REVIEW ARTICLE

COGNITIVE MARKERS IN SCHIZOPHRENIA PRODROME: A REVIEW

Zheng Lu* & Anisha Heeramun-Aubeeluck**

***Department of Psychosomatic Medicine Tongji Hospital, affiliated to Tongji University, School of Medicine; **Division of Adult Psychiatry, Shanghai Mental Health Center, affiliated No. 100 Zhang Wu Road, International Student Building No.4, Room No. 820, Shanghai 200092, China.**

Abstract:

Objective: **This article aims to review findings from studies conducted in prodromal subjects using cognitive domains as potential markers for predicting psychosis and/or schizophrenia.** ***Methods:*** **A total of 49 studies dealing with prodromal subjects were selected, out of which 9 were Genetic/Family High Risk studies, 1 was a birth cohort, 8 used ultra High Risk (UHR) screening criteria, 4 used Basel Screening Instrument Psychosis scale (BSIP), 2 used the Bonn Scale for the Assessment of Basic Symptoms (BSABS), 2 used the Early Recognition Inventory/Interview for the Retrospective Assessment of the Onset of Schizophrenia (ERIraos), 1 used the Comprehensive Assessment of At Risk Mental States (CAARMS), 10 used the Structured Interview for Prodromal States/Scale of Prodromal Symptoms (SIPS/SOPS) and 11 used a combination of screening instruments.** ***Results:*** **Cognitive precursors such as verbal memory, attention, executive function, working memory, olfactory identification and intelligence have been found to be replicable though not always consistently across studies. There are many differences between the various studies not only in terms of their subjects' profiles but also regarding the cognitive tests used and the duration of the study.** ***Conclusion:*** **A standardized agreement of the high-risk group criteria and cognitive tests used needs to be put forward. Moreover, the duration of the study investigating Ultra High Risk groups should be of at least one year period.** ***ASEAN Journal of Psychiatry, Vol. 13 (2): July – December 2012: XX XX.***

Keywords: Cognition, High-Risk, Psychosis, Prodrome, Schizophrenia

Introduction

Cognitive deficits are considered as core features of the pathophysiology of psychotic disorders and schizophrenia [1, 2]. The prodromal period of psychotic disorders including schizophrenia has been documented since the first descriptions of the illness [3]. Currently, it is described as per Yung and McGorry (1996) as being an early or prepsychotic state representing a deviation from the usual behaviour and experience of a person [4]. Despite the non-specificity of the prodromal symptoms and great variability in prodromal manifestations amongst patients, certain symptoms and signs have been frequently described. Besides depressed mood, irritability, aggressive behavior, and suicidal ideations, cognitive deficits and deterioration in social functioning are also common.

Amongst the cognitive deficits, reduced attention and concentration have been commonly described as a prodromal symptom in retrospective studies of schizophrenia and schizophreniform disorders [5]. According to some studies, cognitive deficits appear in childhood preceding its manifestation as adult schizophrenia [3, 4]. In spite of the difficulty posed in identifying patients in the prodromal period, it is believed that early detection would lead to early intervention hence minimizing disability and improving prognosis. Patients in the prodromal period have been termed differently in different studies. For instance, the Melbourne Personal Assessment and Crisis Evaluation Clinic (PACE) used the term "ultra high-risk group" (UHR), the German "Früh-Erkennungs und Therapie-Zentrum für Psychische Krisen" (FETZ services) subdivided the prodromal population into 2 distinct groups namely "early prodromal state" (EPS) and the "late prodromal state" (LPS) while the New York Recognition and Prevention Program (RAP) opted for the term group "Clinical High Risk" (CHR). It should be noted that the characteristics of the prodromal group differ from studies but they all consisted of a defined set of symptoms lasting for a defined period of time accompanied with either a decline in social function and/or a positive family history of psychotic disorders.

Studies investigating prodromal subjects have found promising markers in domains such as working memory [5,6], IQ [7, 8], verbal memory [6, 9] and executive function [8, 10]. Moreover, it is important to distinguish between the terms "endophenotypes" and "biological markers". An endophenotype [11] is characterized by: (a) differentiation from people with and without psychosis; (b) seen independent of the state of disease; (c) is heritable such that first-degree relatives have higher rates than the general population. Biological markers [12] on the other hand, are termed state markers when present only during the acutely ill state and when they are always present they are called trait markers. Also, biological markers need not be genetically or environmentally determined.

This review aims to compare the main cognitive findings in recent studies between high-risk or at-risk groups and their relevance to conversion of psychosis and schizophrenia.

Methods

Pubmed, Medline, Scirus and PsychINFO were searched using the following search terms: cognition, social cognition, ultra high risk, genetic high risk, at-risk mental states, clinical high risk, birth cohorts, and basic symptoms. The reference lists of published studies and reviews were also screened for any relevant publications and included in this review.

Inclusion criteria

Only those studies with clearly defined screening assessment of the prodromal groups, and which reported cognitive findings were included in this review. There was no restriction as per to publication dates, sample age and length of studies. Articles not written in English were excluded. The approaches used to investigate cognitive deficits prior to disease onset can be based on the clinical presentation or characteristics of the group of patients or on the psychopathological instruments used for the early detection of schizophrenia. In this review, these 2 approaches have been merged and the data collected form various studies are presented in Table 1.

