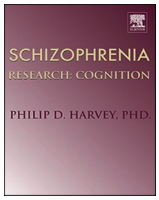
Schizophrenia Research: Cognition 28 (2022) 100246

Contents lists available at ScienceDirect

Schizophrenia Research: Cognition

journal homepage: www.elsevier.com/locate/scog



A systematic review of premorbid cognitive functioning and its timing of onset in schizophrenia spectrum disorders

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ARTICLE INFO

Keywords:
Schizophrenia spectrum disorders
Premorbid cognitive function
Onset of cognitive impairment
Schizophrenia
Cognition

ABSTRACT

Cognitive impairments are core features of established schizophrenia spectrum disorders (SSD). However, it remains unclear whether specific cognitive functions are differentially impaired pre-onset and at what age these impairments can be detected. The purpose of this review was to elucidate these issues through a systematic summary of results from longitudinal studies investigating impairment in specific cognitive domains as antecedents of SSD.

Relevant studies were identified by electronic and manual literature searches and included any original study of cognitive domains any time pre-onset of SSDs that included a control group. Effect sizes were calculated by domain for studies comparing high-risk participants who developed SSD with those who did not.

The strongest evidence for impairment pre-onset was for mental processing speed, verbal learning and memory, executive function, and social cognition. Some verbal impairments, like language abilities at age 3 and verbal learning and memory at age 7, may develop as static deficits. Conversely, some non-verbal impairments, like mental processing speed, visuospatial abilities, and visual working memory manifest as developmental lag and become significant later in life. Most effect sizes were small to moderate, except for verbal fluency (d′ = 0,85), implying this impairment as central in high-risk participants who develop SSD.

The present review documents extensive cognitive impairments pre-onset of SSD, and that these impairments start early in life, in line with the neurodevelopmental hypothesis of schizophrenia. Increased knowledge about cognitive impairments preonset can provide a better basis for understanding the complex pathogenesis of SSD as well as informing cognitive remediation programs.

1. Introduction

Identifying premorbid cognitive deficits in people who develop schizophrenia spectrum disorders (SSD) is important for understanding its pathogenesis. There is agreement that cognitive impairments are a core feature of SSD (Heinrichs and Zakzanis, 1998), and that it affects functioning (Bowie and Harvey, 2006). SSD are neurodevelopmental disorders (Rund, 2018), meaning that subtle cognitive and motor impairments appear early in life and indicate an abnormal neural maturation process increasing the risk of developing SSD (Weinberger, 1987; Niemi et al., 2003). However, several issues remain relatively unexamined: whether specific cognitive functions are differentially affected pre-onset, and whether the age of impairment onset differs across different cognitive functions (Mollon and Reichenberg, 2018).

To properly examine these issues, longitudinal studies are required, including birth and conscript cohort studies, studies of genetic or familial high-risk populations (FHR) and clinical- or ultra-high-risk populations (CHR). CHR studies include participants who experience poor functioning in addition to a family history of SSD, have transient psychotic symptoms, or experience subthreshold psychotic symptoms (Fusar-Poli et al., 2013).

When investigating at-risk participants, studies indicate moderate cognitive deficits compared to those with schizophrenia (Bora et al., 2014). Intelligence has been a frequent focus of research, with those who

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https://doi.org/10.1016/j.scog.2022.100246
Received 21 October 2021; Received in revised form 18 February 2022; Accepted 20 February 2022

develop schizophrenia falling nearly half a standard deviation (SD) below controls (Khandaker et al., 2011). Consequently, intelligence will not be a focus of this review. Increasingly, specific cognitive domains have been studied. A recent meta-analysis found significant differences between those at high-risk for psychosis and healthy controls on specific tests of cognition, identifying cognitive dysfunction as a potential marker for diagnosis and prognosis (Catalan et al., 2021).

In this review, we include a broad sampling of longitudinal studies to determine whether those who develop SSD are different from those who do not on any specific cognitive function, at any time pre-onset, and consider age of onset of cognitive impairment. To our knowledge, this is the only systematic review where specific cognitive impairment pre-dating onset of SSD has been investigated in a wide range of longitudinal studies, including a determination of age of onset.

We aim to answer the following questions:

(1) Are there differences in specific cognitive functions in those who later develop SSD compared to those who do not before illness onset?
(2) If yes, at what age do these differences become apparent?

2. Methods

2.1. Study selection

Relevant articles were found through a systematic search in PsychInfo, MEDLINE, Web of Science, BASE and OpenGrey. Examples of search terms are: [schizophreni* OR SSD] AND [premorbid OR high-risk] AND [cog*OR memor*] AND [cohort stud*OR longitudinal*]. We included any paper that investigated specific cognitive domains pre-onset of SSD. The reference lists of included studies and previous reviews were scanned for relevant articles.

2.2. Inclusion criteria

(1) Original article published in an English language peer-reviewed journal, (2) assessed at least one specific cognitive domain pre-onset of SSD, defined according to DSMIII/IV/V (American Psychiatric Association, 1980, 1994, 2013) or ICD10/11 (World Health Organization, 2016, 2019) criteria, (3) included a control group, and (4) had a longitudinal or prospective design.

The cognitive tests were divided into domains that are commonly used in clinical neuropsychology (Harvey, 2019) and are presented in Table 1. Although the nature of these domains is widely accepted, there are significant inconsistencies in the research literature regarding domains with multiple component processes (Dickinson et al., 2008). The inclusion of a social cognition domain expands on earlier reviews and meta-analyses (Mollon et al., 2018; Catalan et al., 2021). Controls are defined as those participants who did not develop SSD at follow-up and includes healthy controls, help-seeking controls and at-risk participants.

2.3. Study characteristics

The PRISMA flowchart is presented in Fig. 1. A total of 2780 studies were identified in database searches, after removing duplicates. Additionally, 147 studies were identified from reference lists. Papers were screened on title, then abstract, and 167 articles were screened in full. The result was 61 papers representing 43 samples. When two or more studies analyzed data from the same sample, they were included if they had analyzed different aspects of the sample.

2.4. Review and analysis

In reviewing the results for each specified cognitive domain, a broad approach was adopted where all participants who later developed SSD were compared to all participants who did not, collectively referred to as "controls". When considering the second research question regarding age of onset, only longitudinal cohort studies were considered. To further investigate the magnitude of specific cognitive impairments, we calculated the effect sizes for a subsample of the studies included, comparing those in clinical or ultra high-risk who later developed SSD (CHR+) to those at ultra- or clinical high-risk who did not (CHR-) (Table 2). Criteria for inclusion in these analyses were that the domain had to be investigated in at least three separate samples and reported effect size (ES), odds ratio (OR) or mean (m) and SD. Based on these criteria, only reasoning and problem solving was excluded. In other words, this review consists of three separate but integrated processes of review and analysis. Effect sizes were predominantly small or moderate, except for a large effect size in the verbal fluency domain (Table 2).

Table 1
Cognitive domains and measurement.

Domain[a]	Measurements[b]
Processing speed	Trail Making Test A, Digit Symbol Coding, Stroop Color, Stroop Word, OTIS-R, Speed of Comprehension test, Numerical Attention test, Simple Reaction Time, Choice Reaction Time, Finger Tapping, Finger Oscillation, Grooved pegboard, Token Motor Task, Purdue Pegboard Task, Spatial Tapping test, Simultaneous Peg test
Sustained attention	CPT-IP, CPT-AX, CPT-OX[c], Attention Span task or Digit Span task in combination with a CPT task, Sky Search Task, Testbatterie zur Aufmerksamkeitsprüfung (TAP)
Learning and memory	Rey Auditory Verbal Learning Task, Logical Memory, Verbal Paired Associates, California Verbal Learning Test, Verbal Memory task, Hopkins Verbal Learning Test, Dutch 15-word task, Word Memory Test for Children, List learning test, Story Recall, Visual Object Learning Test (short), Visual Reproduction test, Visual Pattern test, Rey-Osterrieth Complex Figure Test, Brief Visuospatial Memory Test, Rey Visual Design Learning Test, Family Pictures
Language	Vocabulary, Similarities, Information, Boston Naming Test, Auditory Vocal Association test, Reynell Developmental Language Scales, Verbal IQ test, Speed and Capacity of Language Processing test, Spot the Word test
Visuospatial ability	Picture Completion, Block Design, Matrix reasoning (in different combinations), Judgement of Line Orientation test, Object Assembly, Visuospatial test
Executive function	Wisconsin Card Sorting Test, Stroop C—W, Tower of London, Trail Making Test B
Verbal working memory	Letter-Number Sequencing Arithmetic, Digit Span, Digit Sequencing task
Visual working memory	N-back task, Computerized Visual Working Memory test, Spatial span, Spatial working memory test, DOT test, Delayed Matching-to-Sample task
Verbal fluency	Category Instances, Controlled Oral Word Association Test, Verbal fluency task (letter or category)
Reasoning and problem solving	Logical Reasoning Test for Children (Short), Mazes, Ravens Progressive matrices
Social cognition	Emotion recognition test for children, Measured Emotion Differentiation Test, Face Emotion Recognition, Prosody Emotion Recognition, False-Belief Picture Sequencing task, Reading the Mind in the Eyes task, Hinting Task, Penn Emotion Discrimination task, Penn Emotion Recognition task, Emotion Recognition - ER40 for faces and auditory emotion recognition, Abbreviated Trustworthiness task, Face Emotion Identification task, Face Emotion Discrimination task, Affective Prosody task, False Belief task, Strange story task, Nonverbal Cartoon task, High-Risk Social Challenge skills interview, Babble task, Snakes in the grass task, Picture Arrangement and Comprehension subtests[d], Social Inference subscale of the Social Inference test, Relationships across domains task, Mayer–Salovey–Caruso Emotional Intelligence Test, Faux Pas test

[a] Tests are placed according to their defined domain in the articles included.
[b] Several tests measure several functions, and there is no unequivocal consensus on this.
[c] Continuous Performance Test.
[d] Used by Ott et al. (1998) as a measurement of social cognition.

