


Regular Article

Cross-sectional associations between adaptive functioning and social cognitive and neurocognitive functions in adolescents with first-episode, early-onset schizophrenia spectrum disorders

J.R.M. Jepsen^{1,2} , J. Rydkjaer^{1,2}, B. Fagerlund¹, Cecilie K. Lemvig¹, A.K. Pagsberg^{2,3}, B.Y. Glenthøj^{1,3} and B. Oranje^{1,3}

¹Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS) and Center for Neuropsychiatric Schizophrenia Research (CNSR), Mental Health Center, Glostrup, Copenhagen University Hospital - Mental Health Services CPH, Copenhagen, Denmark, ²Child and Adolescent Mental Health Center, Copenhagen University Hospital - Mental Health Services CPH, Copenhagen, Denmark and ³Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Abstract

Background: Few studies have explored associations between adaptive functioning and cognition in adolescents with early-onset schizophrenia spectrum disorders (EOS).

Methods: Adaptive functioning, cognition, positive, negative, and general symptoms were characterized in adolescents with EOS and healthy controls. A modified scale of negative, respectively, general symptoms was used. Bivariate analyses identified correlates of adaptive functioning to be included in multivariate analysis.

Results: Adolescents with EOS showed significant impairments of social- and neurocognitive functions ($-0.86 < \text{Cohen's } d < -0.58$) and adaptive functioning (Cohen's $d = -2.23$). Visual memory, verbal working memory, processing speed, reaction time, social cognition, and modified negative and general symptoms correlated significantly with adaptive functioning. The multiple regression analysis revealed only verbal working memory as uniquely associated with adaptive functioning (explaining 22.7 % of its variance). Verbal working memory also associated significantly with adaptive functioning in the context of the nonsignificant modified negative and the significant modified general symptoms dimension.

Conclusions: Adolescents with first-episode EOS had large impairments in adaptive functioning and moderate to large cognitive deficits. Verbal working memory was an important associate to concurrent adaptive functioning and may be a treatment target for trials to improve cognitive and adaptive functioning in adolescents with EOS.

Keywords: adaptive functioning; cognition; early-onset schizophrenia; first-episode

(Received 5 March 2022; revised 19 September 2022; accepted 20 September 2022; First Published online 9 December 2022)

Introduction

The onset of schizophrenia during childhood (before 13 years of age) is considered rare (Driver et al., 2020) whereas the prevalence increases during adolescence (prior to 18 years of age) (Pedersen et al., 2014; Dalsgaard et al., 2020). Recently the incidence rate of early-onset schizophrenia (EOS), defined as onset before 18 years of age, has increased (Okkels et al., 2012; Stenström et al., 2010), also among 15–19 years old adolescents (Amminger et al., 2006); however, this is not consistently observed (Hsu et al., 2019). The incidence of EOS has increased more in girls than in boys (Kühl et al., 2016) but this was not observed in the Hsu et al. (2019) study.

EOS is associated with greater premorbid language, social, and motor impairments than other early-onset psychoses (Hollis, 1995,

2003), and delayed speech milestones and premorbid impairments of reading, spelling, and adjustment have been observed in EOS (Vourdas et al., 2003). Worse illness severity later in the course of EOS is associated with worse premorbid adjustment and worse positive and negative symptoms at baseline (Stentebjerg-Olesen et al., 2016). Those with EOS show longer duration of untreated psychosis (DUP) (McGlashan, 1999) than patients with adult onset schizophrenia (AOS) (Coulon et al., 2020; Stentebjerg-Olesen et al., 2016). Shorter DUP is associated with greater improvement in schizophrenia symptoms during the first years of EOS (Stentebjerg-Olesen et al., 2016) but DUP seems both independent of symptom severity several years after the onset of EOS (Coulon et al., 2020) and of global cognition within the first two years of EOS (Teigset et al., 2018).

The functional prognosis of EOS is generally unfavorable (Lay et al., 2000) and heterogeneous, with 60.1 % of patients having poor, 24.5% having moderate, and 15.4% having good outcome (Clemmensen et al., 2012). Patients with EOS have more inpatient days than patients with AOS during the first two years but beyond they do not differ (Vernal et al., 2020). Earlier age of onset of EOS

Corresponding author: Jens Richardt Moellegaard Jepsen, email: jens.richardt.moellegaard.jepsen@regionh.dk

Cite this article: Jepsen, J. R. M., et al. (2024). Cross-sectional associations between adaptive functioning and social cognitive and neurocognitive functions in adolescents with first-episode, early-onset schizophrenia spectrum disorders. *Development and Psychopathology* 36: 208–218, <https://doi.org/10.1017/S0954579422001110>



associates with worse long-term outcome (Eggers and Bunk, 1997; Fleischhaker et al., 2005), although this is not consistently observed (Röpcke and Eggers, 2005; Xu et al., 2020). Similarly, an earlier age of onset of schizophrenia is associated with worse social/occupational functioning and global outcome (Immonen et al., 2017). Shorter DUP is associated with larger improvements in global functioning in EOS, and milder baseline negative symptoms is associated with better later social functioning (Stentebjerg-Olesen et al., 2016).

Subjects with EOS show large impairments of intelligence and neurocognitive functions across several cognitive domains with most profound impairments in processing speed and intelligence (Nieto & Castellanos, 2011). These cognitive impairments seem in line with those of youth-onset schizophrenia (<19 years of age) (Rajji et al., 2009). Recent studies of adolescents and adults with EOS confirm significant impairments of both executive functions (Han et al., 2019; Holmén et al., 2012) and intelligence (Han et al., 2019). Nearly 39 % of adolescents with EOS have an IQ <1 standard deviation below the normative mean (Hooper et al., 2010). Adolescents with first-episode EOS also show significant attention and non-planning impulsivity traits (Jepsen et al., 2018).

