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Review Article

Lifespan evolution of neurocognitive impairment in schizophrenia - A narrative review☆

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ABSTRACT

Cognitive impairment is a well-recognized key feature of schizophrenia. Here we review the evidence on (1) the onset and sensitive periods of change in cognitive impairment before and after the first psychotic episode, and (2) heterogeneity in neurocognitive presentations across cognitive domains between and within individuals. Overall, studies suggest that mild cognitive impairment in individuals who develop schizophrenia or related disorders is already present during early childhood. Cross-sectional studies further suggest increasing cognitive impairments from pre- to post-psychosis onset, with the greatest declines between adolescence, the prodrome, and the first psychotic episode and with some variability between domains. Longitudinal studies with more than 10 years of observation time are scarce but support mild cognitive declines after psychosis onset until late adulthood. Whether and how much this cognitive decline exceeds normal aging, proceeds further in older patients, and is specific to certain cognitive domains and subpopulations of patients remains to be investigated. Finally, studies show substantial heterogeneity in cognitive performance in schizophrenia and suggest a variety of impairment profiles.

This review highlights a clear need for long-term studies that include a control group and individuals from adolescence to old age to better understand critical windows of cognitive change and its predictors. The available evidence stresses the importance of interventions that aim to counter cognitive decline during the prodromal years, as well as careful assessment of cognition in order to determine who will profit most from which cognitive training.

1. Introduction

Neurocognitive impairment in schizophrenia has been described since the late 19th century (Bleuler, 1950; Kraepelin, 1919). Since then, research yielded important insights corroborating neurocognitive impairments in individuals during the first-episode (Mesholam-Gately et al., 2009) and chronic (Heinrichs and Zakzanis, 1998) phases of schizophrenia, and showed direct links of such impairments with social and functional outcomes (Fett et al., 2011; Green, 1996). Here we review literature on the lifespan evolution of neurocognitive functioning in schizophrenia. Specifically, we will illustrate the current evidence on (1) the onset and sensitive periods of change in cognitive impairment before and after the first psychotic episode, and (2) heterogeneity in neurocognitive presentations across cognitive domains between and within individuals. We will integrate this evidence with insights from general population studies and lifespan developmental psychology and conclude with directions for clinical practice and future research.

Specifically, this selective, narrative review focuses on evidence from meta-analytic and cohort studies of schizophrenia covering at least one cognitive domain. In the absence of published meta-analyses on childhood and adolescence, we selected all available cross-sectional population-based cohort studies that included raw data on cognitive functioning to address the level of cognitive impairment, and sensitive periods of change across these time periods (Table 1). For the other

☆ In loving memory of Dr. Larry Seidman who started this project.

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disorder stages (prodrome, first-episode, and chronic), the most recent, comprehensive meta-analytic work was selected. For the prodromal stage, we considered individuals at Clinical High Risk (CHR) for psychosis who eventually converted to a first psychosis (since non-converters could not be considered prodromal). Longitudinal studies were selected if they included a population-based cohort (Table 2), or if they followed-up on individuals with a diagnosis of schizophrenia or a related psychotic disorder for more than 10 years after the onset (Table 3). To explore heterogeneity in neurocognitive presentations, available clinical studies reporting on variation within and between individuals were included (Table 4).

2. The onset and course of cognitive impairment in schizophrenia

2.1. Evidence from studies reporting on cognitive impairments by illness stage

Cohort studies evaluating data of children who develop schizophrenia many years later show robust evidence of cognitive impairment

Table 1
Effect sizes (Cohen's *d*) of cognitive impairments relative to controls by stage of the disorder.