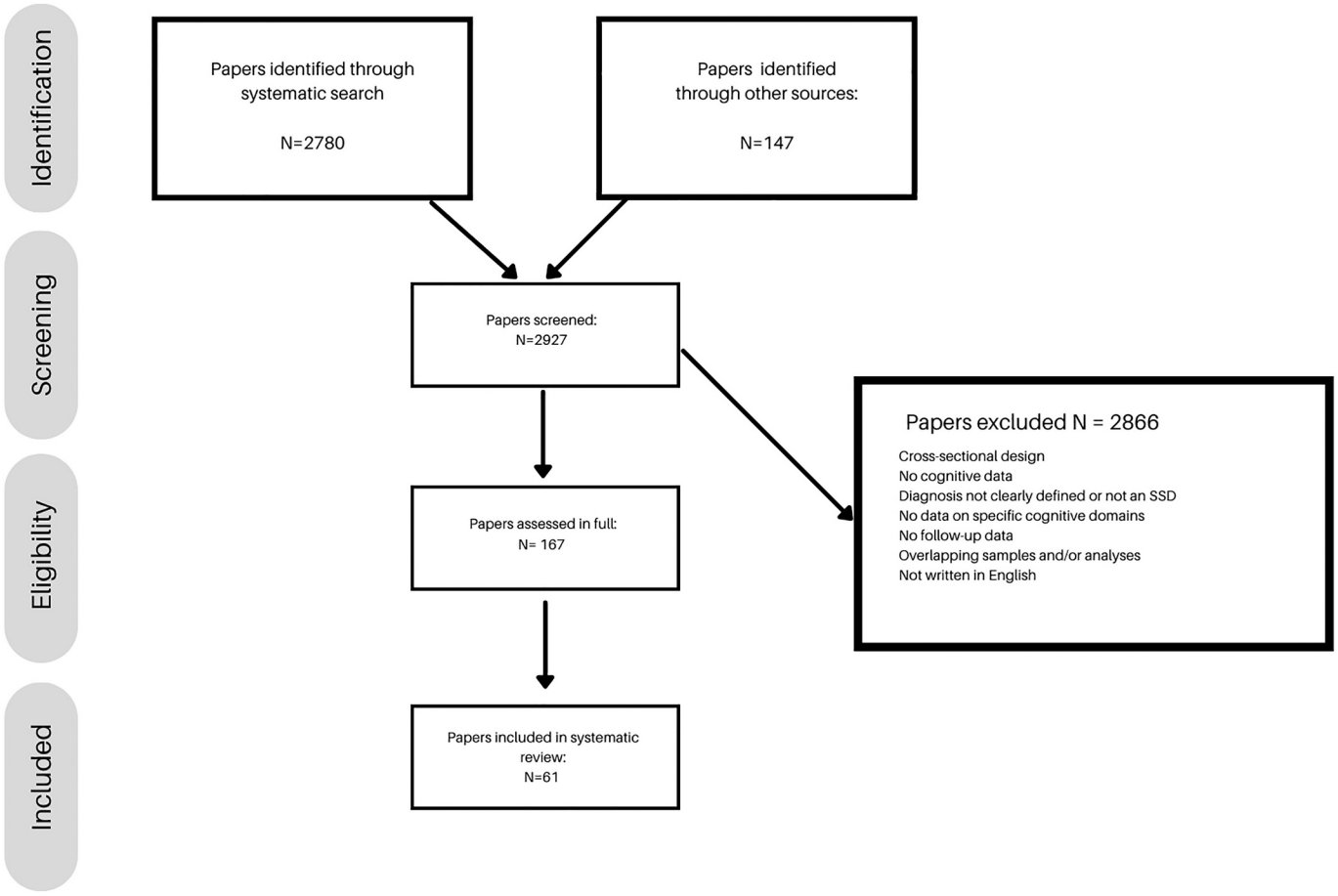

Fig. 1. Flow chart: selection and assessment process.

3. Results

To ease reading, studies have been numbered from 1 through 61 (Table 3), and this is referenced in "Results".

3.1. Processing speed

Mental and psychomotor processing speed was investigated in 37 and 14 studies, respectively. Significant deficits were found for mental processing speed pre-onset compared to controls[1, 3, 4, 6, 8, 13, 15, 17, 19, 22, 23, 27, 33, 34, 37, 39, 42, 45, 46, 48, 52, 53, 56]. Some found a lack of improved performance, or deterioration, in mental processing speed for those who later develop SSD, but not for controls[6, 34, 37, 42, 45]. Eleven studies showed non-significant differences pre-onset[2, 7, 12, 21, 24, 33, 38, 40, 41, 44, 55]. The sub-analysis comparing only CHR+ and CHR- showed a relatively small average effect size (d′ = 0,39).

For psychomotor processing speed, the Copenhagen Perinatal study suggests that FHR+ were significantly impaired compared to controls[54]. Conversely, of the 11 CHR studies, only one found psychomotor processing predicting SSD[12]. Ten studies found no significant differences pre-onset[1, 2, 33, 37, 39, 40, 41, 50, 59, 60]. In spite of many non-significant findings, the sub-analysis found a medium average effect size (d′ = 0,47). However, this average hides a possible task effect, where one task yields large effect sizes, and another yields relatively small ones.

For mental processing speed, significantly lower scores were found at ages 7 and 15 compared to controls[15, 56], as well as developmental lag[16, 47]. Results from the Israeli conscript studies showed significant differences in mental processing speed at 16–17 years[22–23], but no deterioration[19]. For psychomotor processing speed, results from the Dunedin studies showed significant group differences at age 13[13] and significant declines between the ages of 7 and 38[15].

3.2. Sustained attention

Sustained attention was investigated in 26 studies. In three studies attention deficits were significant predictors of SSD[3, 37, 53]. Two studies found that the non-transitioning high-risk group experienced improvement, and the transitioning group remained stable[39, 45]. Six CHR studies report non-significant differences pre-onset[1, 24, 40, 44, 50, 61], while five found impairments at trend-level in those who develop SSD[8, 17, 42, 55, 59]. Furthermore, the sub-analysis found a small average effect size when comparing CHR+ with CHR- (d′ = 0,03). FHR studies found that transitioners performed worse on all tests of attention compared to controls at ages 9–11[28,29]. Poor attention skills at age 11 were correlated with SSD in adulthood and the impairment persisted in adulthood in the whole FHR group[46]. The Edinburgh High-Risk study (FHR) found no significant differences pre-onset[35]. In the ALSPAC birth cohort study, there were increasing deficits from 8 years into early adulthood[47].

3.3. Verbal learning and memory

In the 32 studies investigating verbal learning and memory, most report verbal memory impairment pre-onset as significantly associated with SSD[1, 2, 4, 6, 7, 8, 10, 27, 29, 34, 35, 36, 38, 39, 40, 41, 42, 45, 52, 53, 55, 59]. Others report the same for verbal learning[17, 36, 38]. Seven studies found non-significant differences between groups[12, 33, 37, 44, 50, 58, 61]. When assessing the magnitude of the difference between CHR+ and CHR-, the sub-analysis found a moderate average effect size (d′ = 0,53). In the Dunedin cohort study, they found verbal learning and memory impairment at age 13 that remained relatively stable[13]. This static deficit was

Table 2
Effect sizes by cognitive domain when comparing CHR+ and CHR− - a subanalysis.

