as early cannabis abuse may be responsible for one to two new cases of schizophrenia per 1000 people per year, whereas the vast majority of cannabis abusers will not proceed to frank psychosis. Given the low prevalence of schizophrenia, the utility of environmental risk factors alone in predicting who will develop schizophrenia is miserably low but may contribute to the predictive validity in combination with other markers.

Vulnerability Markers in Schizotypal Personality Disorder and the Schizophrenia Prodrome

The clinical symptoms of schizophrenia spectrum illness including SPD, the prodrome of schizophrenia, psychosis not otherwise specified, brief reactive psychosis, and atypical psychosis identify a heterogeneous population with high psychiatric comorbidity and disability. The identification of brain-based vulnerability markers for schizophrenia spectrum disorders that are more closely linked to neural function and the pathophysiologic mechanisms of schizophrenia could greatly enhance our ability to predict future cases of schizophrenia, understand the neurodevelopmental abnormalities in the early phase of the illness, and identify genetic markers associated with cognition. Important candidate endophenotypes including electro-physiologic, neuroimaging, and neurocognitive measures have all contributed to knowledge regarding the schizophrenia prodrome in studies published in the past year.

P50 event-related potential sensory gating

The P50 event-related potential (ERP) gating paradigm has become an important tool in the study of schizophrenia spectrum illness. Two auditory click stimuli are presented 500 ms apart and the P50 ERP response to both clicks is assessed. In normal subjects, the response to the second click is inhibited by the effect of the first stimulus, whereas in patients with schizophrenia [23] and their relatives [24] the inhibition is decreased. Mature levels of P50 suppression are present from late childhood [25]; therefore, it is possible to assess P50 gating across the full age range of individuals at risk for schizophrenia. Sensory gating deficits have high heritability [25], and have been linked to the α7 subunit of the nicotinic cholinergic receptor gene in families with schizophrenia [26].

In a recently published manuscript [27], we showed that P50 suppression was reduced in subjects putatively prodromal for schizophrenia (at-risk subjects) ($n = 36$) relative to normal subjects ($n = 22$) by a moderate effect size (0.51), but this result was short of statistical significance ($P < 0.06$). The at-risk subjects with a family history of schizophrenia in a first-degree relative had deficient P50 suppression compared with those without this history and

normal subjects (effect size = 2). This result is similar to previous findings in SPD [28], and suggests that P50 suppression deficits identify a subgroup of individuals with greater risk of developing schizophrenia based on an inherited vulnerability. Together, these results support the role of P50 sensory gating as a neurobiological marker for the sensory gating deficits of schizophrenia spectrum patients. This result is also consistent with a recent report by Myles-Worsley *et al*. [29], who found P50 gating deficits in a group of teens from a Pacific Island isolate who had clinical and familial risk for the disorder.

Important issues that need to be addressed are the relationship of vulnerability markers, such as P50, to other neurobiological indices and the ability of the measures to predict outcome. It will be important to determine if the various measures assess different aspects of vulnerability to psychosis, perhaps reflecting the proposed heterogeneity of the schizophrenia spectrum, or if the measures converge to identify specific aspects of vulnerability and perhaps a subgroup of subjects who go on to develop psychosis, specific Axis I disorders or impairment in functioning.

In a preliminary report [6], we have assessed a subgroup of at-risk subjects in the P50 paradigm and prepulse inhibition (PPI) paradigm, another measure of central inhibition that has been found to be reduced in patients with schizophrenia, their first-degree relatives, and in individuals with SPD. In this report, we found that there was a divergence of performance in the P50 and PPI paradigms in at-risk subjects, similar to a previous report on SPD [30]. Given the conceptual links between PPI and P50, it is interesting that these two measures are not significantly assodated in SPD or a putatively prodromal sample, suggesting that the two measures may identify different subgroups with independent automatic sensory processing deficits and perhaps different types of risk.

Mismatch Negativity Paradigm

Mismatch negativity (MMN) is a measure of automatic processing in which the response to standard versus deviant stimuli is compared in an event-related potential paradigm. Patients with schizophrenia show stable, consistent deficits in MMN that also are associated with global assessment of everyday functioning [31]. Salisbury *et al*. [32] showed that MMN deficits were not present in first-episode schizophrenia patients at initial assessment, but these deficits evolved over time. The possibility that MMN may be an index of later neurodevelopmental abnormalities in the early stages of schizophrenia suggests its potential utility in the study of the schizophrenia prodrome.