Domain	Phase	Age range or mean age in years	Meta-analytic review? (If not, what tests were included?)	Average effect size (Cohen's *d*) in patients relative to controls	Study
IQ	Childhood	7–12	Yes	0.39	Khandaker et al. (2011)
	Adolescence	16–19	Yes	0.46	Khandaker et al. (2011)
	Prodrome	16–20 (mean 18.1)	Yes	0.81	Giuliano et al. (2012)
	First-episode	15.6–33 (mean 25.5)	Yes	1.01	Mesholam-Gately et al. (2009)
	Chronic	20.1–48.5 (mean 35.1)	Yes	1.13	Schaefer et al. (2013)
Processing speed	Childhood	7–8	Coding	0.65	Niendam et al. (2003), Seidman et al. (2013), Mollon et al. (2018)
	Adolescence	13	TMT-A and B, time to complete	0.47	Meier et al. (2014)
	Prodrome	16–20	Yes	0.56	Giuliano et al. (2012)
	First-episode	15.6–33	Yes	0.96	Mesholam-Gately et al. (2009)
	Chronic	20.1–48.5	Yes	1.18	Schaefer et al. (2013)
Attention/ vigilance	Childhood	8	Sky	0.45	Mollon et al. (2018)
	Adolescence			–	
	Prodrome	16–20	Yes	0.61	Giuliano et al. (2012)
	First-episode	15.6–33	Yes	0.71	Mesholam-Gately et al. (2009)
	Chronic	20.1–48.5	Yes	1.07	Schaefer et al. (2013)
Working memory	Childhood	7–11	Digit span	0.26	Niendam et al. (2003), Reichenberg et al. (2006, 2010), Seidman et al. (2013), Mollon et al. (2018)
	Adolescence	13	Digit span	0.37	Reichenberg et al. (2010)
	Prodrome	16–20	Yes	0.77	Giuliano et al. (2012)
	First-episode	15.6–33	Yes	0.86	Mesholam-Gately et al. (2009)
	Chronic	20.1–48.5	Yes	0.89	Schaefer et al. (2013)
Verbal abilities	Childhood	7–11	Information; Comprehension; Vocabulary; Similarities	0.36	Niendam et al. (2003), Reichenberg et al. (2010), Seidman et al. (2013), Mollon et al. (2018)
	Adolescence	13–17	Information; Similarities; Vocabulary; Rey test; Otis-R; Reading;	0.35	(2010), Reichenberg et al. (2002), Meier et al. (2014)
	Prodrome	16–20	Yes	0.62	Giuliano et al. (2012)
	First-episode	15.6–33	Yes	1.20	Mesholam-Gately et al. (2009)
	Chronic	20.1–48.5	Yes	1.05	Schaefer et al. (2013)
Visual abilities and memory	Childhood	7–11	Picture arrangement; Object Assembly; Picture Completion	0.49	Niendam et al. (2003), Reichenberg et al. (2006, 2010)
	Adolescence	13	Object Assembly; Picture Completion	0.25	Reichenberg et al. (2010)
	Prodrome	16–20	Yes	0.79	Giuliano et al. (2012)
	First-episode	15.6–33	Yes	0.90	Mesholam-Gately et al. (2009)
	Chronic	20.1–48.5	Yes	0.90	Schaefer et al. (2013)
Reasoning/ problem solving	Childhood	7–11	Arithmetic; Block Design	0.49	Reichenberg et al. (2006, 2010), Niendam et al. (2003), Mollon et al. (2018)
	Adolescence	12–17	Arithmetic; Mathematics; Ravens Matrices; Block Design	0.46	Reichenberg et al. (2010), Ang and Tan (2004), Reichenberg et al. (2002)
	Prodrome	16–20	Yes	0.47	Giuliano et al. (2012)
	First-episode	15.6–33	Yes	0.83	Mesholam-Gately et al. (2009)
	Chronic	20.1–48.5	Yes	0.96	Schaefer et al. (2013)

Note: For childhood and adolescence/young adulthood, no meta-analytic review data was available. We therefore included data of all available population-based follow-up studies. For the prodrome, first episode and chronic stages of the disorder, data from the most recent and comprehensive meta-analytic review was used. It is important to note that chronic sample of patients who partake in research may differ in terms of cognitive performance from patients who do not. NB. The prodrome effect sizes were calculated based on baseline cognitive functioning scores of CHR-converters. Data for the Attention/Vigilance domain was not available for adolescence.

Table 2
Longitudinal population-based studies reporting on the course of cognitive impairment in schizophrenia.

Author	Cohort	Year	Follow-up years	N	Age group	Age (years)	Control	% male	Patients	% male	Cognitive domains	Cognitive tests	Key findings	Decline
Caspi et al. (2003)	Israeli draft board	–	~5–6	88	Adolescence Adulthood	16–17 ~22.8	44	100	44 SZ	100	Verbal ability, Arithmetic, Reasoning & problem solving	Arithmetic-R, Similarities-R, Raven's Progressive Matrices-R; OTIS-R	Within group analysis showed no significant changes in SZ. Between group comparison showed that relative controls, SZ deteriorated on RPM-R and Otis-R, but not on the Similarities-R and Arithmetic-R.	No decline; developmental arrest in some domains
MacCabe et al. (2013)	Swedish population register, Swedish conscription register	1953 1967 1972 1977	5	10,719	Adolescence Adulthood	13 18	–	–	50 SZ, SZA 64 Other non-affective	100	Verbal ability, Visual–spatial ability, Reasoning & problem solving	Verbal Ability: 13: Antonyms, 18: Synonyms; Spatial Ability: 13, 18: Metal Folding. Inductive Ability: 13: Number series: complete items in a number series, 18: Make markings on answer sheet by following instructions on simple arithmetic/ geometric operations. 18 (1977 Cohort): Figure Series: Complete items in figures series	Relative decline in adolescence and young adulthood, particularly in verbal ability, is associated with increased risk for non-affective psychosis in adulthood. Impairment of late neuro-development may affect acquisition of verbal skills in adolescent boys and young men who later develop psychosis.	Yes
Reichenberg et al. (2010)	Dunedin	1972–1973	6	1037	Childhood Adolescence	7 9 11 13	556	–	35 SZ	–	Full scale IQ Verbal ability, reasoning & problem solving, processing speed	WISC–R. information, vocabulary, similarities, perceptual organization, block design, picture completion, object assembly, arithmetic, digit symbol coding	SZ show early static deficits in verbal & visual knowledge acquisition, reasoning & problem solving Developmental lags in processing speed, attention, visual-spatial ability, and working memory. Such patterns were not observed in depression	In some domains, developmental arrest in others
Jones et al. (1994)	British Birth Cohort	1946	7	5362	Childhood Adolescence	8, 11 15	4746	52	30 SZ	60	Verbal ability, non-verbal ability, reasoning & problem solving	Educational test scores: Non-verbal, verbal, Arithmetic, Vocabulary, reading. Group tests non-verbal, verbal, and reading abilities done at 8, 11, and 15,	Performance only declined in non-verbal test scores. Verbal ability and arithmetic remained stable	In some domains