Domain	d′
Mental processing speed	
Addington et al. (2017) TMT-A	0,72
Bolt et al. (2019) Digit Symbol Coding	−0,38
Carrion et al. (2018) TMT-A + Symbol Coding	0,39
Higuchi et al. (2013) Digit Symbol Coding	-4,32
Kim et al. (2011) Stroop Color	0,21
Kim et al. (2011) TMT-A	−0,13
Lin et al. (2013) TMT-A	0.18
Lin et al. (2013) Digit Symbol Coding	−0,33
Lindgren et al. (2017) Composite Score	−0,63
Liu et al. (2015) TMT-A + Digit Symbol Coding	-0,52
Metzler et al. (2015) TMT-A	0,32
Metzler et al. (2015) Digit Symbol Coding	−1,52
Mourik et al. (2017) SRT	0,37
Mourik et al. (2017) CHRT	0,22
Average	**−0,39**
Psychomotor processing speed	
Addington et al. (2017) Finger Oscillation Test	−0,26
Bolt et al. (2019) Token Motor Task	−0,66
Higuchi et al. (2013) Token Motor Task	−1,39
Woodberry et al. (2013) Finger Tapping	0,02
Ziermans et al. (2014) Finger Tapping	−0,05
Average	**−0,47**
Sustained attention	
Addington et al. (2017) CPT-IP + Digit Span	−0,27
Atkinson et al. (2017) Digit Span	0,72
Carrion et al. (2018) CPT-IP	0,16
Corcoran et al. (2015) CPT-IP	0,30
Liu et al. (2015) CPT-IP + Digit Span Forward	−0,37
Mamah et al. (2016) CPT	−0,62
Metzler et al. (2015) CPT-OX	−0,18
Mourik et al. (2017) CPT-IP	0,58
Woodberry et al. (2013) CPT-IP verbal d′	0,14
Woodberry et al. (2013) CPT-IP nonverbal d′	−0,23
Ziermans et al. (2014) CPT-IP d′	0,10
Average	**0,03**
Verbal learning and memory	
Addington et al. (2017) RAVLT	−0,54
Atkinson et al. (2017) CVLT immediate recall	−0,58
Atkinson et al. (2017) CVLT delayed recall	−0,58
Bolt et al. (2019) Verbal Memory task	−0,27
Carrion et al. (2018) HVLT	0,86
Higuchi et al. (2013) Verbal Memory task	−0,48
Kim et al. (2011) CVLT immediate recall	−1,13
Kim et al. (2011) CVLT delayed recall	−1,41
Lin et al. (2013) RAVLT	−0,07
Lin et al. (2013) Logical Memory	−0,18
Lin et al. (2013) Verbal Paired Associates – related pairs	0,09
Lin et al. (2013) Verbal Paired Associates – unrelated pairs	0,09
Lindgren et al. (2017) CVLT immediate recall T1-T5	−2,21
Lindgren et al. (2017) CVLT delayed recall	−1,15
Lindgren et al. (2017) Logical Memory immediate recall	−0,44
Lindgren et al. (2017) Logical Memory delayed recall	−0,13
Liu et al. (2015) Logical Memory + Verbal Paired Associates	−0,07
Mamah et al. (2016) List Learning Test	−0,43
Metzler et al. (2015) RAVLT T1	−0,83
Metzler et al. (2015) RAVLT T1-T5	−1,20
Metzler et al. (2015) RAVLT delayed recall	−1,76
Walder et al. (2008) Logical Memory	−0,13
Woodberry et al. (2013) CVLT T1-T5	−0,88
Woodberry et al. (2013) Logical Memory	−0,56
Ziermans et al. (2014) 15WT immediate recall	0,07
Ziermans et al. (2014) 15WT delayed recall	0,20
Average	**−0,53**
Visual learning and memory	
Atkinson et al. (2017) Visual Patterns test	0,33
Carrion et al. (2018) BVMT	0,25
Kim et al. (2011) ROCFT immediate recall	−0,96
Kim et al. (2011) ROCFT delayed recall	−1,04
Lin et al. (2013) Visual Reproduction test	−0,84
Liu et al. (2015) Visual Reproduction test	−0,13
Mamah et al. (2016) Visual Object Learning test	−0,70
Metzler et al. (2015) RVDLT T1	−0,07
Metzler et al. (2015) RVDLT T1-T5	−1,20
Metzler et al. (2015) RVDLT delayed recall	−0,69
Walder et al. (2008) Family Pictures test	−0,20
Average	**−0,48**
Language	
Lin et al. (2013) Information	0,38
Lin et al. (2013) Similarities	0,00
Lin et al. (2013) Vocabulary	0,13
Lindgren et al. (2017) Vocabulary	−1,25
Liu et al. (2015) Information + Similarities	0,12
Mamah et al. (2016) Language and reasoning test	−0,14
Walder et al. (2008) Vocabulary	0,85
Walder et al. (2008) Similarities	−0,45
Average	**−0,04**
Visuospatial abilities	
Lin et al. (2013) Matrix Reasoning	−0,65
Lin et al. (2013) Picture Completion	−0,31
Lin et al. (2013) Block Design	0,03
Lindgren et al. (2017) Matrix Reasoning + Block Design	−0,56
Liu et al. (2015) Block Design + Arithmetic + Digit Span backwards	−0,08
Walder et al. (2008) Picture Completion	−0,15
Walder et al. (2008) Block Design	0,03
Average	**−0,24**
Executive function	
Addington et al. (2017) WCST + Stroop C-W	0,19
Atkinson et al. (2017) Tower of London	−0,23
Atkinson et al. (2017) Stroop C-W	−0,02
Bolt et al. (2019) Tower of London	−0,62
Corcoran et al. (2015) Stroop	0,60
Higuchi et al. (2013) Tower of London	0,36
Kim et al. (2011) WCST perseverative error	0,85
Kim et al. (2011) Stroop C-W	1,16
Kim et al. (2011) TMT-B	0,37
Lin et al. (2013) TMT-B	0,59
Liu et al. (2015) WCST	−0,51
Metzler et al. (2015) TMT-B	0,15
Mourik et al. (2017) Stroop	−0,09
Woodberry et al. (2013) WCST	0,04
Woodberry et al. (2013) TMT-B	0,08
Ziermans et al. (2014) WCST	0,49
Average	**0,21**
Verbal working memory	
Atkinson et al. (2017) LNS	0,79
Atkinson et al. (2017) Digit Span	0,72
Bolt et al. (2019) Digit Sequencing task	−0,36
Higuchi et al. (2013) Digit Sequencing task	−1,60
Kim et al. (2011) Digit Span	−2,14
Lin et al. (2013) Arithmetic	−0,47
Lin et al. (2013) Digit Span	−0,12
Liu et al. (2015) Arithmetic + Digit Span backwards	−0,25
Metzler et al. (2015) LNS	−1,30
Metzler et al. (2015) Digit span	−0,62
Walder et al. (2008) Arithmetic	−0,15
Walder et al. (2008) LNS	−0,26
Woodberry et al. (2013) LNS	−0,13
Average	**−0,45**
Visual working memory	
Addington et al. (2017) CTVWM + N-back	−0,27
Kim et al. (2011) Spatial Location	−0,70
Mourik et al. (2017) N-back	−0,15
Ziermans et al. (2014) Spatial working memory test	−0,55
Average	**−0,42**

(*continued on next page*)

Table 2 (*continued*)

Domain	d′
Verbal fluency	
Addington et al. (2017) Category Instances + COWAT	−0,51
Atkinson et al. (2017) Verbal Fluency task	−0,70
Bolt et al. (2019) Verbal Fluency task	−0,25
Higuchi et al. (2013) Category and letter fluency tasks	−2,64
Kim et al. (2011) COWAT	−3,84
Lin et al. (2013) COWAT	−0,03
Liu et al. (2015) Letter Fluency task	−0,06
Metzler et al. (2015) Category and letter fluency tasks	−1,26
Woodberry et al. (2013) Category and letter fluency tasks	−0,30
Ziermans et al. (2014) Letter Fluency	−0,15
Ziermans et al. (2014) Category Fluency	0,41
Average	**−0,85**
Social cognition	
Allott et al. (2014) Emotion recognition fear	0,74
Allott et al. (2014) Emotion recognition neutral	−0,74
Allott et al. (2014) Emotion recognition prosody	0,04
Allott et al. (2014) Facial Emotion recognition	0,00
Atkinson et al. (2017) Hinting task	−0,04
Atkinson et al. (2017)Picture Sequencing task	−0,04
Atkinson et al. (2017) Eyes task	−0,58
Healey et al. (2013) Eyes task	−0,49
Healey et al. (2013) Trustworthiness task	0,18
Kim et al. (2011) False belief task	−0,74
Kim et al. (2011) Strange story	−0,58
Kim et al. (2011) Physical story	0,03
Kim et al. (2011) Cartoon task	−0,59
Mamah et al. (2016) ER-40	−0,17
Average	**−0,21**

Abbreviations: TMT-A/B, Trail Making Test A/B; SRT, Simple Reaction Time; CHRT, Choice Reaction Time; CPT-IP, Continuous Performance Test – Identical Pairs; RAVLT, Rey Auditory Verbal Learning Test; CVLT, California Verbal Learning Test; HVLT, Hopkins Verbal Learning Test; 15WT, Dutch 15-Word Task; BVMT, Brief Visual Memory Test; ROCFT, Rey-Osterrieth Complex Figure test; RVDLT; Rey Visual Design Learning Test; WCST, Wisconsin Card Sorting Test; Stroop C/W/C-W, Stroop Color/Word/Color-Word; LNS, Letter-Number Sequencing; CTVWM, Computerized Verbal Working Memory test; COWAT, Controlled Oral Word Association Test; Eyes Task, Reading the Mind in the Eyes task; ER-40, Emotion Recognition 40 faces.

apparent over time, but significant group differences appeared in later adolescence[15].