Verbal memory, executive functions, and real-life functioning improved in adolescents with EOS with cognitive remediation therapy (Puig et al., 2014). Mental flexibility can be improved with remediation despite a lack of effect on functioning in adolescents and young adults with EOS (onset <19 years of age); however cognitive improvement was associated with that of social functioning (Wykes et al., 2007). A relatively small trial observed no association between changes in cognitive functions and those of real-life functioning in adolescents with early-onset psychosis (Ueland & Rund, 2004).

Adolescents with EOS show impaired Theory of Mind (Bourgou et al., 2016; Pilowsky et al., 2000). Also, younger subjects with first-episode schizophrenia show impairments of emotional facial and prosodic communication recognition (Amminger et al., 2012a; 2012b). Further, adolescents with schizophrenia (<19 years of age) show lower specificity of facial emotion discrimination and faster identification of sadness (Seiferth et al., 2009).

The impairments of real-life functioning in adolescents with EOS include domains of social interaction / communication skills, personal living skills, and community living skills (Cervellione et al., 2007) and the overall level of real-world functioning (Cohen's $d = -1.8$) (Puig et al., 2012). Processing speed and executive functioning explained 25% of the variance of the concurrent overall real-life functioning in adolescents with EOS, whereas positive and negative symptoms were not significant associates (Puig et al., 2012). In adolescents with EOS, verbal fluency associated with concurrent psychosocial functioning (Landrø & Ueland, 2008). Further, overall adaptive functioning and its subdomains showed small to moderate, cross-sectional associations with intelligence, motor speed, working memory, attention, problem solving, inhibition, and social cognition in children and adolescents with EOS (Hooper et al., 2010). In line with this, attention / vigilance, working memory, and verbal memory, but not intelligence, were found to be associated with personal living skills and community living skills in adolescents with EOS both cross-sectionally and longitudinally (Cervellione et al., 2007). Additionally, the functional impairments, for example in social functioning (Cohen's $d = -1.9$), of adults earlier diagnosed with EOS were longitudinally associated with two or more neurocognitive functions, for example auditory working memory, verbal memory, and flexibility in their

adolescence (Øie et al., 2011). The observed cognitive associates to functioning in EOS seem in line with those in AOS where functional disability is associated with the severity of several neuro- and social cognitive deficits as well as negative symptoms (Fett et al., 2011; Mucci et al., 2021). Negative symptoms, at least partially, mediate the relationship between cognition and functioning (Lipkovich et al., 2009; Ventura et al., 2009).

Characterization of the associations between neuro- and social cognitive functions and adaptive functioning is relevant for identification of potential cognitive intervention targets (Gold, 2004). The purpose of the current study was to identify neuro- and social cognitive functions associated with concurrent adaptive functioning in adolescents with EOS, because relatively few studies have focused on cognitive associates to functional outcome in this young clinical group with an immature cognitive development. Based on the above-mentioned literature, working memory, verbal memory, processing speed, and social cognition were hypothesized to be uniquely associated with adaptive functioning, and over and above the potentially mediating role of negative symptoms.

Material and methods

The two studies included in the current work were approved by the Ethical Committee of the Capital Region of Denmark (H-C-2008-076; H-6-2014-068). Informed consent was obtained from the legal holders of custody, and both studies were carried out in accordance with the Helsinki declaration.

Participants

To increase the EOS sample size, two studies were combined: The first study took place 2011–14 and the second 2015–17. All patients were recruited from in- and outpatient clinics at the Child and Adolescent Mental Health Center, Copenhagen. Controls were recruited from the same catchment area through an internet advertisement or a letter of invitation by means of the Danish Civil Registration System. The inclusion criteria of the first study for patients with psychosis included schizophrenia, other non-affective psychosis, and affective psychosis according to DSM-IV-TR (APA, 2000). However, the study recruited only patients with non-affective psychotic disorders. Consequently, affective psychoses were excluded in the second study, thus we only included patients with DSM-IV-TR diagnoses of schizophrenia and other non-affective psychosis. The first study also included patients with attention-deficit/hyperactivity disorder (ADHD) (DSM-IV-TR) as a secondary clinical group but these patients were not included in the current study, and the second study excluded patients with a primary diagnosis of ADHD. All other inclusion criteria for patients with psychosis were identical for the two studies: age between 12 and 17 years (both included), a score >4 on minimum one (or >3 on minimum two) of the following items of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987): Delusions (P1), Conceptual disorganization (P2), Hallucinatory behavior (P3), Grandiosity (P5), Suspiciousness/persecution (P6), or Unusual thought content (G9), and maximum 12 months cumulative psychopharmacological treatment. The inclusion criteria for healthy controls in the two studies were identical: no psychiatric disorders according to DSM-IV-TR, no ongoing medical treatment (except contraceptives), and no history of a psychotic disorder or ADHD in first-degree relatives. The exclusion criteria for all participants in both studies were: a history of significant head injury or neurological illness, alcohol or substance use disorder according to DSM-IV-TR/ICD-10, and hearing

impairment (Jepsen *et al.*, 2018; Lemvigh *et al.*, 2020; Rydkjær *et al.*, 2017).