Table 1. General Intelligence in Schizophrenia Prodrome

Cognitive domain	Study/Program	N	Mean Age/ Year of birth	Follow-up/ Transition rate
General intelligence				

Low IQ	Reider et al.[24](1977) BNCPHRS Family High Risk	UHR: 60	1959-1966	0-7 years
UHR-P poor in arithmetic	Brewer et al. [26] (1998) PACE UHR criteria	UHR: 65 HC: 24	N/A	12-18 months 21 UHR-P
Impaired	Byrne et al. [27] (1999) EHRS Family High Risk	UHR: 104 HC: 33	21.1 (2.3)	Launched in 1994
Low IQ	Goldstein et al. [28] (2000) BNCPHRS Family High Risk	UHR: 182 HC: 165	1959-1966	0-7 years
Impaired	Davalos et al.[34] (2003)	UHR: 51 HC: 51	Range: 6-15yrs	Baseline
Impaired	Hawkins et al.[35] (2004) PRIME SIPS/SOPS	UHR: 36	19.8 (4-7)	N/A
Impaired	Brewer et al. [36] (2005) PACE UHR criteria	UHR: 98 HC: 37	19.4 (4.0)P 20.0 (3.6)NP 20.7 (4.3)	12 months
Poor in schizophrenia group	Sørensen et al. [40] (2006) CHRS Family High Risk	UHR :311	15.1 1942-1952	10-48 years
Impaired	Pflueger et al. [48] (2007) FEPSY BSIP criteria	UHR: 60 HC: 51	27.2 (8.7) 23.4 (4.9)	Baseline
Low verbal IQ in UHR-P	Pukrop et al. [49] (2007) FETZ BSABS criteria Eastvold et al. [52]	UHR: 83 HC: 44	23.2 (5.4)P 24.9(5.3)NP 25.1 (3.2)	36 months 44 UHR-P
UHR-P more impaired	(2007) CARE SIPS + own criteria	UHR: 40 HC: 36	20.8 (3.5) 21.8 (3.4)	12 months 5 UHR-P
Impaired Impaired verbal IQ	Keshavan et al. [57] (2010) PREP SCID-I/K-SADS/CPPS Woodberry et al. [58] (2010) PIER COPS criteria	UHR: 75 HC: 82 UHR: 73 HC: 34	15.7 (3.3) 15.9 (3.0) 16.5 (2.7) 16.2 (2.5)	N/A Baseline 13 UHR-P
Impaired	Reichenberg et al.[60] (2010) DMHDS Birth cohort	1,037	1972-1973	3-26 years 35 future schizophrenia cases

Table 2. Memory in Schizophrenia Prodrome

Cognitive domain	Study/Program	N	Mean Age/ Year of birth	Follow-up/ Transition rate
Memory				
Impaired	Brewer et al.[26] (1998) PACE UHR criteria	UHR: 65 HC: 24	N/A	12-18 months 21 UHR-P
Impaired	Byrne et al.[27] (1999) EHRS Family High Risk	UHR: 104 HC: 33	21.1 (2.3)	Launched in 1994
Verbal memory impairments	Erlenmeyer-Kimling et al.[29] (2000) NYHRP Family High Risk	UHR: 136 HC: 133	1959-1972	Launched in 1971
Verbal & visual memory deficits	Hambrecht et al.[30] (2002) FETZ BS criteria	UHR: 29 HC: 29	23.1 (4.4) 24.0 (3.0)	12-15 months 5 UHR-P
Verbal memory impairments in UHR-P	Schall et al. (2003) PAS UHR criteria	UHR: 103	N/A	12-36 months 62 UHR-P
Impaired visual and verbal memory in UHR-P	Brewer et al.[36] (2005) PACE UHR criteria	UHR: 98 HC: 37	19.4 (4.0)P 20.0 (3.6)NP 20.7 (4.3)	12 months
Impaired visual reproduction	Koutsouradis et al.[38] (2005) PACE UHR criteria	UHR: 16 HC: 17	N/A	12-18 months 21 UHR-P
Impaired verbal memory predicted conversion to schizophrenia	Johnstone et al.[39] (2005) EHRS Family High Risk	UHR :147 HC : 7	21.2 (3.0) 21.2 (2.4)	Launched in 1994
Verbal memory impairments	Lencz et al.[41] (2006) RAP	UHR: 38 HC: 39	16.5 (2.2) 15.8 (2.6)	6-12 months 12 UHR-P
in UHR-P Impaired verbal memory	SOPS criteria Niendam et al.[45] (2006) CAPPS SIPS/COPS criteria	UHR: 45	17.7 (4.0)	Baseline
Impaired	Myles-Worsley et al.[46] (2007) PEPS Y-PARQ criteria	UHR: 310 HC: 99	16.9(2.1)GH 17.2(1.2)GL	Baseline
Visual reproduction	Wood et al.[47] (2007) PACE	UHR: 16	17.3 (2.8)P 21.0 (3.1)NP	12-18 months