3.4. Visual learning and memory

Of 13 studies investigating visual learning and memory, six found impaired visual memory[6, 7, 10, 38, 42], and poorer scores associated with risk of SSD transition[8]. Other studies found this domain relatively intact[13, 17, 35, 41, 44, 45, 50, 58]. The average effect size found in the sub-analysis was moderate (d′ = 0,48). No differences were found pre-onset in the birth cohort at age 13[13], nor in the FHR at age 16[35].

3.5. Language

Language was investigated in 23 studies. The birth and conscript cohort studies show consistency in terms of impairment pre-onset. Most high-risk studies found non-significant differences between groups on measures of language pre-onset, although converters scored lower than non-converters and controls[6, 8, 36, 40, 41, 42, 44, 50, 52, 53, 55, 58, 59]. The sub-analysis of the magnitude comparing CHR+ and CHR- found a small average effect size (d′ = 0,04). The birth cohorts found impaired language at age 3 in those who later develop SSD[11, 14, 15, 16, 47]. Two studies tested participants multiple times from age 7 through adulthood and found impairments suggesting static deficit[16, 47]. All conscript studies found impaired language pre-onset[22, 23, 25, 57], but not in a subgroup of affected versus non-affected twins[21]. There was no evidence of deterioration[19].

3.6. Visuospatial ability

Visuospatial ability was investigated in 14 studies. One CHR study found visuospatial abilities significantly associated with transition to SSD[8], while seven did not[6, 40, 41, 42, 44, 50, 52, 53, 58]. The average effect size when comparing CHR+ and CHR- in the sub-analysis was small (d′ = 0,24). Visuospatial ability did not seem impaired pre-onset in high-risk groups, nor in a conscript cohort[25]. The birth cohort studies found impairment pre-onset. However, one found developmental lag[15, 16] - with the exception of one test - while the other found static deficits[47].

3.7. Executive function

Executive function was investigated in 32 studies. Some CHR studies found impaired executive function pre-onset in the high-risk group[1, 10, 27, 34, 38, 39, 42, 45, 48, 55], with larger impairments for converters[2, 4, 12, 40, 42, 52, 53 59]. Eight studies found non-significant group differences[1, 7, 8, 33, 38, 41, 50, 61]. The average effect size in studies comparing CHR+ and CHR- was small (d′ = 0,21). The Dunedin cohort studies found significant differences between SSD and controls at age 13[13], and a significant decline between ages 7 and 38[15], but only for one test. The FHR studies[26, 35, 36, 46] found no differences between those who later developed SSD versus those who did not.

3.7.1. Verbal working memory

This domain was investigated in 26 studies. Significant differences were found in ten high-risk studies[2, 6, 10, 33, 34, 38, 39, 40, 45, 46]. Non-significant differences were found in ten studies[1, 8, 12, 17, 27, 32, 37, 50, 55, 59]. Medium average effect size (d′ = 0,43) was found in studies comparing CHR+ and CHR-. Both birth cohort studies found developmental lag in verbal working memory performance[16, 47] compared to controls. Both the Finnish[57] and Israeli[19, 22, 23] conscript studies found significant group differences in this domain pre-onset[57].

3.7.2. Visual working memory

Fifteen studies examined this domain. Seven studies found significant differences between at-risk individuals and controls[2, 9, 34, 39, 48] and worse for those who transition to SSD[38, 60]. Of the remaining studies, eight found trend level or no significant differences between groups[1, 17, 26, 27, 37, 41, 44, 61]. The average effect size when comparing CHR+ and CHR- was medium (d′ = 0,42).We cannot ascertain whether this impairment develops before participants are classified as “high-risk” due to lack of studies.

3.7.3. Verbal fluency

Verbal fluency was investigated in 26 studies. In the FHR and CHR studies, some found significant group differences[10, 33, 38, 39, 45, 52, 59], but not significantly worse for those who transitioned[1, 2, 37, 42, 53]. Ten studies found non-significant differences between groups[8, 12, 26, 35, 36, 40, 41, 55, 60, 61]. As the only domain in the sub-analysis, the average effect size when comparing CHR+ and CHR- was large (d′ = 0,85). In the Dunedin study the SSD participants were significantly impaired at age 13 compared to controls[13].

3.7.4. Reasoning and problem solving

Nine studies investigated this domain. The Israeli conscript studies found that those who later developed SSD performed worse than controls[22] and experienced deterioration[19], although it could not separate affected and unaffected twins or twin pairs[21]. The Romanian conscript study[31] also found significant differences pre-onset. Two CHR studies found intact reasoning and problem solving[44, 61], while one found significant impairments in those who transitioned[17]. The Dunedin birth cohort found no differences in this domain at age 13[13].

Table 3
Specific cognitive functions pre-onset of an SSD: evidence from longitudinal studies.

Study (first author)	Groups being compared (at-risk vs. controls)	Study design	Age (m)	Cognitive tests	Main findings
Addington et al. (2017)[1] PREDICT	CHR+ = 29 CHR- = 116	CHR	19.8	TMT-A + B, finger oscillation, CPT-IP, digit span, RAVLT, WCTS, stroop C—W, category instances, COWAT, LNS, CTVWM, N-back, WAIS/WISC	• Cognitive variables that predicted transition to psychosis were verbal fluency, verbal learning and memory and processing speed, included in a prediction model with baseline social functioning, unusual thought content, disorganized communication, and older age.
[2] PREDICT					
Barbato (2013a)	CHR+ = 25 CHR- = 126	CHR	19,7	TMT-A + B, finger oscillation, CPT-IP, digit span, RAVLT, WCST, stroop C—W, category instances, LNS, CTVWM, N-back, WAIS/WISC	• There were significant differences on the composite cognitive factor as well as for tests of attention, verbal learning and memory, working memory, verbal fluency and executive function, with an advantage for the non-converters.
Healey et al. (2013)[3] PREDICT	CHR+ = 34 CHR- = 113 HSC = 85	CHR	19.4	The eyes task, abbreviated trustworthiness, WAIS/WISC	• No significant group differences at pre-onset for either IQ or social cognition. Pre-onset theory of mind (ToM) predicted SSD in both high-risk and help-seeking control groups.
Healey et al. (2018)[4] PREDICT	CHR+ = 34 CHR- = 137 HSC = 100	CHR	19.8	TMT-A + B, CPT-IP, RAVLT, WCST, CAT, The Eyes Task, FEIT, FEDT, AP, WAIS/WISC	• When dividing the sample into three classes, class 3 (negative-neurocognitive) exhibited significant cognitive impairment when compared to class 1 and 2. • Transition rates differed sig. Between classes 1 and 3: 5,6% versus 29,3%. Overall transition rate in the full sample was 12,5%.
Allott et al. (2014)[5] Vienna	CHR+ = 11 CHR- = 26	CHR	16.2	Computerized modification of Feinberg et al. (1986) procedure to measure facial emotion recognition, Edwards et al., 2001 task to measure voice emotion recognition	• Significant differences between the two groups for misattribution of fear, with the group who transitioned showing a higher tendency to mislabel neutral emotion as fear.
Allott et al. (2019)[6] PACE 1994–2000	CHR+ = 31 CHR- = 49	CHR	20.2	TMT-A, digit-symbol coding, similarities, information, picture completion, block design, logical memory, verbal paired associates I, RAVLT, visual reproduction, arithmetic, WAIS-R	• CHR+ had lower scores on most measures compared with CHR- at baseline. Cognition was stable or improved except for significant decline in Digit Symbol Coding for those transitioning within a year, and improved scores for those who did not transition.
Brewer et al. (2005)[7] PACE 1995–1998	CHR+ = 38 CHR- = 60 HC = 37	CHR	19.4	TMT-A + B, logical memory, verbal paired associates I, RAVLT, visual reproduction, stroop C—W, COWAT, WAIS-R	• CHR+ scored significantly lower than CHR- on the visual reproduction subtest, and the verbal memory index, where the logical memory task explaining the group differences.
Lin et al. (2013)[8] PACE 1993–2006	CHR+ = 81 CHR- = 244 HC = 66	CHR	19.1	TMT-A + B and digit symbol coding, digit span, vocabulary, similarities, information, matrix reasoning, picture completion, block design, logical memory, verbal paired associates I, RAVLT, visual reproduction, COWAT, arithmetic WAIS-R/WASI	• The total CHR group performed more poorly than the control group, but only performance on digit symbol coding and picture completion was significant. • The risk of transition was significantly associated only with poorer performance on the Visual Reproduction and Matrix Reasoning tasks.
Wood et al. (2003)[9] PACE Focus: visual working memory	CHR+ = 9 CHR- = 29 HC = 49	CHR	18.3	Spatial span, spatial working memory test, DMTS	• Visual working memory abilities are impaired in the high-risk group, more so for CHR+ than CHR-, though this difference did not reach significant levels.
Atkinson et al. (2017)[10] MinT	CHR+ = 7 CHR- = 73 HC = 58	CHR	19.1	CVLT, visual pattern test, stroop C—W and Tower of London, verbal fluency, LNS, digit span, WASI, TMT—B, false-belief picture sequencing, eyes task, hinting task, WASI	• Relative to controls, CHR had lower IQ and scored lower on tasks of verbal working memory, verbal learning and memory, verbal fluency, cognitive flexibility and executive function (Stroop-C-W). • Results on tasks of social cognition were mixed: impairment on the Hinting Task, but not the False-Belief or the Mind in the Eyes Task. • The strongest and only cognitive predictor of transition was verbal learning and memory.
Bearden et al. (2000)[11] CPP Philadelphia	SSD = 59 Controls = 6056	Birth Cohort	7	Auditory vocal association test	• Language at age 7 was found to be a highly significant predictor of schizophrenia outcome.
Bolt et al. (2019)[12] NEUROPARO	CHR+ = 38 CHR- = 256	CHR	19.1	Symbol coding, token motor task, list learning, Tower of London, verbal fluency, digit sequencing, WAIS-III	• Executive function and psychomotor processing speed were significant predictors of transition to SSD.
Cannon et al. (2006)[13] Dunedin	SSD = 23 Controls = 676	Birth Cohort	13	TMT-A + B, G-PEG, RAVLT, ROCFT, WCST, verbal fluency, mazes	• The SSD group differed significantly from the controls on measures of cognitive flexibility, mental and psychomotor processing speed and verbal fluency.
Cannon et al. (2002)[14] Dunedin	SSD = 36 Controls = 1001	Birth Cohort	3, 5, 7, 9 & 11	Reynell developmental language scales, PPVT, Stanford Binet or WISC	• The SSD group had significantly poorer receptive language skills than controls at all ages. Self-reported strong psychotic symptoms