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Table 2 (*continued*)

Author	Cohort	Year	Follow-up years	N	Age group	Age (years)	Control	% male	Patients	% male	Cognitive domains	Cognitive tests	Key findings	Decline
												arithmetic at 11 and 15, and vocabulary at 8 and 11.		
Seidman et al. (2006)	National Collaborative Perinatal Project	1959–1965	28	15,721	Childhood Adulthood	7 36	61	55	31	79	Verbal ability, reasoning & problem solving, processing speed	WISC: Vocabulary, Comprehension, Information, Digit Span, Picture Arrangement, Block Design, and Digit Symbol Coding. IQ estimate based on WAIS-R Vocabulary and Block Design Subtests. Digit Span test used in sub-set of participants.	SZ declined, compared to controls in IQ estimate Magnitude was 2× larger on block design than vocabulary SZ declined 2.3 scale score points, controls 0.3	Yes
Meier et al. (2014)	Dunedin	1972–1973	31	1037	Childhood Adolescence Adulthood	7–11 13 38	517	–	31 SZ	–	Full scale IQ, verbal learning & memory, processing speed, reasoning & problem solving (EF)	WISC-R and WAIS-IV; Rey Auditory Verbal Learning Test, Trail Making Test	SZ declined in IQ and range of domains, particularly processing speed, verbal learning, reasoning & problem solving No decline in verbal abilities or delayed memory Processing speed declined from childhood to beyond early teen years, verbal deficits remained static. Cognitive decline specific to SZ, -no evidence persistent depression, mild cognitive impairment, matched individuals or healthy controls.	In some domains
Kremen et al. (2010)	Developmental Insult and Brain Anomalies in Schizophrenia (DIBS) study, based on representative birth cohort of Oakland, CA	1981–1997	33	12,094	Childhood Adulthood	5 or 9–11 ~40	15	73	10 SZ, SZA	66	Verbal ability	Peabody Vocabulary test	Residualized scores of SDs above or below predicted adult scores suggest significant decline in receptive vocabulary A time × group interaction on cognition was not significant, possibly due to small sample	Yes

Note. Longitudinal population-based studies are included if they report cognitive performance at several time points either before disorder onset or from before to after onset.

Table 3
Longitudinal studies in clinical samples reporting on the course of cognitive impairment in schizophrenia over 10+ years.

Author	Country	Cohort	Follow-up duration	Cognitive assessments	Average age at t1 (years)	Control group N	% male	SZ group N	% male	Symptom levels at first assessment	Cognitive domains	Cognitive tests	Key findings	Decline
(Barder et al., 2013a,b)	Norway DK	FEP	10	5 1, 2, 5, and 10 years after inclusion	28	–	–	43	51	PANSS Pos 20.4 (5.1) PANSS Neg 13.8 (7.4)	Verbal ability; reasoning & problem solving (EF); working memory; Full scale IQ	WAIS-R similarities, block design, digit span.	• Stable cognition in FEP, except for verbal memory in those with relapse/non-remission. • Decline in specific domains specific to those with ongoing psychosis (as indicated by number of relapses), but majority do not show changes.	In some domains for a subset of patients
(Hoff et al., 2005)	US	FEP SZ	10	2	26	8	62	21	71	SAPS 6.6 (3.8) SANS 9.4 (4.2)	Verbal ability, verbal declarative memory, visual ability & memory, attention, processing speed, reasoning and problem solving, and verbal fluency	Pro-rated Wechsler Adult Intelligence Scale-Revised Verbal IQ (Information, Vocabulary, Similarities), Wide Range Achievement Test-Revised Reading, the Logical Memory, Paired Associates, WMS Visual Reproduction, California Verbal Learning Test, Benton Visual Retention Test, Wisconsin Card Sorting Test, Stroop Color–Word Test, Trail making Test.	• Stable cognition, repeated measures analyses showed no differences between patients and controls in degree of change. • Stable negative and improving positive symptoms over time • Reduction in symptoms uncorrelated with change in cognition function	No
(Stirling et al., 2003)	UK	Schizophrenia and other non-affective psychosis	10	2	26	–	–	49	57	Not reported	Verbal ability, visual ability & memory, Reasoning & problem solving, verbal fluency,	WAIS: object assembly, picture completion, picture arrangement, block design, Warrington recognition memory tests faces and words; memory for design test, verbal fluency, modified Wisconsin card sort test, National Adult Reading Test	• Significant decline in object assembly, picture completion, memory for designs, but not reasoning & problem solving. • Visuo-spatial function is spared but may deteriorate. • Neurocognitive change mostly not correlated with symptomatic outcomes	In some domains
(Zanelli et al., 2019)	UK	Schizophrenia and other psychoses	10	2	36; 29	103	38.8	65	~59.4	Not reported		WAIS-R Full-scale IQ was estimated using the vocabulary, comprehension, digit symbol coding, and block design. Rey Auditory Verbal Learning Test; WMS-R visual	• SZ declined in IQ, verbal knowledge and memory but not processing speed or executive functions/ reasoning & problem solving • SZ with severe symptoms showed greater decline than those with mild or	In some domains