impaired in UHR-P	UHR criteria	HC: 17	19.7 (2.4)	
UHR-P impaired in verbal memory	Pukrop et al. [49] (2007) FETZ BSABS criteria	UHR: 83 HC: 44	23.2 (5.4)P 24.9(5.3)NP 25.1 (3.2)	36 months 44 UHR-P
UHR-P more impaired	Eastvold et al. [52] (2007) CARE SIPS + own criteria	UHR: 40 HC: 36	20.8 (3.5) 21.8 (3.4)	12 months 5 UHR-P
LPS more impaired in verbal memory	Hurlemann et al. [53] (2008) GNRS ERIaos criteria	UHR: 36 HC: 30	27.3 (5.1)EPS 26.8 (6.2)LPS 28.2 (6.4)	Baseline 3 EPS & 5 LPS turned psychotic
UHR-P impaired in verbal memory	Woodberry et al. [58] (2010) PIER COPS criteria	UHR: 73 HC: 34	16.5 (2.7) 16.2 (2.5)	Baseline 13 UHR-P
Impaired verbal memory	Seidman et al. [59] (2010) NAPLS SIPS/SCID-I criteria	UHR: 304 HC: 193	18.9 (3.9) 17.8 (5.2)	Baseline
Impaired verbal memory	Kyung et al. [61] (2011) SIPS/COPS criteria	UHR: 27 HC: 33	19.9 (3.9) 19.7 (3.8)	Baseline
UHR-P impaired visual memory	Hee Sun et al. [62] (2011) CAARMS/ SIPS/ modified BPRS	UHR: 49 HC: 45	21.0 (4.8)P 21.1 (3.6)NP 22.7 (3.5)	5.2 years 13 UHR-P

Table 3. Attention in Schizophrenia Prodrome

Cognitive domain	Study/Program	N	Mean Age/ Year of birth	Follow-up/ Transition rate
Attention				
Impaired	Mirsky et al. [25] (1995) IHRS Family High Risk	UHR: 50 HC : 50	32 years 1952-1959	25 years
Impaired	Brewer et al. [26] (1998) PACE UHR criteria	UHR: 65 HC: 24	N/A	12-18 months 21 UHR-P
Attention deficits predicted conversion to schizophrenia	Erlenmeyer-Kimling et al. [29] (2000) NYHRP Family High Risk	UHR: 136 HC: 133	1959-1972	Launched in 1971
Impaired	Gschwandtner et al. [33](2003) FEPSY BSIP criteria	UHR: 32 HC: 32	26.5 (8.8) 25.5 (4.4)	Baseline only
Impaired	Hawkins et al. [35] (2004) PRIME SIPS/SOPS criteria	UHR: 36	19.8 (4-7)	Not reported
Impaired	Francey et al. [37] (2005)	UHR: 70	20.9P	12 months

	PACE UHR criteria	 HC: 51	19.9NP 23.3	
Impaired	Gschwandtner et al. [43] (2006) FEPSY BSIP criteria	UHR: 40 HC: 42	27.9 (9.1) 25.9 (5.2)	Baseline only
Impaired	Myles-Worsley et al. [46] (2007) PEPS Y-PARQ criteria	UHR: 310 HC: 99	16.9(2.1)GH 17.2(1.2)GL	Baseline
Developmental lags in pre-schizophrenic	Reichenberg et al. [60] (2010) DMHDS Birth cohort	1,037	1972-1973	3-26 years 35 future schizophrenia cases
Impaired	Kyung et al.[61] (2011) SIPS/COPS criteria	UHR: 27 HC: 33	19.9 (3.9) 19.7 (3.8)	Baseline

Table 4. Working Memory in Schizophrenia prodrome

Working memory				
Impaired	Wood et al. [32] (2003) PACE UHR criteria	UHR: 38 HC: 49	18.3 (3.2)P 19.7 (2.8)NP 20.3 (2.7)	12-24 months 9 UHR-P
Impaired	Davalos et al. [34] (2003) K-SADS-PL criteria	UHR: 51 HC: 51	Range: 6-15yrs	Baseline
Imapired	Lencz et al. [41] (2006) RAP SOPS criteria	UHR: 38 HC: 39	16.5 (2.2) 15.8 (2.6)	6-12 months 12 UHR-P
Impaired spatial working memory	Smith et al. [42] (2006) RAP SOPS criteria	UHR: 8 HC: 10	16.3 (2.6) 16.6 (2.9)	Baseline only
Impaired	Gschwandtner et al. [43] (2006) FEPSY BSIP criteria	UHR: 40 HC: 42	27.9 (9.1) 25.9 (5.2)	Baseline only
Poor performance	Keefe et al. [44] (2006) PRIME COPS/SIPS criteria	UHR: 37 HC: 21	24.2 (5.4) 20.7 (5.4)	12 months 11 UHR-P
Impaired	Pflueger et al. [48] (2007) FEPSY BSIP criteria	UHR: 60 HC: 51	27.2 (8.7) 23.4 (4.9)	Baseline
UHR-P impaired	Pukrop et al. [49] (2007) FETZ BSABS criteria	UHR: 83 HC: 44	23.2 (5.4)P 24.9(5.3)NP 25.1 (3.2)	36 months 44 UHR-P
UHR-P more impaired	Eastvold et al. [52] (2007) CARE SIPS + own criteria	UHR: 40 HC: 36	20.8 (3.5) 21.8 (3.4)	12 months 5 UHR-P
Impaired	Chung et al. [54] (2008) SYC	UHR: 33 HC: 36	Range: 16-29 years	Baseline

	CAARMS criteria			
UHR-P more impaired	Riecher-Rössler et al. [56] (2009) FEPSY BSIP criteria	UHR: 64	26.5 (6.8)P 26.2 (9.7)NP	7 years 21 UHR-P
UHR less impaired in spatial working memory	Keshavan et al. [57] (2010) PREP SCID-I/K-SADS/ CPPS	UHR: 75 HC: 82	15.7 (3.3) 15.9 (3.0)	N/A
Developmental lags in pre-schizophrenic	Reichenberg et al. [60] (2010) DMHDS Birth cohort	1,037	1972-1973	3-26 years 35 future schizophrenia cases
Impaired	Kyung et al. [61] (2011) SIPS/COPS criteria	UHR: 27 HC: 33	19.9 (3.9) 19.7 (3.8)	Baseline
UHR-P impaired	Hee Sun et al. [62] (2011) CAARMS/ SIPS/ modified BPRS	UHR: 49 HC: 45	21.0 (4.8)P 21.1 (3.6)NP 22.7 (3.5)	5.2 years 13 UHR-P