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Table 3 (*continued*)

Study (first author)	Groups being compared (at-risk vs. controls)	Study design	Age (m)	Cognitive tests	Main findings
					at age 11 years were associated with significant developmental impairments in both receptive language and IQ.
Meier et al. (2014)[15] Dunedin	SSD = 31 Controls = 875	Birth Cohort	7, 9, 11, 13 & 38	TMT-A + B, digit symbol coding, G-PEG, information, similarities, vocabulary, RAVLT, arithmetic, WISC-R/WAIS-IV	• The progression of cognitive deficits from 7 to 38 years varies across functions. Decline was greatest on the Digit Symbol Coding task. Little evidence of decline in language or delayed memory, and deficits could be tracked back to childhood deficits that remained stable.
Reichenberg et al. (2010)[16] Dunedin	SSD = 35 Controls = 937	Birth Cohort	7, 9, 11, 13 & 32	Digit symbol coding. information, similarities, vocabulary, arithmetic, block design, picture completion, object assembly, WISC-R	• There was no evidence of cognitive deterioration among future SSD subjects. However, they exhibit early and static deficits on Information, Similarities, Vocabulary and Picture Completion. Block Design, Arithmetic and Digit Symbol showed evidence of developmental lag.
Carrion et al. (2018)[17] EDIPPP	CHR+ = 12 CHR- = 193 HSC = 89 HC = 60 EFEP = 28	CHR	16.5	TMT-A, symbol coding, CPT-IP, HVLT, BVMT, LNS, spatial span, mazes	• Significant group differences in processing speed, verbal learning and memory and IQ. Trend level differences in working memory and attention. Intact reasoning and problem-solving. CHR+ closely resembled EFEP.
Guo et al. (2020)[18] EDIPPP and Understanding Early Psychosis Program (EP)	CHR+ = 19 CHR- = 98 CHR-Rem = 52 HC = 170	CHR	16.3	AX-CPT	• AX-CPT was robust for discriminating CHR+ and CHR-. Performance was less impaired in CHR-Remitted compared to both CHR+ and CHR-Persistent groups
Caspi et al. (2003)[19] Israeli Draft Board	SSD = 44 HC = 44	Conscript Cohort	16–17	OTIS-R, similarities, arithmetic, RPM-R	• The SSD group performed worse at baseline, but there were no significant changes between first and second assessments. Relative to controls, SSD patients deteriorated on the RPM-R and OTIS-R.
Goldberg et al. (2011)[20] Israeli Draft Board	SSD = 1961 Controls = 809,526	Conscript Cohort	16–17	OTIS-R, similarities, arithmetic, RPM-R	• Compared to those with high cognitive functioning, those with low cognitive functioning had 5 times higher risk of being hospitalized for SSD, and those with average cognitive functioning had two times higher risk (also related to SES).
Reichenberg et al. (2000)[21] Israeli Draft Board - twin subsample	SSD = 20 Controls = 2218	Conscript Cohort	16–17	OTIS-R, similarities, arithmetic, RPM-R	• The affected twin pairs scored significantly worse than the control twin population on measures other than cognition, and NS worse on the RPM task. There was a pattern where affected twins performed worse, controls in between and unaffected twins best.
Reichenberg et al. (2002)[22] Israeli Draft Board	SCZ = 526 SCZAff = 31 BP = 68	Conscript Cohort	16–17	OTIS-R, similarities, arithmetic, RPM-R	• Schizophrenia subjects showed significant premorbid deficits on all cognitive tests compared to controls. • Language performance, including verbal working memory, did not differentiate between those who go on to develop SSD or bipolar disorder
Reichenberg et al. (2006)[23] I Israeli Draft Board	SSD = 297 Controls = 53,731	Conscript Cohort	16–17	OTIS-R, similarities, arithmetic, RPM-R	• There was a significant relationship between lower scores on both IQ and all subtests, and later SSD.
Corcoran et al. (2015)[24] New York, US	CHR+ = 7 CHR- = 42 HC = 31 Dev. Control group = 43 SCZ = 93	CHR	18.2	CPT-IP, stroop, EMODIFF, auditory emotion recognition, WAIS-III	• Significant differences between CHR+ and both HC and CHR- on both tasks of social cognition. No significant differences between CHR+ and CHR- on tasks of attention and processing speed.
David et al. (1997)[25] Swedish Draftboard	SSD = 387 HC = 49,581	Conscript Cohort	18	Language, visuospatial test, full draft board test battery (IQ)	• The effect of IQ and later psychosis is highly significant for both those who develop schizophrenia as well as SSD as a whole.
Eack et al. (2008)[26] US	FHRhigh = 66 FHRlow = 20 FHR+ = 5	FHR	15.2	WCST, category and letter fluency, spatial working memory test, WAIS-R	• At-risk relatives who had less total brain volume, and experienced greater cognitive dysfunction and psychosis proneness at baseline were significantly more likely to develop psychopathology.
Eastvold et al. (2007)[27] CARE program	CHR+ = 5 CHR- = 35 HC = 36 FEP = 15	CHR	20.8	Stroop C, numerical attention test, vocabulary, block design, HVLT, WCST, stroop C—W, LNS, spatial span, WAIS-III	• Significant group differences were present for all tasks. For the 5 CHR+ performance fell between the FE sample and the CHR- sample, with verbal learning and memory and vocabulary comparable to the FE group, processing speed and executive function comparable to the CHR- group, and working memory similar for all groups.

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Table 3 (*continued*)