Psychopathology

The diagnostic classification was established according to the DSM-IV-TR and ICD-10 (WHO, 1992) and based on the semi-structured Kiddie-Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL) (Kaufman *et al.*, 1997) in the patient group. If needed, supplementary information was gathered from medical records. The K-SADS-PL was also used to screen control participants to secure they were mentally healthy. The severity of positive and negative schizophrenia symptoms and general symptoms was rated in patients and controls using the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.*, 1988). Two modified PANSS syndrome scales were established to avoid conceptual overlap (statistical redundancy) between some negative and general symptoms and real-life and cognitive functioning. Three negative syndrome scale items relating, at face value, to cognitive or real-life functioning were excluded from the negative syndrome scale: Emotional withdrawal (N2), Passive/Apathetic withdrawal (N4), and Abstraction (N5) (Mohamed *et al.*, 2008; Perlick *et al.*, 2008). The modified PANSS Negative Syndrome Scale and the full PANSS Negative Syndrome Scale correlated highly in the EOS group ($r = 0.924$, $p < 0.001$). Similarly, the modified PANSS General Syndrome Scale excluded Motor Retardation (G7), Poor Attention (G11), and Active Social Avoidance (G16) and correlated highly with the full PANSS General Syndrome scale in the EOS group ($r = 0.965$, $p < 0.001$).

The severity of depressive symptoms was assessed using Hamilton Rating Scale for Depression (Hamilton, 1960) to calculate HAM-D-6 (Bech *et al.*, 1975; Timmerby *et al.*, 2017). DUP was calculated as the time period from the estimated onset of psychosis to the first day of antipsychotic treatment or the first day of testing in the study. The clinical interviews and all psychopathological ratings were performed by a child and adolescent psychiatrist (JR) or a clinical child neuropsychologist (JRMJ); final diagnostic classifications and psychopathological ratings were based on consensus between them. All participants were medically examined to rule out somatic illnesses causing psychopathological symptoms.

Real-life adaptive functioning

Adaptive functioning was assessed using the Vineland Adaptive Behavior Scale, Second Edition (VABS-II) (Sparrow *et al.*, 2011) administered as a semi-structured parental interview with clinician rating. The VABS-II covers three domains: Communication, Daily Living Skills, and Socialization included in an overall adaptive behavior composite score with an age-corrected normative mean of 100 (SD = 15). The VABS-II domains overlap with the major functional domains proposed relevant in Western culture (Harvey & Bellack, 2009). The VABS has been widely used (Chatham *et al.*, 2018) and also in EOS (Hooper *et al.*, 2010). We found very few missing data and thus performed mean imputation (Hemager *et al.*, 2018). One subject with EOS missed one of the nine Vineland-II subscale scores and the rounded mean of the subject's two other standardized subscale scores in that domain was imputed. The VABS-II interview was missing for two participants with EOS and here the mean total score of the remaining EOS group was imputed (the VABS-II total score revealed no significant sex or age effects). The interrater agreement on the VABS-II total score between JR and JRMJ was assessed with interclass

correlation coefficient; $N = 6$ VABS-II interviews were administered by one of the two while the other was present and separately rated the parental responses. The average measures interclass correlation coefficient = 0.977, $p = .001$.

Cognitive functioning

Cognitive tests were selected from a comprehensive battery to assess the cognitive domains included in the Measurement and Treatment Research to Improve Cognition in Schizophrenia (Nuechterlein *et al.*, 2008) plus a motor domain. Verbal memory, verbal working memory, motor speed, planning, fluency, and processing speed were assessed with subtests of the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe *et al.*, 2004). Spatial working memory, reaction time, and sustained attention were assessed with the Spatial Working Memory (total errors), Reaction Time (RTI) (mean simple- and five-choice reaction times), and the Rapid Visual Information Processing (A') from the Cambridge Neuropsychological Test Automated Battery (Fray & Robbins, 1996; Sahakian & Owen, 1992). Visual memory was assessed with the Rey Complex Figure Test and Recognition Trial (RCFT) (Meyers & Meyers, 1995). Social cognition (social perception) was assessed with the Awareness of Social Inference Test – Part A2 Social Inference (minimal) (TASIT) (total correct) (McDonald *et al.*, 2003, 2006), Danish version (Bliksted *et al.*, 2014). Estimated intelligence was assessed using the Vocabulary, Similarities, Block Design, and Matrix Reasoning subtests from the age relevant Wechsler Intelligence Scale for Children, Fourth Edition (Wechsler, 2003) or the Wechsler Adult Intelligence Scale, Third Edition (Wechsler, 2002). One subject with EOS missed the RCFT and the means of the remaining EOS group were imputed. One HC subject missed the TASIT-2 test and the total mean of the remaining controls was imputed. The remaining participants had complete cognitive data sets. Composite scores were constructed (Frazier *et al.*, 2012), and for visual memory and reaction time the composite measures were created by averaging two highly correlated outcomes z-scores followed by restandardization (RCFT: Immediate and Delayed recall, $r = 0.926$, $p < 0.001$; RTI: mean Simple and mean Five-choice Reaction Time, $r = 0.869$, $p < 0.001$).