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Table 3 (*continued*)

Author	Country	Cohort	Follow-up duration	Cognitive assessments	Average age at t1 (years)	Control group N	% male	SZ group N	% male	Symptom levels at first assessment	Cognitive domains	Cognitive tests	Key findings	Decline
												reproduction, vocabulary, comprehension subtests WAIS-R, WAIS-R digit symbol coding TMT-A; TMT—B, letter-number span category and letter fluency, block design subtest.	moderate symptoms in memory.	
(Øie et al., 2008)	Norway	Early onset SZ	13	2	16	30	50	15	66	BPRS Pos13.3 (8.3) Neg 6.3 (3.1)	Reasoning & problem solving (EF), visual ability & memory; verbal ability & memory	Wisconsin Card Sorting Test, WAIS matrix reasoning, digit span, digit symbol, California Verbal Learning Test recall & recognition, Kimura Recurring Figures Test, Seashore Rhythm Test, Digit Repetition Test, Trail Making Test A & B WASI Similarities, vocabulary, Block Design, Backward Masking Test	• SZ show decline or arrest in cognition, particularly in verbal memory, attention, and processing speed.	In some domains
(Fett et al., 2020)	US	Schizophrenia spectrum and other psychoses	18	2	29	–	–	195	58	SAPS 13.17 (10.13) SANS avolition 12.22 (7.10)	Verbal ability, verbal declarative memory, visual ability & memory, attention, processing speed, reasoning and problem solving, and verbal fluency	WAIS-R Vocabulary test; WMS-R Verbal Paired Associates I (immediate) and II (delayed); WMS-R Visual Reproduction I (immediate) and II (delayed); Symbol Digit Modalities Test (written and oral); Trail Making Test-A; Trenerry Stroop Color-Word Form (Stroop); Trail Making Test-B; Controlled Word Association Test	• Regardless of diagnosis all cognitive domains, except vocabulary and verbal fluency declined. • Magnitude of declines ranged from d = 0.17–0.54 • Increase in avolition most consistently correlated with declining cognition	In some domains
(Russell et al., 1997)	UK	Help seeking children later diagnosed with SZ	19.8 (range 3–44 yrs)	2	13	–	–	34	72.5	Not reported	Full scale IQ	WISC–R; WAIS–R	• No significant differences between child and adult Iqs, suggesting stable IQ • Participants who were tested while psychotic and those whose testing predated onset of psychosis	No

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Table 3 (*continued*)

Author	Country	Cohort	Follow-up duration	Cognitive assessments	Average age at t1 (years)	Control group N	% male	SZ group N	% male	Symptom levels at first assessment	Cognitive domains	Cognitive tests	Key findings	Decline
													showed no differences in IQ deterioration	
(Bonner-Jackson et al., 2010)	US	FEP SZ	20	5	23	–	–	84	62	Not reported	Processing Speed, Verbal ability	WAIS Digit symbol coding; information	• After acute phase SZ show cognitive improvements • No evidence of cognitive decline over further assessments. • Psychotic vs. non-psychotic individuals showed lower processing speed	No

Note. Only longitudinal studies in clinical sample that cover an observation time of at least 10 years are reported.

relative to children who do not develop the disorder (Cannon et al., 2002; Cannon et al., 2000; Seidman et al., 2013). In further support of neurodevelopmental models of schizophrenia, a recent study by Mollon et al. (2018) suggests that mild cognitive impairments are already present in toddlers as young as 18 months of age (Mollon et al., 2018). While this work shows the presence of very early cognitive deficiencies, the periods of the most dramatic loss in cognitive functioning in individuals who are later diagnosed with schizophrenia have remained inconclusive (Keefe and Kahn, 2017). To increase our understanding of potential crucial periods of cognitive change, we pooled evidence from epidemiological cohort studies that cover childhood and/or adolescence, and data from the most comprehensive meta-analytic studies on cognition in the psychosis prodrome, first-episode and chronic schizophrenia. Reported effect sizes (Cohen's *d*) of cognitive impairments in patients relative to controls by life phase of these studies are shown in Table 1.

The evidence presented in Table 1 suggests that up to half of the cognitive deficits in general IQ and various cognitive domains found in first-episode psychosis are already evident during childhood (range of estimated effect sizes $d = 0.26–0.65$). Cognitive impairments appear to increase mostly from prodrome to the first psychotic episode, although the timing of this increase varies somewhat between cognitive domains. The effect sizes reported in Table 1 further suggest that the level of cognitive impairment from the first episode to more chronic phases of schizophrenia is relatively stable.