Study (first author)	Groups being compared (at-risk vs. controls)	Study design	Age (m)	Cognitive tests	Main findings
Erlenmeyer-Kimling and Cornblatt (1992)[28] NYHRP	FHR+ = 107 FHR- = 165 AFF = 83	FHR	9, 12, 15, 18, 20 & 23	Attentional Deviance Index	• Childhood attentional impairment is significantly associated with later psychopathology, but only for high risk, and not low risk, participants. • Attentional performance in childhood of those who develop SSD predicted behavioral adjustment in adolescence as well as an adult social isolation score
Erlenmeyer-Kimling (2000)[29] NYHRP Included those with data in both childhood and adulthood only	FHR+ = 79 FHR- = 133 AFF = 57	FHR	9, 12, 15, 18, 20, 23 & 30	CPT, attention span task, digit span, Lincoln-Oseretsky motor development scale	• Sensitivity in correctly predicting SSD was unusually high for verbal memory and gross motor skills. Differences between high- and low risk offspring were significant for both the attentional deviance index, memory and motor function.
Ott et al. (1998)[30] NYHRP	FHR+ = 31 FHR- = 174 HC = 283	FHR	9,4 & 15,2	Picture arrangement and comprehension, WISC/WAIS-R	• IQ was lower in the FHR+ group than the total FHR group, and at 15 years only performance IQ differed between the outcome groups, and only at trend level. Social cognition did not evidence either deficit or a decrease across time.
Gheorghe (2004)[31] Romanian Draft Board	SSD = 157 HC = 169	Conscript Cohort	18	RPM-R (operationalized as a measurement of nonverbal IQ)	• As a group, future patients obtained significantly worse scores on the RPM compared to controls
Hawkins et al. (2008)[32] PRIME	CHR+ = 13 CHR- = 47	CHR	17.8	TMT-A + B, stroop C and W, digit symbol, finger tapping, CPT-IP, VIDA, LNS, CVLT, visual reproductions, WCST	• Participants who developed an SSD tended to perseverate more on a design fluency task and were relatively impaired on visual memory. No evidence of decline in neuropsychological functioning from pre- to post onset.
Higuchi et al. (2013)[33] Toyama, Japan	CHR+ = 17 CHR- = 20 SCZ = 31	CHR	19.4	Symbol coding, token motor task, list learning, Tower of London, category and letter fluency, digit sequencing	• CHR+ performed significantly worse on tests of working memory, verbal fluency and attention.
Jahshan et al. (2010)[34] California, US	CHR+ = 6 CHR- = 42 HC = 29 FEP = 20	CHR	18.7	Numerical attention, stroop C, HVLT, WCST, LNS, spatial span, WAIS/WISC-III	• Significant group differences across all cognitive domains as well as a significant group x time interaction in verbal learning and memory. Evidence deterioration in working memory and mental processing speed for CHR+.
Johnstone et al. (2005)[35] Edinburgh High-Risk Study	FHR+ = 20 FHR- = 143 HC = 36	FHR	16–25	Digit symbol coding, speed-of-comprehension test, CPT, RAVLT, RBMT story, visual reproduction, stroop C—W, category and letter fluency, HSCT, WAIS-R	• Group differences in verbal learning and memory scores are just significant, but it is the behavioral measures that clearly separate FHR+ from FHR-.
Whyte et al. (2006)[36] Edinburgh High-Risk Study	FHR+ = 13 FHR- = 105 HC = 30	FHR	19.3	Digit symbol coding, Speed-of-comprehension test, CPT. RAVLT, RBMT story, visual reproduction, stroop C—W, category and letter fluency, HSCT, WAIS-R	• Results indicate that the total FHR group perform poorly relative to controls, but do not deteriorate over time. Symptoms and cognitive function appear unrelated.
Keefe et al. (2006)[37] University of North Carolina and University of Toronto	CHR+ = 11 CHR- = 26 HC = 47 FEP = 59	CHR	20.7	Digit symbol coding, finger oscillation test, CPT-IP, CVLT, COWAT, category instances, LNS, dot test	• CHR+ performed significantly worse than controls, while CHR- were indistinguishable from controls Poor CPT performance and better Digit Symbol Coding performance predicted transition to an SSD.
Kim et al. (2011)[38] Seoul Youth Clinic	CHR+ = 13 CHR- = 36 HC = 45	CHR	21.5	Stroop C, TMT-A + B, K-CVLT, ROCFT, WCST, stroop C—W, COWAT, digit span, spatial location, false belief task, strange story task, cartoon task, K-WAIS	• At baseline, the CHR+ group were more impaired on tasks involving social cognition and neurocognition than the CHR- and control groups. Progressive ToM deficits may serve as specific indicators of transition.
Lam et al. (2018)[39] LYRS (Singapore)	CHR+ = 17 CHR- = 156 CHR-Rem = 84 HC = 384	CHR	20.4	Symbol coding, token motor task, CPT-IP, list learning, tower of London, verbal fluency, digit sequencing, spatial span, the high-risk social challenges interview, babble task, snakes in the grass test	• Results point to that the deficits observed are transient. Cognition improved as a function of time, where remitters' performance at follow-up was not different from that of controls. • Cognitive deficits in CHR non-remitters tend to be stable and impaired on nearly all components.
Lencz et al. (2006)[40] RAP	CHR+ = 12 CHR- = 26 HC = 39	CHR	16.5	TMT-A + B, finger tapping, G-PEG, CPT-IP, vocabulary, information, Boston naming test, block design, visual reproduction, CVLT, logical memory, WCST, COWAT, Ruff figural fluency, digit span, LNS, WISC/WAIS, WRAT-II	• At baseline, the total CHR group had significantly impaired global cognitive performance relative to controls. Verbal learning and memory, executive function and working memory showed significantly greater impairments, while visuospatial abilities were spared. • Verbal learning and memory scores at baseline discriminated CHR+ and CHR-.
Lindgren et al. (2017)[41] Helsinki Prodromal Study	CHR+ = 7 CHR- = 140	CHR	16.7	TMT-A + B + C, Digit symbol, choice/simple reaction time (Therman et al.), Purdue pegboard, spatial tapping vocabulary,	• CHR+ performed worse on Vocabulary and CVLT, but not on logical memory. None of the cognitive factors, only the intensity of positive

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Table 3 (*continued*)

Study (first author)	Groups being compared (at-risk vs. controls)	Study design	Age (m)	Cognitive tests	Main findings
				similarities, matrix reasoning, block design, CVLT, logical memory, visual reproduction, letter fluency, dot cancellation	symptoms, were significant predictors of transition
Liu et al. (2015)[42] SOPRES Taiwan	CHR+ = 18 CHR- = 35 HC = 137 FEP = 49 InterR = 42 MarR = 43	CHR	21.4	TMT-A + B, digit symbol coding, CPT, digit span, information, similarities, block design, logical memory, verbal paired associates, visual reproduction, WCST, arithmetic, letter fluency, WAIS-III	• CHR+ showed relatively poorer performance than CHR- at baseline. At follow-up, the performance of CHR+ was comparable to that of FEP, while CHR- generally improved. • Executive function, mental processing speed, verbal fluency and verbal and visual learning and memory were significantly worse in all three risk-groups at baseline compared to controls.
MacCabe et al. (2013)[43] Swedish Draft Board + UGU	SSD = 114 BP = 34 Controls = 10,717	Birth/ conscript cohort	13, 18	Verbal ability test, spatial ability test, inductive ability tests (SDB battery)	• A relative decline in cognitive performance in adolescence and young adulthood, particularly for language abilities, was associated with increased risk of SSD in adulthood. • A relative decline between ages 13 and 18 is a stronger predictor than language abilities at 18 years alone
Mamah et al. (2016)[44] Machakos county, Kenya	CHR+ = 5 CHRhigh = 135 CHRlow = 142	CHR	17	CPT-IP, N-back, word memory test for children, facial memory test, visual object learning test – short, logical reasoning test for children – short, motor praxis test, matrix analysis test, list learning test, emotion recognition test for children – 40 faces, measured emotion differentiation	• CHRhigh showed a unique pattern of cognitive functioning compared to CHRlow individuals, with relatively worse performance on tests of attention and reasoning and problem-solving.
Metzler et al. (2015)[45] SinEP	CHR+ = 12 CHR- = 48 HR-BP = 10	CHR	19.1	TMT-A + B, digit symbol coding, CPT-OX, RAVLT, RVDLT, category and letter fluency, LNS, digit span, PPVT	• CHR- improved performance on all cognitive domains except working memory, while CHR+ remained stable • CHR+ differed significantly on general cognitive performance from CHR- at baseline
Mirsky et al. (1995)[46] IHRS	FHR = 50 HC = 50	FHR	11, 17, 26 & 30	TMT-A + B, digit symbol substitution, CPT-X, CPT-AX, WCST, stroop, arithmetic, digit span	• At age 11, FHR participants showed significantly lower levels of verbal working memory (arithmetic) proficiency and achievement, and mental and psychomotor processing speed performance. They were also more distractible on tasks of attention compared to controls. • Poor Digit Cancellation task scores at age 11 was highly correlated with SSD in adulthood, while poor attention skills persisted in adulthood and characterized the FHR group as whole.
Mollon et al. (2018)[47] ALSPAC	SSD = 16 AffPSY = 9 PSYexe = 63 MDD = 32 Controls = 106	Birth Cohort	8, 20	Digit symbol coding, sky search, vocabulary, block design, digit span, WISC-III	• The SSD group showed significant main effect on language and visuospatial abilities, suggesting static deficits in these domains. • For processing speed, verbal working memory and attention there was evidence of increasing developmental lag.
Mourik et al. (2017)[48] New York and Columbia University, US	CHR+ = 14 CHR- = 38 HC = 58	CHR	19.1	CHRT, SRT, CPT-IP, stroop, N-back	• Overall, CHR individuals performed significantly worse on all measures when compared to controls. NS differences were found between CHR+ and CHR-.
Nieman et al. (2014)[49] DPPS	CHR+ = 18 CHR- = 43	CHR	19.9	Motor speed, sustained attention, verbal learning and memory, category and letter fluency, spatial working memory (This paper did not list specific tests for each domain)	• Of the cognitive variables, Category Fluency was the most predictive of transition, but not statistically significant in this model.
Olvet et al. (2010)[50] RAP	CHR+ = 24 CHR- = 115 BP = 8	CHR	17.1	TMT-A + B, finger tapping and G-PEG, CPT-IP, vocabulary, information, BNT, JOLO, block design, CVLT, logical memory, visual reproduction, WCST, COWAT, LNS, digit span, Ruff fluency test, WISC-II, WRAT-III	• The CHR+ group had significantly lower current IQ and were significantly more impaired than CHR- on the overall neurocognitive score. This was not the case for those who later developed bipolar disorder.
Piskulic et al. (2016)[51] NAPLS-2	CHR+ = 86 CHR- = 679 HC = 264	CHR	18.5	TASIT, penn emotion recognition and discrimination tasks, RAD	• The CHR group performed poorer on all tests of social cognition across all time points compared to controls. • No difference in social cognition was found between CHR+ and CHR-.
Seidman et al. (2010)[52] NAPLS (1&2?)	CHR+ = 33 CHR- = 271 FHR = 52 HC = 193	CHR	18.2	Digit symbol coding, TMT—B, CPT-IP, vocabulary, block design, story recall, children's memory scale, HVLT, RAVLT, CVLT, WCST, COWAT	• The total CHR group were significantly impaired in cognitive functioning compared to controls, and significantly more severe for CHR+ than CHR-. • CHR and FHR were similarly impaired on composite scores, but had different profiles.