In a recent report, Brockhaus-Dumke *et al*. [33] assessed MMN in a cross-sectional sample of normal subjects, putatively prodromal subjects selected with the Bonn Criteria, and antipsychotic-free patients with schizophrenia. Although patients with schizophrenia showed clear deficits in MMN in the left frontal regions, the putatively prodromal subjects were intermediate to normal subjects and schizophrenic patients with reductions in MMN amplitude that were nonsignificant. The authors acknowledge that the heterogeneity of their putatively prodromal sample could confound the results and that the number of false positives is unknown. Only longitudinal data will provide information regarding the potential of MMN to predict future risk of psychosis.

Structural and Functional Neuroimaging

In a longitudinal structural neuroimaging study published in 2003, Pantelis *et al*. [34] have shown that UHR patients who later convert to psychosis already show less gray matter (right medial temporal, lateral temporal, and inferior frontal cortex and cingulate cortex bilaterally) at baseline screening compared with those who do not progress to psychosis, and show further gray matter loss (left parahippocampal, fusiform, orbitofrontal and cerebellar

cortices, and the cingulated gyri) at the time of conversion, suggesting that different gray-matter abnormalities develop before and during the expression of first-episode psychosis.

In an examination of genetic versus environmental contributions to the observed hippocampal and anterior cingulate anomalies in UHR subjects, Wood *et al*. [35] assessed the relationship of family history of psychosis to structural abnormalities in a sample of 79 UHR subjects and 49 healthy control subjects. They found that a family history of psychosis was not associated with a greater degree of structural brain abnormalities in UHR subjects. The UHR subjects without a family history of psychosis had greater abnormalities in the left hippocampi. Wood *et al*. suggest that the left hippocampal abnormalities may be related to environmental rather than genetic influences.

In one of the first functional magnetic resonance imaging reports in a hypothetically prodromal population, Morey *et al*. [36] examined frontal and striatal functions during a visual oddball continuous performance task (CPT) in a sample of 10 UHR subjects, and 15 early and 11 chronic schizophrenia patient samples compared with 16 normal subjects. The UHR group showed smaller differential activation between the task-relevant stimuli and task-irrelevant stimuli in a CPT paradigm in the anterior cingulate gyrus, the middle frontal gyrus, and the inferior frontal gyrus, suggesting that there may a decline in prefrontal functioning before the onset of illness that represents a vulnerability marker for psychosis.

Continuous Performance Task

Consistent with the findings of Morey *et al*. [36], Francey *et al*. [37] compared a UHR group to normal control subjects and first-episode schizophrenia patients on the CPT-Identical Pairs. The UHR group showed deficits in sustained attention as indexed by the CPT, but the performance on the CPT did not predict psychotic outcome in UHR subjects. The authors did not compare the outcomes of affective versus nonaffective psychosis, which could be another important direction in prodromal schizophrenia research. If it were possible to specify the outcome of subjects at risk for psychosis, it may be possible to better determine effective preventative treatments.

Neurocognition

Neurocognitive deficits have long been noted in patients with schizophrenia and have been shown to be present before the onset of psychosis [38]. Children at high genetic risk [39] for schizophrenia and unaffected first-degree relatives [40] of patients with schizophrenia also show evidence of cognitive deficits. Hawkins *et al*. [41], compared performance of high risk subjects to published norms of control subjects and schizophrenia patients. The high-risk subjects performed intermediate to normal subjects and patients with schizophrenia on a comprehensive neuropsychologic battery. The high-risk group did normally on some intellectual functioning and memory measures that are often abnormal in schizophrenia, but showed deficits on measures of processing speed, working memory, memory, and executive functioning. Hawkins *et al*. highlight the possibility that subjects who are prodromal for schizophrenia do not yet show the generalized deficits of patients with schizophrenia and the potential for intervention before the full decline in cognitive functioning may be a reality. Brewer *et al*. [42•] assessed neurocognitive functioning in a sample of 37 normal subjects and 98 UHR subjects, of whom 34 later developed a psychotic illness. Overall the UHR subjects had deficits in premorbid functioning, performance intelligence quotient (IQ), and measures of visual and verbal new learning compared with normal subjects. The problems in verbal learning observed in the UHR sample were specific to deficits in logical memory in those individuals who later developed a psychotic illness. Brewer *et al*. conclude that individuals who later develop psychosis have compromised organizational strategies, implicating vulnerabilities in prefrontal networks.