Statistical Analyses

Chi-square test, independent samples *t*-test, and Mann–Whitney test were used to compare the groups in terms of socio-demographic, educational, and clinical characteristics for Table 1. The distribution of all cognitive, psychopathological, and adaptive functioning data was evaluated and, when appropriate, logarithmic or square root transformed to approximate a normal distribution. All raw or transformed scores were converted to z-scores based on the mean and standard deviation of healthy controls. For all z-scores lower values designate worse function (for error scores and reaction time scores, z-scores equal the mean raw score of the healthy controls minus the observed raw score divided by the standard deviation of the healthy controls). Potential outliers were checked by visual inspection of histograms and box plots but for final identification an interquartile range outlier labeling rule using a k-value of 2.2 (Hoaglin & Iglewicz, 1987) was applied to the standardized data and identified the following outliers, all within the EOS group: the RTI z-scores of three subjects, BACS Verbal memory z-score for one subject, BACS Token Motor z-score for one subject, BACS Tower of London z-score for four subjects, and Spatial Working Memory total error z-score of

Table 1. Sociodemographic, educational, clinical, global functioning, and antipsychotic medication characteristics

	EOS (<i>N</i> = 59)	Healthy controls (<i>N</i> = 72)	<i>p</i> -value
Age, Mean Years (S.D.)	16.09 (1.29)	15.68 (1.41)	0.131
Female/male, No. (% Female)	46/13 (78.0%)	48/24 (66.7%)	0.176
School education, Mean Years (S.D.) ^a	9.26 (1.30)	9.13 (1.49)	0.582
Special education class, No. (%) ^b	12 (21.1%)	1 (1.4%)	<0.001
Final school test passed, Percentage ^c	77.8%	100%	0.007
Income, No. (high/moderate/low) ^d	26/24/9	57/12/3	<0.001
Current THC use, No. (%) ^e	3 (5.4%)	1 (1.4%)	0.320
Schizophrenia, No. (%)	42 (71.2%)		
Schizoaffective disorder, No. (%)	6 (10.2%)		
Psychotic disorder NOS, No. (%) ^f	11 (18.6%)		
Depressive Disorder NOS, No. (%) ^g	26 (44.1%)		
PANSS Total, Mean (S.D.)	81.49 (13.42)	33.40 (2.20)	<0.001
PANSS Positive, Mean (S.D.)	19.17 (3.21)	7.13 (0.33)	<0.001
PANSS Negative, Mean (S.D.)	23.12 (6.42)	8.76 (1.38)	<0.001
Modified PANSS Negative, Mean (S.D.) ^h	12.90 (4.08)	4.47 (0.99)	<0.001
PANSS General, Mean (S.D.)	39.20 (7.77)	17.51 (1.52)	<0.001
Modified PANSS General, Mean (S.D.) ⁱ	31.88 (6.09)	14.42 (1.41)	<0.001
Depressive symptoms, Mean (S.D.) ^j	7.73 (3.60)	0.44 (0.75)	<0.001
CGAS, Mean (S.D.) ^k	40.86 (6.57)	89.35 (3.16)	<0.001
Current antipsychotic medication No., (%) ^l	39 (66.1 %)		
Chlorpromazine equivalent, Mean (S.D.) ^m	313.03 (175.50)		
DUP, Mean days (S.D.) ⁿ	619 (72)		
Comorbidity No., (%) ^o	40 (67.8 %)		

^aNumber of years in school excluding preschool year; EOS: *N* = 57.

^bPlacement in special education class ever; EOS: *N* = 57.

^c*N* = 27 participants with EOS and *N* = 31 healthy control participants were old enough to have taken the final school graduation examination. EOS: 21 of *N* = 27 passed; HC: 31 of *N* = 31 passed.

^dParental household income (if parents lived separately, the primary home for the participants was selected): high income > 500.000 DKK; 500.000 DKK < moderate income < 300.000 DKK; low income < 300.000 DKK.

^eTetrahydrocannabinol (THC) urine testing (Rapid response, Jepsen HealthCare); EOS: *N* = 56; HC: *N* = 71.

^fPsychotic disorder Not Otherwise Specified.

^gComorbid Depressive Disorder Not Otherwise Specified.

^hThe modified PANSS negative syndrome scale excludes N2: Emotional withdrawal, N4: Passive/Apathetic withdrawal, and N5: Abstraction.

ⁱThe modified PANSS general syndrome scale excludes G7: Motor retardation, G11: Poor attention, and G16: Active social avoidance.

^jThe 6-item Hamilton Depression Rating Scale (HAM-D₆) includes item 1 (depressed mood), item 2 (guilt feelings), item 7 (work and interests), item 8 (psychomotor retardation), item 10 (psychic anxiety), and item 13 (somatic symptoms, general) from the HAM-D₁₇.

^kThe Children's Global Assessment Scale (CGAS).

^lNumber of subjects in current treatment with antipsychotic medications at the time of the cognitive assessment. *N* = 1 patient with EOS began treatment after the psychophysiological assessment and before the cognitive assessments: *N* = 18: Aripiprazole + Olanzapine; *N* = 1: Aripiprazole + Paliperidone; *N* = 1: Aripiprazole + Chlorprothixene; *N* = 1: Risperidone; *N* = 9: Quetiapine; *N* = 4: Quetiapine Prolong; *N* = 1: Aripiprazole + Quetiapine Prolong; *N* = 1: Olanzapine; *N* = 1: Ziprasidone; *N* = 1: Clozapine + Ziprasidone.

^mChlorpromazine equivalents (mg. per day) according to Gardner et al., (2010) Am. J. Psychiatry. Median: 300,00 and range: 40,00-700,00.

ⁿDuration of untreated psychosis (DUP): median = 428 days; range: 17 – 1883 days.