Table 5. Executive Functioning-Processing Speed in Schizophrenia Prodrome

Executive function-Processing speed				
Executive function deficits	Brewer et al.[26] (1998) PACE UHR criteria	UHR: 65 HC: 24	N/A	12-18 months 21 UHR-P
Poor performance	Schall et al. [31] (2003) PAS UHR criteria	UHR: 103	N/A	12-36 months 62 UHR-P
Impaired executive function	Gschwandtner et al. [33] (2003) FEPSY BSIP criteria	UHR: 32 HC: 32	26.5 (8.8) 25.5 (4.4)	Baseline only
Impaired	Hawkins et al. [35] (2004) PRIME SIPS/SOPS criteria	UHR: 36	19.8 (4-7)	Not reported
Impaired	Koutsouradis et al. [38] (2005) PACE UHR criteria	UHR: 16 HC: 17	N/A	12-18 months 21 UHR-P
Imapired	Lencz et al. [41] (2006) RAP SOPS criteria	UHR: 38 HC: 39	16.5 (2.2) 15.8 (2.6)	6-12 months 12 UHR-P
Impaired	Gschwandtner et al. [43] (2006) FEPSY BSIP criteria	UHR: 40 HC: 42	27.9 (9.1) 25.9 (5.2)	Baseline only
Impaired processing speed.	Keefe et al. [44] (2006) PRIME COPS/SIPS criteria	UHR: 37 HC: 21	24.2 (5.4) 20.7 (5.4)	12 months 11 UHR-P
Impaired processing speed	Niendam et al. [45] (2006) CAPPS	UHR: 45	17.7 (4.0)	Baseline

	SIPS/COPS criteria			
Impaired	Myles-Worsley et al. [46] (2007) PEPS Y-PARQ criteria	UHR: 310 HC: 99	16.9(2.1)GH 17.2(1.2)GL	Baseline
Impaired in UHR-P	Wood et al. [47] (2007) PACE UHR criteria	UHR: 16 HC: 17	17.3 (2.8)P 21.0 (3.1)NP 19.7 (2.4)	12-18 months
Impaired	Pflueger et al. (2007) FEPSY BSIP criteria	UHR: 60 HC: 51	27.2 (8.7) 23.4 (4.9)	Baseline
UHR-P impaired	Pukrop et al. [49] (2007) FETZ BSABS criteria	UHR: 83 HC: 44	23.2 (5.4)P 24.9(5.3)NP 25.1 (3.2)	36 months 44 UHR-P
LPS more impaired than EPS	Schultze-Lutter et al. [50] (2007) FETZ BSABS/SPI-A criteria	UHR: 102	23.7 (5.0)EP 24.1 (5.4)LP	Baseline
UHR-P more impaired	Eastvold et al. [52] (2007) CARE SIPS + own criteria	UHR: 40 HC: 36	20.8 (3.5) 21.8 (3.4)	12 months 5 UHR-P
Impaired executive function	Chung et al. [54] (2008) SYC CAARMS criteria	UHR: 33 HC: 36	Range: 16-29 years	Baseline
UHR more affected in psychomotor speed and verbal fluency than executive function	Keshavan et al. [57] (2010) PREP SCID-I/K-SADS/ CPPS	UHR: 75 HC: 82	15.7 (3.3) 15.9 (3.0)	N/A
Processing speed developmental lags in pre-schizophrenic	Reichenberg et al. [60] (2010) DMHDS Birth cohort	1,037	1972-1973	3-26 years 35 future schizoph-renia cases
Impaired executive function	Kyung et al. [61] (2011) SIPS/COPS criteria	UHR: 27 HC: 33	19.9 (3.9) 19.7 (3.8)	Baseline
UHR-P impaired executive function	Hee Sun et al.[62] (2011) CAARMS/ SIPS/ modified BPRS	UHR: 49 HC: 45	21.0 (4.8)P 21.1 (3.6)NP 22.7 (3.5)	5.2 years 13 UHR-P
EPS more impaired	Fromman et al. [63] (2011) GNRS ERIaos	UHR: 205 HC: 87	25.6 (6.1)EP 25.3 (6.4)LP 25.5 (4.4)	Baseline

Table 6. Social Cognition in Schizophrenia Prodrome

Social cognition				
Impaired executive function	Chung et al. [54] (2008) SYC CAARMS criteria	UHR: 33 HC: 36	Range: 16-29 years	Baseline
UHR more impaired than ES and HC	Couture et al. [55] (2008) PREDICT COPS/SIPS	UHR: 88 ES: 26 HC: 41	18.9 (4.6) 24.9 (5.1) 23.0 (5.9)	Baseline
UHR-P impaired	Hee Sun et al. [62] (2011) CAARMS/ SIPS/ modified BPRS	UHR: 49 HC: 45	21.0 (4.8)P 21.1 (3.6)NP 22.7 (3.5)	5.2 years 13 UHR-P