2.2. Evidence from longitudinal cohort studies investigating change in cognitive impairment over time

The cross-sectional cohort studies described in Table 1 provide insights into the average level of cognitive impairment by illness stage. Yet, to reliably determine long-term change in cognitive functions within individuals, follow-up studies that include a control group, begin in childhood, and have follow-up assessments at various points over decades into late-life are required. Only a few population-based studies investigated cognitive functioning longitudinally and across different illness stages (see Table 2). Three of these studies focused on premorbid cognition in childhood and adolescence. In congruence with results from cross-sectional work, available evidence from these longitudinal studies suggests that both cognitive arrest and decline mostly take place before or during the early course of the disorder, with the exception of verbal impairments that appear to be stable during this time (Jones et al., 1994; Meier et al., 2014; Reichenberg et al., 2010). Three studies that investigated overall cognitive decline from pre-illness-onset in childhood to post-onset in mid-adulthood (ages 30–50) demonstrated significant declines in overall IQ (Kremen et al., 2010; Meier et al., 2014; Seidman et al., 2006). Interestingly, the two papers that specifically focused on verbal functions found notable declines in individuals who would later develop schizophrenia (Kremen et al., 2010; MacCabe et al., 2013). This work contrasts findings from studies that included different cognitive domains, suggesting that declines from pre- to post onset are more severe in performance based than verbal cognitive functions (Caspi et al., 2003; Kremen et al., 2010; Meier et al., 2014). Unfortunately, all studies suffered from large gaps between the assessments and therefore could not pinpoint specific periods of decline.

2.3. Evidence from longitudinal clinical studies investigating change in cognitive impairment over time

Longer-term clinical studies (i.e., with a follow up of 10 years or longer) are also still scarce and their results are conflicting (Table 3). For example, a recent 10-year longitudinal study in relatively young individuals with first episode psychosis showed significant declines in overall IQ ($d = 0.28$), as well as in the domains memory (a fluid cognitive domain) and verbal knowledge (a crystalized cognitive domain) (Zanelli et al., 2019). However, while deteriorating fluid

cognitive functions in individuals with schizophrenia have also been reported by others (Fett et al., 2020; Jones et al., 1994; Meier et al., 2014; Øie et al., 2008), most studies have shown relatively stable or improving cognitive functioning in crystallized cognitive domains (Barder et al., 2013b; Fett et al., 2020; Hoff et al., 2005; Stirling et al., 2003). Only two studies continuously followed-up individuals for as long as two decades after their first hospitalization for psychosis. The first assessed processing speed and verbal ability over 20 years (Bonner-Jackson et al., 2010) and showed that the acute psychotic phase was followed by improvements in cognition and stable cognitive performance thereafter. However, the sample was very young (aged 43 at follow-up) and it is possible that further declines may have occurred at older ages, as suggested by some studies in older individuals with schizophrenia (Harvey, 2014). The second study assessed performance in six cognitive domains from two to 20 years after first hospitalization. The study showed mild to modest declines in most cognitive domains, including verbal memory, visual memory, attention and processing speed, and abstraction-executive function ($d = 0.17$ to $d = 0.54$). However, the study showed improvement in verbal knowledge and stability in verbal fluency (Fett et al., 2020). Critically, both long-term studies lacked a control group. Thus, a key question that remains is whether the observed patterns diverge from normal age-related changes in cognition. A comparison to data from longitudinal general population studies suggests relatively stable cognitive functioning until the 50s (Anstey et al., 2014; Davis et al., 2017; Hughes et al., 2018; Rönnlund et al., 2005; Schaie, 1994; Singh-Manoux et al., 2012). Only processing speed already shows an earlier and steeper decline in healthy individuals, starting during early to mid-adulthood (Anstey et al., 2014; Hughes et al., 2018). Although this finding is broadly in line with findings from Bonner-Jackson et al. (2010), suggesting relatively stable cognitive functioning until mid-adulthood, it contrasts with findings from Fett et al. (2020), showing earlier decline compared with controls in some cognitive domains, including in processing speed. This work could suggest that age-related cognitive decline in processing speed in individuals with a psychotic disorder might be shifted forward in time.

With respect to late-life cognitive functioning in individuals with schizophrenia relative to controls meta-analytic evidence from shorter longitudinal studies shows mixed results. Some studies found no declines over a 1–6 year follow-up period in older individuals (Irani et al., 2010) while others suggest that there some evidence for cognitive decline in late life, with progressive deterioration beyond age 65 (Rajji and Mulsant, 2008; Shah et al., 2012). Some of the contradictory findings might be explained by the fact that cognitive decline in schizophrenia in old age is heterogenous, and particularly present in specific sub-groups of individuals with an extensive history of illness and protracted institutionalization (Friedman et al., 2001),

In sum, the existing studies point towards earlier cognitive decline in schizophrenia compared to the healthy population, and possibly more severe decline in some cognitive domains. Long-term studies that follow individuals from the first episode into old age and that include a control group will be indispensable to elucidate whether decline in schizophrenia exceeds age-normative aging and identify specific trajectories and potential predictors of cognitive decline.

3. Heterogeneity of neurocognitive functioning between and within individuals diagnosed with schizophrenia

To facilitate (preventive) treatment efforts, it is crucial to determine heterogeneity in cognitive profiles. Below we will present available evidence of data on heterogeneity in cognitive performance (2.1.) between and (2.2.) within individuals diagnosed with schizophrenia.

3.1. Heterogeneity of neurocognitive functioning between individuals diagnosed with schizophrenia

In the early 90s, Seidman proposed that there may be substantial neurocognitive heterogeneity between vulnerable children who later develop schizophrenia (Seidman, 1990), and that neurocognitive profiles after first diagnosis can vary from relatively normal to severely impaired range (Seidman et al., 1992).