^oComorbid disorders included: Depressive Disorder Not Otherwise Specified (*N* = 16), Attention-Deficit / Hyperactive Disorder, Combined Type or Predominantly Inattentive Type (*N* = 8), Obsessive-Compulsive Disorder (*N* = 6), Specific Phobia (*N* = 5), Eating Disorder Not Otherwise Specified (*N* = 4), Asperger's Disorder (*N* = 3), Posttraumatic Stress Disorder (*N* = 2), Panic Disorder with Agoraphobia (*N* = 2), Panic Disorder without Agoraphobia (*N* = 2), Autistic Disorder (*N* = 1), Mild Mental Retardation (*N* = 1), Generalized Anxiety Disorder (*N* = 1), Oppositional Defiant Disorder (*N* = 1), Tourette's Disorder (*N* = 1), Tic Disorder Not Otherwise Specified (*N* = 1), Chronic Motor or Vocal Tic Disorder (*N* = 1), Anorexia Nervosa (*N* = 1), Adjustment Disorder with Mixed Anxiety and Depressed Mood (*N* = 1), Agoraphobia Without History of Panic Disorder (*N* = 1), Adjustment Disorder Unspecified (*N* = 1).

one subject which were truncated at each lower interquartile range cutoff. The between-group differences in adaptive and cognitive functioning scores were assessed using multivariate analyses of variance (MANOVA); if significant, this was followed by univariate analyses of variance (ANOVA). Effect size estimates were represented using Cohen's *d*.

The selection of demographic variables, cognitive functions, and illness characteristics to be included in the multiple regression models was based on the significance of their bivariate associations

with the VABS-II total z-score (Puig et al., 2012). We used Pearson's product-moment correlations (illness characteristics and cognitive functions z-scores), independent samples *t*-test (gender), and ANOVA (household income). The primary analysis was a multiple regression analysis (Enter method) including significant demographic variables and neuro- and social cognitive functions z-scores as independent variables and VABS-II total z-score as the dependent variable. Because of the mediating role of negative symptoms between cognition and functioning, a second multiple

regression analysis (Enter method) included the significant cognitive associates observed in the primary analysis plus the illness characteristics that were significantly associated to the VABS-II total z-score. The terms "predictor variable" and "explained variance" are used in a strictly statistical sense and do not imply causality. For the explorative comparisons of adaptive functioning z-scores between the EOS subgroup with comorbidity versus that without and between the EOS subgroup treated with antipsychotic medication versus the antipsychotic unmedicated subgroup, ANCOVA with age and gender as the covariates were performed; in the case that covariates were nonsignificant, ANOVA was then performed. Alpha level was set at 0.05 due to the specific hypothesis (Parellada et al., 2009; Perneger, 1998). All analyses were performed in SPSS, version 25.

Results

The demographic, educational, and psychopathological characteristics of the EOS and healthy control group are presented (Table 1). A relatively high percentage of the EOS group were females. Significantly fewer participants with EOS than healthy controls had been in regular education classes throughout their school years.

The mean VABS-II total scale score, estimated FSIQ, and neuro- and social cognitive functions raw scores in the groups are presented (Table 2). The MANOVA indicated an overall significant effect of group ($F_{(15,115)} = 13.55$, $p < 0.001$; Wilks' Lambda = 0.361). The following ANOVAs revealed significantly lower VABS-II total and all cognitive functions scores in the EOS than HC group; effect sizes ranged: -2.23 to -0.58 .

In terms of bivariate associations within the EOS group, the parental household income, age, and gender were not associated with the VABS-II total z-score (Table 3). The social cognitive and four neurocognitive functions z-scores (visual memory, verbal working memory, reaction time, and processing speed), the modified PANSS Negative, and modified PANSS General z-score were significantly associated with the VABS-II total z-score.

The primary multivariate regression analysis revealed verbal working memory z-score as the single unique associate of concurrent VABS-II total z-score in a model that included five cognitive functions, and this model explained 22.7 % of the variance of the VABS-II total z-score (Table 4). The second multiple regression analysis included the verbal working memory, modified PANSS Negative, and PANSS General z-scores as independent variables, and this model revealed only verbal working memory z-score and the modified PANSS General z-score as significant associates of the VABS-II total z-score; this model explained 34.3 % of its variance (Table 4). The bivariate correlations between cognitive functions, DUP, and psychopathological dimensions are shown in Table 5.

The following analyses are explorative. Reanalyzing the data including $N = 57$ subjects without imputation of the VABS-II total z-score did not change the results substantially (data not shown). An ANOVA revealed no significantly lower VABS-II total z-score in the EOS subsample currently treated with antipsychotic medications than the antipsychotic unmedicated subgroup ($F_{(1,57)} = 2.529$, $p = 0.117$) (Cohen's $d = 0.43$). An ANOVA comparing the EOS subgroup with any comorbidity versus the EOS subgroup without showed comorbidity to be associated with a significantly lower mean VABS-II total z-score ($F_{(1,57)} = 4.525$, $p = 0.038$) (Cohen's $d = 0.61$). Any comorbidity versus no comorbidity was thus exploratively added as a predictor variable in addition to verbal working memory, modified PANSS Negative, and modified PANSS General z-scores in a multiple regression analysis with the VABS-II total z-score as the dependent variable.