Appendix I

List of abbreviations used in Tables 1-5 (in alphabetical order):

BS: Basic Symptoms; BNCPPHRS: Boston and Providence cohorts of the National Collaborative Perinatal Project; BPRS: Brief Psychiatric Rating Scale; BSABS: Bonn Scale for the Assessment of Basic Symptoms; BSIP: Basel Screening Instrument Psychosis;

CAARMS: Comprehensive Assessment of At Risk Mental States ; CANTAB: Cambridge Neuropsychological Testing Automated Battery; CAPPS: Staglin Music Festival Center for the Assessment and Prevention of Prodromal States, UCLA Neuropsychiatric Institute; CARE: Cognitive Assessment and Risk Evaluation, University of California, San Diego; COPE: Center of Prevention and Evaluation, New York State Psychiatric Institute, Columbia; COPS: Criteria of Prodromal Symptoms; CPPS:Chapman Psychosis Proneness Scale

DMHDS: Dunedin Multidisciplinary Health and Development Study;

EPS: Early Prodromal State; ES: Early Schizophrenia;

FEPSY: Früherkennung von Psychosen, Basel, Germany; FETZ: Früh-Erkennungs und Therapie-Zenrtum für Psychotische Krisen, University of Cologne, Germany;

GH: Genetic High-risk; GL: Genetic Low-risk; GRNS: German Research Network on Schizophrenia;

HC: Healthy Control

K-SADS-PL: Kiddie Schedule of Affective Disorders and Schizophrenia, Present and Lifetime Version
LPS: Late Prodromal State

NYHRP: New York High Risk Project; NP: Non-Psychotic; N/A: Not available

P: Psychotic; PACE: Personal Assessment and Crisis Evaluation Clinic, Melbourne, Australia; PAS: Psychological Assistance Service, Newcastle, Australia; PIER: Portland Identification and Early Referral Program, Portland; PREDICT: multi-site study at University of Toronto, University of North Carolina and Yale University; PRIME: Prevention through Risk Identification, Management, and Education Clinic, Yale University;

RAP: Recognition and Prevention Program, New York

SIPS: Structured Interview for Prodromal Syndromes ; SOPS: Scale of Prodromal Symptoms; SPI-A: Schizophrenia Proneness Instrument, Adult version;

UHR: Ultra High Risk; UHR-NP: Ultra High Risk Nonpsychotic; UHR-P: Ultra High Risk Psychotic;

Y-PARQ: Youth Psychosis At Risk Questionnaire

Types of approaches and their rationale

Based upon symptoms or clinical presentation, five main subtypes were identified and are presented in this review: (i) "Ultra High-Risk" or "At-Risk Mental State" or "Clinical High Risk" approach: These studies have a relatively high rate of transition to illness over a short follow-up period [13]. They allow the examination of potential premorbid markers of psychosis and schizophrenia but it is to be noted that the high transition rate is dependent on "help-seeking" populations; (ii) "Basic symptoms Approach": This approach was put forward by the Germans under the rationale that cognitive, affective and social disturbances often manifest much before the onset of illness. However, up to 20% of individuals with Basic symptoms do not turn psychotic [14]; (iii) "Birth Cohorts" approach: These studies are a follow-up throughout a defined time period of a group of individuals born in the same year. The number of people identified with schizophrenia is relatively small in these cohorts and thus making these studies cost ineffective. However, data reported have shown that specific cognitive domains are affected since an early age [15]; (iv) "Genetic High-Risk" or "Family High Risk" approach: The advantage of such studies is that they are directed towards potential biological markers, as trait and not state, dependent variables for schizophrenia. However, there are drawbacks regarding sample size which is not representative of the population presenting with first-episode of schizophrenia as not all people with genetic risk of schizophrenia develop the illness [27]. Moreover, only around 10% of people with first- episode of psychosis have a positive family history [14]; (v) "Retrospective Approach": These studies give an insight into the various cognitive deficits long before the onset of illness. However, they are non-specific, and pose a problem in formulating hypotheses regarding the onset, course or nature of cognitive impairments.

Psychopathological instruments

A set of instruments have been put forward for the early recognition of schizophrenia. The most commonly used are: (i) Ultra High Risk (UHR) criteria [16] includes mild positive symptoms (Attenuated Positive Symptoms syndrome, APS) lasting at least 1 week, self-limiting brief psychotic episodes (Brief Limited Intermittent Psychotic Symptoms, BLIPS) lasting at least 1 week, functional deterioration on the Global Assessment of Functioning (GAF, 5th axis, DSM-IV) and a trait risk factor such as schizotypal personality disorder or a first degree relative with a history of psychotic disorder. The psychotic symptoms were measured by either the Brief Psychiatric Rating Scale (BPRS) or Comprehensive Assessment of Symptoms and History scale (CASH). Patients who fulfilled at least one of these criteria had a 40% probability of having a psychotic episode within one year [17]; (ii) Structured Interview for Prodromal Syndromes (SIPS) [18] consists of a DSM-IV schizotypal personality disorder checklist, the 19-item Scale of Prodromal Symptoms (SOPS) which has been subdivided into 4 main scales namely positive symptoms , negative symptoms, disorganization symptoms and general symptoms, the Criteria of Prodromal Symptoms (COPS) checklist, a positive family history of mental disorders and a version of the Global Assessment of Functioning (GAF). About half of prodromal patients developed schizophrenia within one year. It should be pointed out that in some studies the SIPS criteria were used a whole as described above, but in some, only the SOPS were used or only the COPS were used; (iii) Bonn Scale for the Assessment of Basic