Although there is now broad consensus that a sizable proportion of individuals with schizophrenia presents with cognitive impairment in at least some domains (Keefe et al., 2005; Kremen et al., 2000; Palmer et al., 1997; Wilk et al., 2005), around 30% of individuals with a schizophrenia diagnosis seems to perform within the 'normal' range of performance on most cognitive functions (Table 4). Indeed, a recent meta-analysis found cognitive subgroups characterized by high, intermediate and a globally impaired cognitive functioning (Carruthers et al., 2019).

It is important to note, however, that while the studies presented in Table 4 use definitions such as 'intact' or 'normal' cognitive functioning, their conclusions about what constitutes 'normal' mostly stem from data driven latent class analyses; holding that 'normal functioning' represents the better functioning group compared to the rest of the study sample. It is questionable whether such profiles actually represent completely intact cognitive functioning. In fact, as mentioned previously, it has been argued that almost no one with a diagnosis of schizophrenia is completely free of any cognitive impairment, even in the highest functioning patient group. This is supported by evidence from clinical- as well as from twin research, suggesting that patients' current level of cognitive functioning falls below the level predicted by their premorbid estimates (Keefe et al., 2005), or by their unaffected twins (Goldberg et al., 1990), respectively. Whether such performance differences are indeed meaningful in terms of daily life functioning or warranting intervention is unclear (Ammari et al., 2014).

One key question that remains is whether sub-groups with different degrees of cognitive impairment also show distinct cognitive trajectories over time. Recent meta-analytic evidence of thirteen studies on the relationship between estimated premorbid and current IQ, suggests that over time 33% show stable preserved cognitive functioning, 41% deteriorate, and 21% showed continuously compromised functioning pre- to post-onset. Stable trajectories over six years follow-up have been reported for patients with different degrees of cognitive impairment (Islam et al., 2018). Further evidence on trajectories of cognitive functioning over time from before the onset to old age is needed, and will be important to determine for whom and when cognitive intervention will be useful (Carruthers et al., 2019).

3.2. Heterogeneity of neurocognitive functioning within individuals diagnosed with schizophrenia

While cognitive impairment in schizophrenia is broad-based and has even been characterized by one factor by some studies (Dickinson et al., 2006, 2008), differences in the magnitude of impairment in different cognitive domains have been clearly shown by others (Dickinson et al., 2007; Heinrichs and Zakzanis, 1998; Jirsaraie et al., 2018; Nuechterlein et al., 2004).

The most consistent evidence for heterogeneity in cognitive performance within individuals diagnosed with schizophrenia stem from epidemiological cohort studies, showing that performance on premorbid non-verbal reasoning tasks is associated with greater risk for schizophrenia than performance on verbal reasoning tasks (David et al., 1997; Jones et al., 1994; Reichenberg et al., 2006).

Crucially, even in individuals with severe cognitive deficits, there may be specific cognitive functions that remain relatively or fully intact and that could potentially serve as building blocks for rehabilitation. To illustrate this cross-domain heterogeneity, several studies have explored the presence of specific cognitive strengths and weaknesses (Goldstein et al., 1998; Goldstein and Shemansky, 1995; Goldstein and Zubin, 1990; Heinrichs and Awad, 1993; Heinrichs et al., 1997; Hill et al., 2002; Kremen et al., 2004; Lewandowski et al., 2014). This, mostly cross-sectional work, seems to indicate three to four significant subgroups of

Table 4
Studies reporting on heterogeneity of neuropsychological presentations in (risk for) schizophrenia.