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Table 3 (*continued*)

Study (first author)	Groups being compared (at-risk vs. controls)	Study design	Age (m)	Cognitive tests	Main findings
					• Tests of verbal learning and memory and processing speed were most sensitive in discriminating CHR from controls.
Velthorst et al. (2019)[53] NAPLS-1	CHR = 166 FHR = 49 HC = 109	CHR	18.4	Digit symbol coding and TMT—B, CPT-IP, vocabulary, block design, story recall, children's memory scale, HVLT, RAVLT, CVLT, WCST, COWAT	• Four clusters of cognitive impairment were identified, and the significantly impaired cluster showed the largest deviations on processing speed and verbal learning and memory and had a transition rate of 58%.
Rakhshan et al. (2016)[54] Copenhagen Perinatal Cohort	FHR+ = 33 FHR- = 211 HC =150	FHR	11.7	Simultaneous peg test	• Findings suggest that FHR+ children were less likely to complete the task within time limit relative to controls, and took significantly longer time to complete the task compared to controls.
Simon et al. (2012)[55] Switzerland	CHR+ = 19 CHR- = 54 BS = 26 HSC = 49 FEP = 48	CHR	20.4	TMT-B, TAP, vocabulary, RAVLT, WCST, Letter and category fluency, LNS	• CHR+ showed similar impairment at baseline to FEP, while those who remitted were more similar to controls. • Normal immediate verbal memory uniquely predicted remission from CHR-state.
Sorensen et al. (2006)[56] Copenhagen High-Risk Study	SSD = 84 Controls = 227	Birth Cohort	15.1	Digit symbol coding, WISC	• The SSD group had significantly lower scores only on the digit symbol coding task compared to controls, after controlling for IQ.
Tiihonen et al. (2005)[57] Finnish Draft Board	SSD = 1148 BP = 100 Controls = 193,771	Conscript Cohort	19.9	Verbal reasoning, visuospatial reasoning, arithmetic (FDB test battery)	• Results indicate that premorbid visuospatial reasoning is impaired in SSD and BP, and to a smaller extent PNOS.
Walder et al. (2008)[58] Emory University Adolescent Development Project, US	CHR+ = 12 CHR- = 25	CHR	14.3	Vocabulary, similarities, block design, picture completion, logical memory, family pictures, LNS, arithmetic, WISC/WAIS	• There were no significant differences between groups at baseline.
Woodberry et al. (2013)[59] Portland Identification and Early Referral (PIER) program in Portland, ME (US)	CHR+ = 10 CHR- = 43 HC = 32	CHR	16.0	Finger tapping, CPT-IP, vocabulary, similarities, CVLT, logical memory or children's memory scale stories, WCST, verbal fluency, LNS, TMT—B, WASI	• Results showed an overall failure of the total CHR group to perform at predicted levels at one year follow-up, most notable for verbal learning and memory and executive function.
Zhang et al. (2018)[60] Shanghai Psychotherapy and Psychological Counseling Center, DRC	CHR+ = 26 CHR- = 57 HC = 90	CHR	18.8	TMT-A + B, digit symbol coding, CPT-IP, HVLT, BVMT, category fluency, spatial span, mazes, RMET, FP	• The association between cognition and social cognition is stronger in CHR than controls, and especially so for CHR+. • CHR are impaired in both global cognition and social cognition, especially for CHR+.
Ziermans et al. (2014)[61] Department of Psychiatry, University Medical Center Utrecht, Netherlands	CHR+ = 10 CHR- = 33 HC = 47	CHR	15.2	Finger tapping, CPT-IP, 15WT, WCST, letter and category fluency, spatial working memory test, WISC	• Low IQ was the single cognitive parameter that discriminated CHR+ from CHR- and controls. • The severity of attenuated positive symptoms was the only significant predictor of conversion.

Abbreviations: SSD, schizophrenia spectrum disorders; CHR+, Clinical high-risk transitioned to SSD; CHR-, clinical high-risk non-transitioned to SSD; CHR-Rem, clinical high-risk remitted from high-risk state; CHR+, ultra high-risk transitioned to SSD; CHR-, ultra high-risk non-transitioned to SSD; FHR, familial high-risk; FHR+, familial-high risk transitioned to SSD; FHR-, familial high-risk non-transitioned to SSD; FHRhigh; familial high-risk high familial burden; FHRlow, familial high-risk low familial burde; HSC, help-seeking controls; HR-BP, high-risk for bipolar disorder; InterR, intermediate risk; MarR, marginal risk; HC, healthy controls; Controls, those in a birth cohort who did not develop an SSD; FEP, first-episode psychosis; EFEP, Early first-episode psychosis; SCZ, schizophrenia; SCZaff, schizo-affective; BP, bipolar; BS, basic symptoms; AffPSY, affective psychosis; PSYexe, psychotic experience; MDD, major depressive disorder; Dev. Control group, developmental control group (matched for age); TMT-A/B/C; Trail Making Test A/B/C; CPT-IP, Continuous Performance Test – Identical Pairs; *CPT-OX, Continuous Performance Test OX; CPT-X, Continuous Performance Test X;* AX-CPT, AX Continuous Performance Test; RAVLT; Rey Auditory Verbal Learning Test; ROCFT, Rey Osterrieth complex figure test; WCST, Wisconsin Card Sorting Test; Stroop C/W/C-W, Stroop color/word/color-word condition; COWAT, Controlled Word Association Test; LNS, Letter-Number Sequencing; CTVWM, computerized test of visual working memory; WAIS, Wechsler Adult Intelligence Scale; WISC, Wechsler Intelligence Scale for Children; Eyes Task, Reading the Mind in the Eyes task; FEIT, Face Emotion Identification Task; FEDT, Face Emotion Discrimination Task; AP, Affective Prosody task; DMTS, Delayed matching-to-sample task; CVLT, California Verbal Learning Task; G-Peg, Grooved Pegboard; PPVT, Peabody Picture Vocabulary Test; HVLT, Hopkins Verbal Learning Test; BVMT, Brief Visuospatial Memory Test; OTIS-R, Otis-Revised; RPM-R, *Raven's Progressive Matrices-Revised; VIDA, Variable Interval Delayed Alternation test; RBTM Story, Rivermead Behavioral Memory Test; HSCT, Hayling Sentence Completion Test; K-WAIS, Korean Wechsler Adult Intelligence Scales; WRAT-II/III, Wide Range Achievement test II/III; SDB battery; Swedish Draft Board test battery; JOLO, Judgement of Line Orientation; CHRT, Choice Reaction Time; SRT, Simple Reaction Time; BNT, Boston Naming Test; TASIT, The Awareness of Social Inference test; RAD, Relationship Across Domains; TAP, Testbatterie zur Aufmerksamkeit-sprüfung; FDB test battery, Finnish Draft Board test battery; FP, Faux Pas test; 15WT, Dutch 15-Word task.*

3.8. Social cognition

Evidence from 11 studies on social cognition points to impairment pre-onset. Nine studies found significant differences between those who later developed SSD and those who did not [3, 4, 5, 10, 24, 38, 39, 51, 60]. Two studies found no significant group differences pre-onset[30, 44]. On average, the effect size when comparing CHR+ and CHR- was small (d′ = 0,21). Longitudinal studies are sparse, and it remains uncertain when social cognitive impairment appears.

4. Discussion

4.1. Main findings

We found the strongest evidence for impairment pre-onset for mental processing speed, verbal learning and memory, executive function, and social cognition. However, when estimating magnitude differences between CHR+ and CHR-, only verbal fluency stands out with a large effect size (d′ = 0,85). There is a large degree of heterogeneity in the samples included, but this is a reflection of the heterogeneity of at-risk and SSD populations in general. The significant variability in results may be due in part to measurement differences between studies, as well as the fact that the at-risk group is clinically and demographically diverse. Another possible explanation of the heterogeneity of results may that there are differences in the timing and trajectory of the emergence of cognitive deficits in this group.

The high-risk studies included in this review evidence considerable variability in whether results for specific domains are significant or not. This may have several causes, but relatively small samples are probably a part of the explanation. Some high-risk studies stand out with almost exclusively non-significant results, e.g. Lindgren et al., 2017, Mamah et al., 2016, Nieman et al., 2014, Simon et al., 2012, Olvet et al., 2010, Walder et al., 2008 and Lencz et al., 2006. There is no specific characteristic all these studies have in common, but some have tests that are not widely used and may not be suitable for use in this population, others have small sample sizes or very few participants who transition to SSD, which may also reflect a short follow-up period. Some have relatively young participants and others have older participants. These are all characteristics that affect the quality of the high-risk studies included in this review and thus how we interpret the results in this review.