Symptoms (BSABS) [19] is made of a cluster of symptoms referring to formal thought disorder, disturbances in speech, disorders of perception and movements. In some studies, the sample was subdivided into Early Prodromal State (EPS) and Late Prodromal State (LPS). The EPS met criteria defined by presence of one of the basic symptoms (occurring within the past 3 months, and once in the past year), a decline in social function as measured by the GAF (within the past year), first degree relative with schizophrenia or psychotic disorders or pre-natal or peri-natal complications and absence of attenuated or transient psychotic symptoms. On the other hand, the LPS were defined by presence of one symptoms from the APS present within the past 3 months, and or one symptoms from the BLIPS present for less than 1 week and resolving spontaneously; (iv) The Schizophrenia Proneness Instrument, Adult version (SPI-A) [20] has been combined with the BSABS or the SOPS in some studies. SPI-A is derived from the basic symptoms concept. It assesses the affective-dynamic disturbances, cognitive-attentional impediments, cognitive disturbances, disturbances in experiencing the self and surroundings, body perception disturbances, and perception disturbances. It also includes additional items dealing with thought disorders, movement disturbances and disturbances involving the sensory organs; (v) Comprehensive Assessment of At-Risk mental States (CAARMS) [21] is a semi-structured interview developed to measure subthreshold symptoms of the prodromal phase of psychotic disorders. It consists of 27 items which are further subdivided into 7 scales namely positive symptoms, negative symptoms, cognitive change, emotional disturbance, behavioral change, motor and/or physical changes, and general psychopathology. These symptoms are rated upon their severity, duration and frequency by the Brief Psychiatric Rating Scale (BPRS). One third of all patients meeting the CAARMS criteria had developed psychosis within one year; (vi) Basel Screening Instrument Psychosis (BSIP) [22] is a 46 item checklist that has been developed and based upon the DSM-III prodromal symptoms and other prodromal symptoms that have been derived form literature. It also includes prepsychotic symptoms rated by the Brief Psychiatric Rating Scale and other factors such as social decline, drug abuse, past history of mental disorders, a family history (first or second degree relatives) with schizophrenia or psychoses, and age of less than 30 for female and less than 25 for male; (vii) Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS) [23] is a retrospective semi-structured interview using data provided by the patient, a key informant and clinicians' notes; (viii) Early Recognition Inventory/Interview for the Retrospective Assessment of the Onset of Schizophrenia (ERIraos) [23] is available as both an interview and a questionnaire and the items have been selected from the most suitable items from the IRAOS, BSABS, SIPS and CAARMS. It comprises of 110 signs subsumed in 12 symptom groups; (ix) Youth Psychosis At Risk Questionnaire (Y-PARQ) is a self-report questionnaire was derived from prodromal and early psychotic symptomatology as evaluated by the CAARMS and addition of a modified version of Kiddie-SADS-PL (Schedule of Affective Disorders and Schizophrenia for school age children, Present and Lifetime Version). The K-SADS-PL is a semi-structured interview that is designed to assess the current and past episodes of psychopathology in children and adolescents according to DSM-III-R and DSM-IV criteria. It also allows objective rating of the individual symptoms.

Other assessment scales that have been used in some studies include the Diagnostic Interview for Genetic Studies (DIGS), the Present Mental Examination (PSE), Chapmann Psychosis Proneness scale, behavioral scales such as Childhood Behavior Checklist (CBC), Rust Inventory of Schizotypal Cognitions (RISC), and Structural Interview for Schizotypy (SIS) and personality assessment scales such as Kiddie Interview for Personality Syndromes (K-SKIPS).

Results

A total of 49 studies were identified and selected for this review, out of which 9 were Genetic/Family High Risk studies, 1 was a birth cohort, 8 used ultra High Risk (UHR) screening

criteria, 4 used Basel Screening Instrument Psychosis scale (BSIP), 2 used the Bonn Scale for the Assessment of Basic Symptoms (BSABS), 2 used the Early Recognition Inventory/Interview for the Retrospective Assessment of the Onset of Schizophrenia (ERIraos), 1 used the Comprehensive Assessment of At Risk Mental States (CAARMS), 10 used the Structured Interview for Prodromal States/Scale of Prodromal Symptoms (SIPS/SOPS) and 11 used a combination of screening instruments. Out of the 49 studies, 2 reported only olfactory deficits, 1 reported no significant differences between prodromal group and healthy control and 3 described non-significant differences between prodromal group and those who transited to psychosis. These studies were excluded from the tabular display. The positive cognitive findings have been tabulated into 6 tables under the following headings: general intelligence, memory, attention, working memory, executive function-processing speed, and social cognition. The term UHR was adopted to refer to all those prodromal subjects and UHR-P represent prodromal who turned psychotic or converted to schizophrenia in the tables and text below. The terms EPS and LPS was described above in text and are used as per that definition. Other abbreviations used in Tables 1-5 are described in Appendix I. It should be noted that the samples from studies from the same centers are not necessarily independent samples across these studies.

Discussion

The findings from these different studies are discussed under the sub-headings of the cognitive domains as described in results section.