Table 2. Mean real-life, adaptive functioning VABS-II total score, estimated FSIQ, neurocognitive, and social cognitive raw scores between the EOS and the healthy control group

	EOS	HC	p-value	Cohen's d
Vineland-II total, Mean (S.D.)	85.70 (13.55)	108.11 (4.39)	<0.001	-2.23
Intelligence, Mean estimated FSIQ (S.D.)	96.46 (19.20)	108.93 (13.06)	<0.001	-0.76
Verbal memory, Mean (S.D.)	47.31 (9.84)	52.58 (7.18)	0.001	-0.61
Visual Memory, Immediate, Mean (S.D.)	17.61 (7.21)	22.31 (5.09)	<0.001	-0.75
Visual memory, Delayed, Mean (S.D.)	17.83 (6.79)	21.99 (5.01)	<0.001	-0.70
Verbal working memory, Mean (S.D.)	16.64 (3.92)	19.94 (3.79)	<0.001	-0.86
Spatial working memory, Mean (S.D.)	20.39 (17.68)	11.88 (10.06)	0.001	-0.59
Motor speed, Mean (S.D.)	60.17 (12.82)	69.94 (9.94)	<0.001	-0.85
Processing speed, Mean (S.D.)	53.10 (11.69)	60.10 (9.95)	<0.001	-0.64
Fluency total, Mean (S.D.)	45.54 (11.97)	55.36 (11.07)	<0.001	-0.85
Planning, Mean (S.D.)	17.58 (2.81)	19.03 (2.10)	0.001	-0.58
Reaction time simple, Mean (S.D.)	325.62 (79.73)	283.61 (35.68)	<0.001	-0.68
Reaction time five-choice, Mean (S.D.)	371.98 (107.72)	318.46 (43.84)	<0.001	-0.65
Sustained attention, Mean (S.D.)	0.846 (0.059)	0.887 (0.045)	<0.001	-0.78
Social cognition, Mean (S.D.)	51.27 (4.47)	53.79 (3.39)	<0.001	-0.64

Comorbidity was not a significant predictor ($p = 0.426$) in this model, and the results did not change substantially (data not shown). For information, age did not correlate significantly with any cognitive function ($0.178 < r < 0.875$) except spatial working memory ($r = 0.339$, $p = .009$) or with any PANSS dimension ($0.310 < r < 0.773$). The chlorpromazine equivalent was not significantly associated with adaptive functioning, and with regard to cognitive functions it was only significantly associated with reaction time and planning. The chlorpromazine equivalent was included as an additional predictor in the primary and second multiple regression analysis with the VABS-II total z-score as the dependent variable. The chlorpromazine equivalent was a nonsignificant predictor in both models and the reported results did not change substantially (data not shown).

Discussion

This cross-sectional study aimed to identify cognitive functions associated with adaptive functioning in adolescents with EOS. Adolescents with EOS showed a large adaptive functioning deficit

Table 3. Associations between the real-life, adaptive functioning VABS-II total z-score and the psychopathological dimensions z-scores, cognitive functions z-scores, DUP, and demographic variables in the EOS group

	VABS-II total z-score
Gender ^a	n.s.
Age	n.s.
Household income	n.s.
DUP	n.s.
PANSS Positive z-score	n.s.
Modified PANSS Negative z-score	$r = 0.260, p = 0.046$
Modified PANSS General z-score	$r = 0.437, p = 0.001$
HAM-D ₆ Depressive symptoms z-score	n.s.
Verbal Memory z-score	n.s.
Visual Memory z-score	$r = 0.257, p = 0.049$
Verbal Working Memory z-score	$r = 0.485, p < 0.001$
Spatial Working Memory z-score	n.s.
Planning z-score	n.s.
Verbal fluency z-score	n.s.
Motor Speed z-score	n.s.
Processing Speed z-score	$r = 0.259, p = 0.048$
Reaction Time z-score	$r = 0.278, p = 0.033$
Sustained attention z-score	n.s.
Social Cognition z-score	$r = 0.328, p = 0.011$
Estimated FSIQ z-score	n.s.

^aVery small VABS-II total z-score effect size between males ($N = 13$) and females ($N = 46$) (Cohen's $d = 0.08$).

Table 4. Multiple regression analysis of associations between the selected cognitive functions z-scores and the real-life, adaptive functioning VABS-II total z-score as the dependent variable and a second multiple regression analysis including the observed significant cognitive associate and two psychopathological z-scores

	B	SE	Beta	t-value	p-value
Visual Memory	0.107	0.291	0.049	0.367	0.715
Verbal Working Memory	0.979	0.384	0.356	2.550	0.014
Processing Speed	0.111	0.345	0.043	0.323	0.748
Reaction Time	0.246	0.268	0.115	0.916	0.364
Social Cognition	0.456	0.282	0.198	.1614	0.112
Adjusted R Square = 0.227, $F = 4.40$, $df = 5$, $p = 0.002$					
Verbal Working Memory	1.138	0.303	0.414	3.755	<0.001
Modified PANSS Negative	0.110	0.059	0.204	1.878	0.066
Modified PANSS General	0.164	0.064	0.288	2.556	0.013
Adjusted R Square = 0.346, $F = 11.23$, $df = 3$, $p < 0.001$					

and a generalized profile of moderate to large neuro- and social cognitive deficits. Visual memory, verbal working memory, processing speed, reaction time, and social cognition were associated with their concurrent adaptive functioning, when assessed in a bivariate perspective. Contrary to our hypothesis, only verbal working memory emerged as being uniquely associated with adaptive functioning in the multivariate analysis and explained 22.7 %

of the variance of adaptive functioning. Secondly, verbal working memory remained uniquely associated with adaptive functioning in the context of modified negative and general symptoms dimensions and only the general symptoms dimension associated with adaptive functioning, and this model explained 34.6 % of its variance.