Evidence from cohort studies suggests that verbal deficits, including language abilities at age 3 and verbal learning and memory at age 7, may develop as static deficits. Non-verbal impairments, such as mental processing speed, visuospatial abilities and visual working memory may present as developmental lag and become significant in adolescence and adulthood. Mollon and Reichenberg (2018) also found evidence for a similar division between static and lagging deficits, which is in line with the findings in this review.

4.1.1. Processing speed

Impairment in mental processing speed pre-onset is in line with previous studies for both schizophrenia (Dickinson et al., 2007), and psychotic symptoms in children (Niarchou et al., 2013). Psychomotor speed impairment may be associated with genetic risk (Rakhshan et al., 2016), as suggested by significant differences for th FHR study and the large majority of CHR studies finding no significant differences. Our review shows that impairment in mental processing speed can be identified before onset of SSD, but that its effect size is relatively small.

4.1.2. Learning and memory

Impairment in verbal learning and memory is the most consistent finding of this review, with moderate effect size, similar to the findings of Catalan et al. (2021). However, the diverse and general tests used may obscure the differential impairment of various memory components. This partly contrasts with research on adolescents with established schizophrenia, indicating a general memory impairment involving both verbal and visual domains (Øie et al., 1999). Our results may also reflect the relative paucity of studies investigating visual learning and memory, or it may be that this impairment is more closely related to the onset of SSD.

4.1.3. Executive functions

Executive functions are impaired pre-onset in those who later develop SSD, although the domain magnitude statistics are different for different subtests. As in previous reviews of cognition in schizophrenia we also found discrepancy in effect sizes across different tests. Furthermore, executive function impairments seem to appear later in adolescence, possibly caused by the later maturation of frontal brain regions (Cannon et al., 2003). This also holds true for verbal and visual working memory, although the evidence for the latter is based on high-risk studies only, preventing firm conclusions.

For verbal fluency, the picture is less clear, as several studies found no significant relationship between impairment pre-onset and later SSD. On the other hand, verbal fluency evidenced the largest ES in this review (d′ = 0.85), suggesting that CHR+ may be more impaired than CHR-. This may imply that verbal fluency is a particularly sensitive measure of cognitive impairment in the pre-onset period. It has been found to be one of the most affected areas of cognition in established schizophrenia (Henry and Crawford, 2005). Furthermore, it has been noted that in prediction models where cognition is one of several prediction variables, they are generally weaker than clinical measures (Studerus et al., 2017). As such, targeting measures of cognitive domains that may be more effective in differentiating between CHR+ and CHR- can be particularly useful in clinical settings.

Lastly, the evidence for impairment pre-onset in reasoning and problem solving are weaker, perhaps due to few studies of this domain. However, the Israeli and Romanian conscript studies found pre-onset impairment in this sub-domain in men aged 16–18, suggesting that at least for men who later develop SSD, this function may be impaired pre-onset.

4.1.4. Social cognition

The tasks used to measure social cognition are diverse and measure different aspects, including emotion recognition, emotional prosody, and theory-of-mind. Most studies found significant differences in those who later develop SSD pre-onset, but the effects are small. Barbato et al. (2013b) note that in SSD, neurocognition, social cognition and functional outcome are inter-related, but due to the relatively small cognitive impairment compared to what is observed in established illness, this relationship may be weaker pre-onset or in high-risk samples. This is supported by Zhang et al. (2018), who found that the relationship between neurocognition and social cognition is strongest in CHR+, followed by CHR as a whole, and weakest for controls. Further investigation of this relationship is warranted, especially concerning remediation and therapy interventions targeting function.

4.2. Age of onset

For mental processing speed, significant differences in the group who later develop SSD were observed at ages 15–16 (Sorensen et al., 2006), as well as developmental lag that can be traced back to deficits as early as age 7 (Mollon et al., 2018; Meier et al., 2014; Reichenberg et al., 2010). Psychomotor processing speed deficits have been identified as early as age 13 (Cannon et al., 2006), and possibly declining into adulthood (Meier et al., 2014). In other words, processing speed deficits can be found at an early age, and possibly the deficits in speed of processing affect the development of other specific cognitive deficits, as the speed of processing hypothesis suggests (Rodríguez-Sánchez et al., 2007). For sustained attention, only one cohort study found increasing deficits from age 8 into adulthood (Mollon et al., 2018), which is not sufficient to draw any firm conclusions on timing of onset.

Language exhibits the earliest identifiable impairments, as early as age 3 (Cannon et al., 2002). This impairment showed stability in both the Dunedin (Meier et al., 2014) and the Avon Longitudinal Study of Parents and Children (Mollon et al., 2018) cohort studies. This finding may be due to language abilities being early developing functions, which lends itself to earlier testing. Verbal learning and memory impairments seem to debut early in adolescence. Cannon et al. (2006) identified impairment at age 13 in the Dunedin study, while most high-risk studies found significant differences later in adolescence. This may be explained by the age of participants in most high-risk studies and consequently we cannot draw firm conclusions on the timing of onset.

The results are mixed in longitudinal studies of visuospatial reasoning, possibly pertaining to measurement differences, where some indicate static deficit (Mollon et al., 2018) and others developmental lag (Reichenberg et al., 2010).

Executive impairment seems to appear in high-risk groups in adolescence or young adulthood. For verbal fluency, evidence from cohort studies point to impairment debut as early as age 13 (Cannon et al., 2006), while reasoning and problem solving show gender and age-specific deficits in men between the ages of 16–18 (Goldberg et al., 2011; Gheorghe et al., 2004). For visual learning and memory, visual working memory and social cognition, the evidence does not support identifying a specific age of onset.

Furthermore, as Fett et al. (2022) observe, heterogeneity in cognitive profiles is a central feature of the evidence pertaining to cognition in SSD, as is the case with at-risk participants included in this review. Moreover, as we have already pointed out, the paucity of longitudinal cohort studies that follow participants from childhood to adulthood and assess them multiple times makes it difficult to draw any firm conclusions concerning age of onset of specific cognitive impairment, even though considerable efforts have been made to understand what happens to cognitive functioning and development in people in an at-risk state and which cognitive factors that predict illness development and difficulties in functioning.

Overall, some similarities in longitudinal studies stand out, with some domains, like language, showing early and static deficit and others, like processing speed, evidencing developmental lag. These findings point to trajectories of cognitive deficits that start pre-onset, are different for specific domains and are in line with a neurodevelopmental model of SSD. In sum, there is ample evidence that people in an at-risk state and people who later develop SSD experience cognitive deficits pre-onset. As a marker of transition to SSD however, specific cognitive deficits may be too weak, although verbal fluency could be a stronger marker for risk of transition in a high-risk state.

4.3. Strengths and limitations

Strengths of this review are the inclusion of a larger number of tests making up each cognitive domain compared to previous reviews and meta-analyses. Another strength is the inclusion of the social cognition domain and the determination of age of onset for cognitive impairment which has not been previously examined in a systematic review. A possible limitation is a task effect where the average can hide when specific tasks are sensitive to cognitive deficits in SSD or where homogeneity of test use may not detect a deficit that is present. A limitation is the lack of meta-analysis. Even though meta-analysis is a highly valued method for assessing effects across multiple studies, a systematic review was considered more appropriate because there is considerable variation in terms of how cognitive domains are defined and measured, and in terms of study design and the timing of follow-up.

5. Conclusions

There is evidence for impairment in specific cognitive domains predating onset of SSD, with the largest deficits in mental processing speed, verbal learning and memory, executive function, and social cognition. Some verbal impairments may develop as static deficits evident as early as age 3, while some non-verbal impairments may present as developmental lag and become significant later, in adolescence and adulthood. Investigation of specific cognitive functions in different sub-diagnoses under the SSD umbrella and other severe mental disorders such as bipolar and major depressive disorders, are still warranted. Furthermore, discussion and further investigation is needed concerning areas of preserved cognitive function and how this may play into the pathogenesis of SSD and functional outcome. Only thus can differences in cognitive impairment, its onset and course, be identified and used to predict and intervene early in severe mental disorders.

CRediT authorship contribution statement

Caroline Ranem Mohn-Haugen: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **Christine Mohn:** Conceptualization, Methodology, Writing – review & editing. **Frank Larøi:** Conceptualization, Methodology, Writing – review & editing. **Charlotte M. Teigset:** Conceptualization, Writing – review & editing. **Merete Glenne Øie:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Bjørn Rishovd Rund:** Conceptualization, Methodology, Investigation, Writing – review & editing, Project administration, Supervision, Funding acquisition.

Declaration of competing interest

The authors have no conflicting interests to declare.

Acknowledgments

Funding

Grants from Vestre Viken Hospital Trust (#96G002) and South-Eastern Norway Regional Health Authority: (# 2013061) to Dr. Rund.

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