General Intelligence

Intelligence is the ability to acquire, retain, and use experience, knowledge, understanding, judgment and reasoning in dealing with new experiences and solving problems. It has been found that the Ultra High Risk (UHR) had lower IQ as compared to the healthy controls. Erlenmeyer-Kimling et al., (2000) [29], proposed that general intelligence might be influenced by "polygenic potentiators" rather than specific genotypes. Interestingly, in the EHRS39, the general IQ did not predict a formal diagnosis of schizophrenia. However, in a recent study, Seidman et al. (2008) found that children at age 7 years who later developed schizophrenia were more impaired in measures of attention [64]. This may suggest that intellectual decline starts at an early age in children prone to developing schizophrenia and that remains stable till the period of developing schizophrenia. Moreover, as pointed out by Woodberry et al. (2008) [65], there might be specific cognitive domains that are selectively impaired long before the onset of schizophrenia. Deficits in coding subset of the WISC test was suggested to be linked with perceptual motor speed or working memory processing speed impairment in those who later developed schizophrenia [40]. Two studies [49, 57] also reported that Ultra High Risk turned Psychotic (UHR-P) were characterized by poor performance in Verbal IQ. In a 30-year birth cohort, Reichenberg et al., (2010) [59], used the Wechsler Intelligence Scale for Children, Revised edition (WISC-R) to investigate prodromal subjects. Their findings revealed that conversion to schizophrenia was predicted by 2 models: the neurodevelopmental deficits theory and the developmental lag hypothesis. In the former model, by age 7 children who later developed schizophrenia were already impaired in reasoning, verbal and visual learning, and conceptualization. These deficits however remained stable throughout puberty. On the other hand, the developmental lag theory showed deficits in freedom from distractibility and visual-spatial problem solving subtests.

Memory

Memory can be assessed by verbal or nonverbal tasks. The verbal component is assessed via the presentation of stimuli such as words, digits, sentences or nonsense syllables that must then be recalled. Verbal memory was proposed as a phenotype in the NYHRP study for schizophrenia [29] with a prediction rate of up to 83% patients. Five other studies reported transition to psychosis from verbal memory

deficits [31, 36, 39, 41, 57]. It is to be noted that studies using logical memory subtests suggested impairments in prefrontal networks whereas those utilizing verbal paired associates showed intact hippocampal function [36, 41]. In a recent Genetic High Risk (GHR) study, Myles-Worsley et al., (2007) [46] identified verbal memory deficits in adolescents as a genetically mediated trait risk factor. Similarly in another study, Seidman et al., (2010) [59] also found that verbal deficits differentiated the UHR from the GHR. Late Prodromal State (LPS) subjects who share similar characteristics of the UHR sample, were found to have increased verbal memory deficits [63]. Lencz et al., (2006) [41] also found verbal memory impairments to be predictive of impending psychosis. Thus, to some investigators, verbal memory deficits represent a marker of disease progression which is largely independent of psychotic symptoms and remain stable over time [67]. Early Prodromal State (EPS) show more deficits in encoding than recall whilst LPS are more impaired in storing or retaining information. From a neuroanatomical point of view, LPS have a low hippocampal volume and thus supporting the storage and retention problems whereas EPS are able to make up for mediotemporal structural vulnerability [63]. Hurlemann et al., (2008) [53] using the Rey Auditory Verbal Learning Test (RAVLT) found greater deficits in delayed recall in the LPS. Delayed recall dysfunction could be due to disturbances in episodic encoding and/or retrieval related frontotemporal function. Finally, verbal memory could also be used to determine social outcome, and poor verbal memory performance is associated with poorer social functioning [45].

Visual memory deficits have been less frequently studied. It is believed to be a state dependent marker [68] and also impairments in visual recall have been observed in high-risk relatives [27]. This review found few significant findings related to visual memory and so is not discussed here.

Attention

Attention has been subdivided into 2 components by Luck & Gold [69]. They state that attention consists of "input selection" (requiring preferential selection of sources of input for processing" and "rule selection" (requiring selection among different rules that might dictate the ongoing process). Interestingly, attention was one of the first cognitive markers in predicting the transition to schizophrenia [25] in 58% of GHR children [29]. In a smaller sample, Keefe et al., (2006) [44] also reported attentional deficits coupled with a comparatively better performance on processing speed as a predictor of conversion to psychosis. However, attentional deficits proved to be non-specific in other studies [26, 31, 33, 37, 41, 43, 52, 61]. One explanation could be due to the use of different versions of the Continuous Performance Test (CPT). Pflueger et al., (2007) [48] argued that simpler versions of the CPT such as CPT-AX or CPT-OX solely measure sustained attention whilst more complex versions such as CPT-IP challenge the working memory of patients. The difficulty posed by attention as a separable cognitive domain can further be illustrated from the above definition of attention where the "rule selection" component is intrinsically linked with executive control and "input selection" is linked to working memory [69].

Working memory

Working memory refers to a storage system with limited capacity for maintaining and manipulating information on a temporary basis. The maintenance component includes tasks like spatial delayed response tasks or digit span forward tasks while the combined maintenance and manipulation component comprises of digit or spatial span backward tasks or letter number sequencing. It should be noted that the latter is more commonly impaired in schizophrenia [70] whilst Keshavan et al., (2010) [57] found less working memory deficits in UHR as compared to other domains, other investigators found more working memory deficits as characteristic of UHR [32, 34, 35, 42, 43, 46, 48, 54, 61] and even predictive of conversion to schizophrenia [41, 49, 56, 62]. Interestingly, the Early Prodromal State (EPS) were not impaired in working memory tasks while the Late Prodromal State (LPS) showed moderate impairment.