The course of the observed cognitive deficits in schizophrenia spectrum subjects has recently been addressed in reports by Bollini *et al*. [43] and Gochman *et al*. [44], who both show evidence that performance on measures of general intelligence in schizophrenia spectrum subjects declines over time, and that the greatest rate of deterioration occurs premorbidly. Bollini *et al*. [43] report on the longitudinal assessment of Wechsler Intelligence scales in 207 offspring of mothers with schizophrenia. Individuals who later developed psychosis (n = 19) showed a decline in IQ scores premorbidly, suggesting that during the pre-illness and perhaps prodromal period there is deterioration in cognitive functioning. Gochman *et al*. investigated the long-term IQ trajectory in subjects diagnosed with childhood-onset schizophrenia. Although there initially were progressive changes in cognitive decline noted in the first 2 years after psychosis onset, these changes stabilized for up to 13 years after the onset of illness and were not correlated with persistent symptoms or substantial gray matter loss. A subgroup of patients with premorbid intelligence testing, however, showed an initially steep decline in IQ before illness onset. Both studies bring into question whether the brain changes in schizophrenia are the result of neurodevelopmental abnormalities, neurodegenerative processes, or both.

Conclusions

The concept of the schizophrenia prodrome and identifying at-risk populations is tantalizing and exciting, to say the least. Several lines of evidence suggest that pathogenic processes in schizophrenia are active for many years during the vulnerable period in which the brain is still developing, before the onset of florid psychiatric illness [45] and even after the onset of schizophrenia [46]. This view is bolstered by the intriguing findings of progressive changes in measures of IQ over time [43,44], and the report [34] of gray matter loss in UHR individuals destined to convert to psychosis. Information gained from longitudinal analysis of vulnerability markers over time may add insight to our knowledge of the neurodevelopmental processes occurring in the prodromal phase of illness. The prevailing neurodevelopmental hypotheses of schizophrenia suggest that environmental insults, in combination with a genetic predisposition to abnormalities in the control of early brain development, produce the neuronal phenotype that manifests as schizophrenia [47].

Early identification of prodromal individuals is of crucial importance as these individuals already subjectively report a decreased quality of life [48] and exhibit impairment on neurobiological markers that may represent a preexisting vulnerability and/or emerging neuropathological changes. The idea of intervening before a psychotic conversion provides a compelling argument that prevention, or at the very least, delay of functional decline and disability is truly a worthwhile and humanistic goal. However, difficult ethical questions arise from this surge toward early identification and intervention (reviewed in [3,4•]), which raises a cautionary note. There still is a significant “false-positive” rate in putatively prodromal patients; at least one half do not progress to a clear psychotic illness and could be unduly stigmatized and labeled as susceptible or prone to psychosis. How an individual (or family member, physician, teacher or insurance company) deals with the knowledge of being “at risk,” and how that may shape that person’s self-concept cannot be minimized or ignored [4•]. What of the proposed interventions themselves, which may include the administration of psychotropics? The at-risk population by default is young, including children and adolescents, where there is a distinct lack of data regarding the use of psychotropics, including atypical antipsychotics in this population. Although some studies have shown efficacy of using atypicals [12,49] in putatively prodromal patients, side effects have been observed and the long-term effects are not known. Not all interventions must include psychotropics. Bechdolf *et al*. [50] followed 10 putatively prodromal individuals who received 12 months of cognitive-behavioral therapy with improvements in prodromal, depressive, and anxiety symptoms, in addition to an improvement in Global Assessment of

Functioning scores. Many programs, including the University of California San Diego Cognitive Assessment and Risk Evaluation Program, provide comprehensive assessment and regular follow-up with sensitive, nonjudgmental psychoeducation, which may be a psychosocial intervention of undetermined benefit. Open dialogue and honest communication regarding the risks and benefits of diagnosis and treatment of at-risk individuals is vital to providing the best care for the individual, no matter what treatment course is decided. As with any issue regarding diagnosis and treatment, a careful risk/benefit analysis must be performed in each identified case because the potential benefits of minimizing the development of illness and related disability must be counterbalanced with a thorough review of the possible risks of exposure to treatments that may not be benign to the individual [3].

Ultimately it may become possible to develop an algorithm of risk that combines factors including genetics, clinical symptomatology, environmental risks, and neurobiological measures to more accurately determine which individuals are likely to go on to develop schizophrenia and as such are the best candidates for potential protective interventions. Armed with such information, more rational, informed decisions can be made about possible intervention and treatment with the hope for improved outcomes in vulnerable populations.

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