Study	Age (yrs) Mean (SD)	Total study sample	N included in current analysis (% male)	Outcome
Velthorst et al. (2019)	18.9 (3.9)	324	54 (68.5)	• High functioning (13.0%) • Normal (29.6%) • Mildly impaired (31.4%) • Significantly impaired (25.9%)
Sauvé et al. (2018)	23.7 (4.6)	326	80 (71.3)	• No impairment (54%) • Intermediately impaired (38%) • Generally impaired (9% FEP)
Reser, Allott et al. (2015)	20.36 (2.41)	135	128 (~67)	• Strongly performing (19.5%) • Poor visual recognition and memory (20.3%) • Flat profile (35.9%) • Significant impairments (24.2%)
Ilonen et al. (2004)	Mean ages: 31–34	27	27 (37.0)	• Normal (18.5%) • Memory dysfunction (37.0%) • Global dysfunction (44.5%)
Islam et al. (2018) (nb. looked at trajectories)	27.58 (7.94)	2764	1119 (76.1)	• High trajectory (3.8%) • Normal trajectory (26.7%) • Mild trajectory (30.4%) • Moderate trajectory (28.4) • Severe trajectory (3.8%)
Bechi et al. (2019)	35.22 (10.56)	452	452 (66.6)	• High-level performance (29.9%) • Medium level performance (38.3%) • Low-level performance (31.9%)
Sauvé et al. (2018)	35.2 (8.0)	326	80 (71.3)	• No impairment (25%) • Intermediately impaired (50%) • Generally impaired (25%)
Van Rheenen et al. (2017)	42.80 (10.43)	1541	564 (63.0)	• Relatively intact (13.3%) • Mild-moderate (46.5%) • Relatively severe (40.2%)
Ohi et al. (2017)	37.6 (10.4)	126	81 (44.4)	• Neuropsychologically normal (11.1%) • Intermediately impaired (53.1%) • Globally impaired (35.8%)
Gilbert et al. (2014)	41.1 (9.6)	112	112 (72.3)	• Near-normal functioning (42.9%) • Selectively impaired (41.1%) • Generally impaired (16.1%)
Lewandowski et al. (2014)	37.60 (11.15)	151	28 (ns)	• Neuropsychologically normal (12.2%) • Visual/verbal learning and memory impairments, relatively intact processing speed and executive function (12.2%) • Impaired verbal memory, verbal fluency, executive functioning, processing speed; intact visuo-spatial learning/memory (34.1%) • Significantly impaired (41.5%)
Kremen et al. (2004)	Mean ages: 36–45	165	74 (66.7)	• Within normal range (26.6%) • Left temporal/verbal memory (9.4%) • Frontal/abstraction (53.1%) • Other (10.9%)
Horan and Goldstein (2003)	Mean ages: 36–44	382	223 (100)	• Near normal (38.6%) • Moderate (18.4%) • Moderate motor (24.7%) • Compromised (18.4%)
Hill et al. (2002)	Mean ages: 30–37	151	151 (58.3)	• Near normative performance with mild dysfunction in in verbal memory (50.3%) • Moderate severe with more prominent executive than memory dysfunction (25.2%) • Moderate severe with more prominent memory than executive dysfunction (12.6%) • Severe and profound global dysfunction (9.9%)
Kremen et al. (2000)	Mean ages: 42–44	166	75 (81.3)	• Within normal range (22.7%) • Neuropsychologically abnormal (77.3%)
Weickert et al. (2000)	Mean ages: 32–34	144	117 (71.8)	• Preserved (24.8%) • Deteriorated (based on WRAT-R Reading) (51.3%) • Compromised (23.9%)
Goldstein and Shemansky (1995), Goldstein et al. (1998)	38–47	221	221 (100)	• Normal range (WCST good functioning), (25.8%) • Moderate impairment (38.9%) • Pronounced impairment, exceptionally poor on category test and relatively good on TMT (16.3%) • Severe pervasive impairment (19.0%)
Heinrichs and Awad (1993), Heinrichs et al. (1997)	40.9 (10.3)	104	104 (65.3)	• Normative function (15.4%) • Selective motor-basal ganglial deficit (18.3%) • Selective executive-prefrontal dysfunction (23.1%) • Executive-motor/cortico-basal ganglial deficit (19.2%) • Dementia/multi-focal disturbance (24.0%)
Goldstein and Zubin (1990)	Mean ages: 30–43	136	136 (100)	• Relatively cognitively intact (20.6%) • Good performance on TRB on both a relative and absolute basis, otherwise average (19.1%)

(*continued on next page*)

Table 4 (*continued*)

Study	Age (yrs) Mean (SD)	Total study sample	N included in current analysis (% male)	Outcome
				• Relatively average (25.0%) • Poor performance on the Category, Tactual Performance Test and TRB relative to the WCST (16.2%) • Most cognitively impaired (19.1%)

Note: Only studies covering various cognitive domains, and reporting on patient distribution per cluster were included here. Seaton et al. (1999) was excluded for this reason. Uren et al. (2017) and Lewandowski et al. (2014) were not included because it also included social cognition, which was beyond the scope of our current study. Joyce et al. (2005) only examined IQ.

cognitive profiles: one characterized predominantly by memory impairments with other cognitive functions remaining largely intact, one with executive functioning deficits without significant memory deficits, one without any severe cognitive deficits, and one with a globally impaired profile (see Table 4). Variable cognitive profiles were found both in first-episode and chronic schizophrenia (Kremen et al., 2004; Seidman et al., 2006; Weickert et al., 2000).

In sum, the variability in cognitive profiles emphasizes why it is important for studies to consider within and between individual variability instead of examining group averages in studies to cognition, thus far the most common approach (Revell et al., 2015). Including individuals without any substantial cognitive deficits on a particular domain that is the focus of cognitive enhancement interventions may obscure meaningful results, when in fact the cognitive intervention might be very successful for a specific subgroup. The identification of cognitive profiles is also necessary to develop personalized clinical approaches and is essential to identify who might benefit most from cognitive training and how cognitive training should be fitted to the pattern of cognitive impairments (Velthorst et al., 2019).

4. Mechanisms that may account for cognitive change and cognitive heterogeneity in schizophrenia

It has been hypothesized that latent abnormalities in cognitive functions (resulting from early neurodevelopmental insults) become visible when they interact with normal neurodevelopment (Reichenberg et al., 2010). Research in general population samples (e.g. Craik and Bialystok, 2006; Shing and Lindenberger, 2011) shows that most cognitive abilities increase steeply from infancy to young adulthood, which may explain why cognitive difficulties in schizophrenia gradually start to emerge in childhood (Kail, 2000). However, the time windows of these developments vary across cognitive domains. For instance, there is an acceleration in processing speed from early childhood up to adolescence; 8- to 10-year-olds have been found to respond at a speed that is five to six standard deviation units below the average processing speed for young adults, while 12- and 13-year olds respond at a speed around one standard deviation below (Kail, 2000). Thus, deficits in this domain may be evident earlier compared to other domains. It has been argued that reduced processing speed may lead to lags in multiple cognitive functions during adolescence and early adulthood (Gathercole et al., 2004; Mollon et al., 2018). For example, it is believed that a slower processing of visual or verbal information may cause decay of material already during processing, leading to lower memory performance (Gathercole et al., 2004). Thus increasing cognitive demands in late adolescence in the school or work environments and when individuals become more independent, might lead to more noticeable deficits, e.g. poorer academic outcomes (Dickson et al., 2020).