The generalized impairments of neurocognition in our EOS group is generally consistent with earlier meta-analytic findings (Nieto & Castellanos, 2011) and a recent report (Smelror et al., 2021). The observed social cognitive impairment is in line with earlier findings in EOS (Bourgou et al., 2016; Pilowsky et al., 2000).

The level of adaptive functioning observed in our EOS group is relatively similar to earlier findings in EOS (Cervellione et al., 2007) and its large effect size is in line with an earlier result in EOS (Cohen's $d = 1.80$) (Puig et al., 2012).

In a bivariate perspective relatively few cognitive functions were associated with the adaptive functioning of the current EOS group compared to previous results in EOS where the majority of cognitive functions were cross-sectionally associated with real-world living skills (Hooper et al., 2010; Puig et al., 2012). One possible explanation may be the larger sample size in the Hooper et al. (2010) study. Another may be the aggregation of scores from different tests in creation of predictors in that study which was also the case for two cognitive variables in the Puig et al. (2012) study. Further, our early recruitment strategy may have led to more instability in both adaptive functioning, psychotic symptoms, and psychopharmacological treatment than in the stabilized patients with EOS in the Puig et al. (2012) study.

Neither in the current nor in the Puig et al. (2012) study were attention and intelligence associated with adaptive functioning; however, processing speed, verbal working memory, and visual memory were associates in both studies. In the Hooper et al. (2010) study, working memory was also associated with adaptive functioning in children and adolescents with EOS, as were attention and intelligence. In the Cervellione et al. (2007) study, working memory as well as verbal memory and attention were also cross-sectionally associated with adaptive functioning in adolescents with EOS. The currently observed pattern of weak to moderate bivariate associations between cognitive and adaptive functioning seems in line with earlier findings in EOS (Cervellione et al., 2007; Hooper et al., 2010; Puig et al., 2012).

Our finding of verbal working memory as a unique associate of adaptive functioning of adolescents with EOS seems in line with meta-analytic findings in AOS where immediate verbal memory shows a pooled estimated r of 0.40 to functional outcome (Green et al., 2000). Verbal working memory correlates with community functioning ($r = 0.22$) and with social problem solving ($r = 0.25$) (Fett et al., 2011). Additionally, only working memory differed between high- and low-functioning adults with AOS (Alden et al., 2015). Finally, working memory improvements were found to be associated with functional improvements in a cognitive treatment trial (Rispaud et al., 2016). Working memory allows for storage and manipulation of the information that is necessary for complex cognitive tasks such as comprehension and reasoning. This may explain why better verbal working memory associates with better adaptive functioning and why the other cognitive functions included in this study were significantly and positively associated with verbal working memory.

Contrary to our significant bivariate association between social cognition and adaptive functioning, the multivariate analysis did not confirm social cognition as a unique associate. This contrasts with results in adults with AOS, where aspects of social cognition

Table 5. Pearson's product-moment correlation estimates between cognitive functions z-scores, duration of untreated psychosis, and psychopathological dimensions z-scores within the EOS group

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1 Verbal memory	1	0.453***	0.539***	0.198	0.439**	0.561**	0.207	0.463***	0.088	0.488***	0.355**	0.388**	0.245	0.136	0.074	0.110	0.030
2 Visual memory		1	0.346**	0.380**	0.377**	0.496***	0.203	0.429**	0.074	0.427**	0.292*	0.413**	0.184	0.079	0.203	0.034	0.043
3 Verbal working memory			1	0.375**	0.428**	0.511***	0.110	0.391**	0.379**	0.431**	0.264*	0.538***	0.174	0.114	-0.010	0.257*	0.040
4 Spatial working memory				1	0.476***	0.493***	0.290*	0.311*	0.218	0.352**	0.110	0.452***	0.217	0.077	-0.005	0.007	-0.067
5 Planning					1	0.398**	0.327*	0.462***	0.221	0.358**	0.199	0.459***	0.237	0.035	0.068	0.162	-0.050
6 Verbal fluency						1	0.222	0.386**	-0.049	0.420**	0.301*	0.558***	0.161	-0.135	0.225	0.034	0.146
7 Motor speed							1	0.315*	0.058	0.207	0.293*	0.140	0.014	-0.109	0.233	0.221	-0.059
8 Processing speed								1	0.116	0.393**	0.213	.0309*	0.040	-0.068	-0.034	0.076	-0.120
9 Reaction time									1	0.150	0.100	0.155	0.114	0.202	-0.065	0.364**	0.134
10 Sustained attention										1	0.288*	0.460***	0.299*	0.042	0.026	0.013	0.088
11 Social cognition											1	0.366**	0.075	0.007	0.243	0.226	0.233
12 Intelligence												1	0.203	-0.234	-0.093	-0.191	-0.078
13 DUP													1	-0.089	0.230	-0.047	0.084
14 PANSS Positive														1	-0.122	0.407**	0.123
15 PANNS Negative Modified															1	0.209	0.376**
16 PANNS General Modified																1	0.417**
17 Depressive symptoms																	1

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$.

are more strongly associated with community function than neurocognition (Fett et al., 2011). In our sample, verbal working memory shared variance with social cognition which may have caused it not to reach statistical significance. This may suggest our measure of social cognition acts as a mediator between neurocognitive functioning and adaptive functioning (Schmidt et al., 2011). Similarly, the shared variance between verbal working memory and processing speed, reaction time, and visual memory may have led them not to reach statistical significance in the multivariate perspective. This pattern of findings questions an unequivocal interpretation of the significant bivariate correlations between these neuro- and social cognitive functions and adaptive functioning because their correlations with verbal working memory suggest that executive functioning was involved in the performance on these tests. Our results suggest verbal working memory as the primary cognitive function to be targeted in future cognitive remediation trials to improve cognitive and adaptive functioning in adolescents with EOS.