Smith et al., (2006) [42], reported that only spatial working memory was impaired in UHR and that non-working memory spatial tasks were intact. Thus, working memory as an endophenotype for schizophrenia needs further consideration.

Executive function-Processing speed

Executive function-Processing speed includes complex thought and action such as abstraction, reasoning, future planning, multi-tasking, problem solving and ability to modify behavior to adjust to inputs from the internal and external environment. The Wisconsin Card Sorting Test (WCST) and Trail Making Test (TMT) have been commonly used to assess executive functions. Some investigators have reported their findings as that of two separate domains, whereas others have merged it as one. In this review, they are considered as one single domain. There is evidence suggesting that executive performance is affected before the onset of psychosis or the Early Prodromal State (EPS) [63]. Similar findings have also been reported in 2 studies assessing children at ages 7 and 13 respectively [71, 72]. Many investigators agree on poor executive performance in UHR [26, 31, 33, 35, 43, 48, 50, 51, 52, 57, 59, 61] and some have even found execution-processing speed as a predictor of schizophrenia38,44,47,49,62. Niendnam et al., (2006) [45] also reported poor performance on reasoning and problem solving was associated with a poor Global Assessment Functioning (GAF) score. Moreover, it was found that Late Prodromal State (LPS) had more errors on WCST than the Early Prodromal State (EPS) [50]. This may indicate that as the disease progresses there is an increased risk in patients having poor executive performance.

Social cognition

This term has its origin in social psychology dating late 1960's and early 1970's. It represents a person's conceptualization of the self and others as well as the ability of using social judgments in decision making [73]. Most research in schizophrenia has been concentrated on the following subdomains of social cognition: emotion processing and theory of mind, social perception, social knowledge and attributional bias. Few prodromal studies have utilized social cognition as a cognitive measure and the predictive value of social cognition remains ambiguous. Nevertheless social cognition deficits have been identified in 3 studies [54, 55, 62] where in 1 study [62] theory of mind task predicted conversion to schizophrenia. However, yet another more recent study, found no relationship between theory of mind tasks and social cognition [64]. Further studies are needed in this field.

Future directions and conclusions

Despite years of research on schizophrenia prodrome, cognitive markers are still in its infancy period. Future research in this field needs to address current limitations. These include a standardized consensus on the high risk criteria inclusion is necessary since there are different criteria used, the comparison of findings becomes difficult to interpret. The inclusion of an Early Prodromal State seems to be promising in differentiating cognitive deficits that might reflect a neurodevelopmental origin. Furthermore, Early Prodromal State and Late Prodromal State have different cognitive dysfunctions. There might be some advantage in including a Genetic High Risk group in the sample in view of identifying endophenotypes and gaining insight into the pathophysiology of the disease. This also implies that a standardized agreement also needs to be reached on the psychopathological instrument used for screening subjects such that different Early prodromal State, Late Prodromal State and Genetic High Risk are all included in the sample screening. Another important point is the inclusion of matched control groups to premorbid IQ and years of education which increases the reliability of the results.

Cognitive battery used for assessing cognitive domains varies considerably between studies. Moreover, some tests assess different domains (e.g., CPT-IP assessing not only attention but also working memory) at the same time and this may lead to impaired sensitivity and specificity. Since there is no international agreement on

which tests to use for which cognitive domain, interpretation of results becomes ambiguous (e.g., processing speed is considered as a separate domain to executive function in some studies, or verbal fluency is a measure of executive function in some and a separate domain in others). Cognitive domains may need to be broken down into subunits during assessment since when assessed as a whole, compensatory mechanism might mask the deficits in specific subunits. The National Institute of Mental Health has put forward a cognitive battery known as the Measurement And Treatment Research Improve Cognition Schizophrenia (MATRICS) which through a series of factor analysis has selected assessment of specific cognitive domains. These domains include speed of processing, attention/vigilance, working memory, verbal memory, visual learning, reasoning and problem solving and social cognition. The addition of social cognition is recent and many studies have neglected this aspect in schizophrenia prodrome. Although it is too early to comment on its predictive value, it might be an indicator of social outcome and interventions improving social cognition may reduce social dysfunction. Other domains, that have some promising value, are the olfactory identification and motor function, which are not regularly integrated in cognitive assessment of schizophrenia prodrome.

The role of behavioral tests has been highlighted in the EHRS study. The Structural Interview for Schizotypy (SIS) and Rust Inventory of Schizotypal Cognitions (RISC) could predict with some accuracy transition to psychosis. Future research should investigate the roles of these tests in schizophrenia prodrome.
The duration of studies plays an important role in identifying transition to psychosis. Riecher-Rössler and colleagues suggested in a recent 7 year longitudinal study that most transition to psychosis or schizophrenia occurred at 1 year interval and about 29% occurred after 1 year.

An ethical issue is still being debated as to labelling individuals as UHR. Since not all UHR turn psychotic, these individuals might be victim of the stigma of mental disorder. Moreover, with the growing interest in early intervention, these individuals might be unnecessarily prescribed antipsychotics and may be at risk of developing side-effects. Yet, some early intervention strategies such as cognitive behavioural therapy, family therapy and support for social skills and employment have shown promising results. Further research in schizophrenia prodrome would not only help in decreasing disease burden and disability rate but also provide insight into the disease aetiopathology.

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Corresponding author: ***Dr. Zheng Lu, Tongji Hospital, Department of Psychosomatic Medicine, No. 389 Xincun Road, Shanghai 200065, China.***

Email: luzheng@tongji.edu.cn

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