Heterogeneity in terms of cognitive performance and decline may, at least in part, reflect individual differences linked to genetic variation implicated in neural development and function (Joyce and Roiser, 2007), their interaction with environmental risk factors and physiological/brain processes that are related to the developing illness (Jirsaraie et al., 2018; Kelly et al., 2019). For example, at-risk individuals who later develop schizophrenia have been found to show greater gray matter loss in frontal cortical regions and a larger expansion of the third ventricle compared to individuals who do not develop the disorder (Cannon et al., 2015). Interestingly, results from a 18-year follow-up of first episode patients found widespread decreases in gray and white matter that were most pronounced immediately after psychosis onset and that were related to cognitive impairment rather than other clinical measures (Andreasen et al., 2011). This finding is somewhat at odds with findings that show stable or improved cognitive performance after psychosis onset. However, Andreasen et al. (2011) also suggest that progressive neural changes only occur in a sub-set of individuals. Other longitudinal research in patients with chronic schizophrenia found evidence for accelerated loss of gray matter over time, with more pronounced changes in poor- vs. good-outcome patients (Dietsche et al., 2017). Some of these structural brain changes might be due to the use of anti-psychotic medication (Fusar-Poli et al., 2013; Voineskos et al., 2020). Cognitive impairment post-illness onset could further be caused by a variety of environmental factors that result from the disorder, such as reduction in vocational or social participation which may lead to a lack of 'cognitive practice' (Fett et al., 2020; Small et al., 2012; Stern, 2002). Progressive cognitive impairment in schizophrenia over ten years has been related to the number of relapses early after onset (Barder et al., 2013a) and to worse or worsening negative and disorganized symptoms (Fett et al., 2020; Hoff et al., 2005), which may reflect all three mechanisms.

In older individuals, age-related medical and neurological conditions associated with cognitive problems are more frequent in schizophrenia and might, at least in some individuals, contribute to further cognitive deterioration, through disruption of neural architecture and cognition promoting opportunities (Bora et al., 2016; Cai and Huang, 2018; Casey et al., 2011; Fan et al., 2013; Lancon et al., 2012).

5. Conclusions and clinical and research implications

Overall, this narrative review suggests that most cognitive deficits in schizophrenia already start early, but that the extent and timing of the most severe declines may differ between cognitive domains. These findings suggest that different cognitive domains may warrant differently timed interventions. Comparison with evidence from lifespan developmental psychology suggests that processing speed deficits may be an important driver of the earliest cognitive deficits, while deficits in working and verbal memory may only appear later (Andersen et al., 2013; Rodríguez-Sánchez et al., 2007). An early focus on improving deficiencies in the processing speed domain in vulnerable individuals may therefore potentially help preventing further impairments across other domains, although this hypothesis, needs to be tested formally.

Epidemiological cohort studies and long-term clinical studies also show moderate declines in cognitive performance after psychosis onset that appear to be more pronounced in some cognitive domains relative to others. Some studies suggest that there may be further cognitive decline during late-life in schizophrenia; however, it is unclear whether and to what extent this decline exceeds typical cognitive aging. It is possible that cognitive decline in old age may be specific to patients with the largest illness severity, characterized by persistent and/or repeatedly emergent psychotic episodes (for a review see Harvey and Rosenthal,

2018). Research suggests that cognitive decline over 20-years is associated with real-life functional outcomes (Fett et al., 2020; Friedman et al., 2002), but further research is needed to understand the magnitude and direction of effects.

In addition, the current evidence stresses that clinicians need to be alert to heterogeneity in their patients' cognitive performance profiles and cognitive course. Being able to address these individual differences in clinical practice, for instance through tailored cognitive remediation training, psycho-education for families or the implementation of cognitive aids, may improve outcomes more effectively. A cognitive assessment as part of the standard patient evaluation in clinical settings is therefore warranted. It will be important for such assessments to include standardized measures that are sensitive to detect change, that are not hampered by floor or ceiling effects, and that consider premorbid functioning. For example, it is questionable whether individuals with cognitive performance in the normal, but below expected range, would benefit from cognitive interventions to the same extent as lower functioning individuals with schizophrenia, given that participants with greater cognitive impairment benefit differentially more from cognitive remediation than less cognitively impaired participants (DeTore et al., 2019; Harvey et al., 2020; Strassnig et al., 2018). Through the implementation of standard cognitive evaluation, it will become it easier to capture whether patients experience clinically meaningful decline and to detect 'islands' of preserved functions.

CRediT authorship contribution statement

Anne-Kathrin Fett & **Eva Velthorst**: literature search, original draft preparation: **Abraham Reichenberg**: study conceptualization, reviewing and editing.

Declaration of competing interest

The authors report no conflict of interest.

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