In the current study, the modified negative symptoms dimension associated with adaptive functioning in the bivariate but not the multivariate perspective. This may reflect a Type II error, however, negative symptoms were also not significantly associated to functioning in the multivariate perspective in another study of adolescents with EOS (Puig et al., 2012), but were associated to functioning in adults earlier diagnosed with EOS (Röpcke & Eggers, 2005). Also longitudinally, negative symptoms relate inversely to later functioning in EOS (Maziade et al., 1996; Vyas et al., 2007). Additionally, Digit Span performance, an often-used verbal working memory measure, explained 41% of the predicted variance of negative symptoms in the acute phase of AOS (Goldman et al., 1993). The currently observed association between the modified general symptom dimension and adaptive functioning is in line with a similar finding in adults with EOS (Röpcke & Eggers, 2005).

Comorbidity was found to be associated with lower adaptive functioning in our adolescents with EOS but this effect did not survive in our multivariate model. In line with this, psychiatric comorbidity was found not to predict future functioning in AOS (Mucci et al., 2021).

In terms of limitations, the cross-sectional nature of the current study does not allow for causal inferences nor prediction of functional prognosis. The uneven gender distribution of the EOS sample did not allow for assessments of potential gender differences; the results may have less applicability to males. We included the total adaptive functioning score and the functional subdomains may have differential associations to the cognitive functions. The testers (JRMJ; CKL) were not blinded to the clinical and adaptive functioning data. Finally, the level of adaptive functioning may vary with differential parental support (Couture et al., 2006) which was not assessed in the current study.

We observed no significant difference in adaptive functioning in the antipsychotic medicated versus non-medicated participants. The medication dose associated with few cognitive functions but not with adaptive functioning; taking medication dose into account did not change the results. Only a modest improvement in community functioning with antipsychotic medication has been reported in AOS (Swartz et al., 2007). Females with EOS were highly prevalent in our sample, which is inconsistent to the male predominance in earlier studies of youths with EOS, for example (Frazier et al., 2007). There are indications that the EOS incidence rate for females has become higher than for males (Dalsgaard et al.,

2020; Köhl et al., 2016; Okkels et al., 2012); however, there is inconsistency in this finding (Hsu et al., 2019; Stenström et al., 2010).

Conclusions

Visual memory, verbal working memory, processing speed, reaction time, and social cognition are in the current study cross-sectionally associated with adaptive functioning in adolescents in the early illness phase of EOS. Of these cognitive functions, only verbal working memory was uniquely associated to adaptive functioning in a multivariate perspective. In contrast to general symptoms, neither the severity of modified negative nor of positive symptoms dimensions was associated with that of adaptive functioning. We suggest verbal working memory as the primary target in future cognitive remediation therapy trials to improve cognitive and adaptive functioning in adolescents with EOS.

Acknowledgements. The authors would like to thank the participants and their parents in addition to the students Rókur av Flötum Jespersen, Nanna Pagsberg and Andreas Elleby from the Center for Neuropsychiatric Schizophrenia Research for assistance.

Funding statement. This work was supported by a Post. Doc. scholarship from the Research Foundation of Mental Health Services in the Capital Region of Denmark (JRMJ); a Ph.D. scholarship from the Research Foundation of Mental Health Services in the Capital Region of Denmark (JR); Lundbeck Foundation Center for Clinical Intervention and Neuropsychiatric Research (JR, R25-A2701); Læge Gerhard Linds Legat (JR); Fru C. Hermansens Legat (JR; JRMJ); Slagtermester Wörzners og Hustru Inger Wörzners Mindelegat (JR); and Psykiatrisk Forskningsfond af 1967 (JR); Tømrermester Jørgen Holm og Hustru Elisa F. Hansens Mindelegat (JRMJ); Jascha Fonden (JRMJ). No funding source was involved in the study.

Conflicts of interest. None.

References

- Alden, E. C., Cobia, D. J., Reilly, J. L., & Smith, M. J. (2015). Cluster analysis differentiates high and low community functioning in schizophrenia: Subgroups differ on working memory but not other neurocognitive domains. *Schizophrenia Research*, 168(1-2), 273–278. <https://doi.org/10.1016/j.schres.2015.07.011>
- Amminger, G. P., Harris, M. G., Conus, P., Lambert, M., Elkins, K. S., Yuen, H. P., & McGorry, P. D. (2006). Treated incidence of first-episode psychosis in the catchment area of EPPIC between 1997 and 2000. *Acta Psychiatrica Scandinavica*, 114(5), 337–345. <https://doi.org/10.1111/j.1600-0447.2006.00790.x>
- Amminger, G. P., Paul, Schäfer, M. R., Klier, C. M., Schölgehofer, M., Mossaheb, N., Thompson, A., Bechdorf, A., Allott, K., McGorry, P. D., & Nelson, B. (2012a). Facial and vocal affect perception in people at ultra-high risk of psychosis, first-episode schizophrenia and healthy controls. *Early Intervention in Psychiatry*, 6(4), 450–454. <https://doi.org/10.1111/j.1751-7893.2012.00362.x>
- Amminger G. P., Schafer M. R., Papageorgiou K., Klier C. M., Schlogelhofer M., Mossaheb N., Werneck-Rohrer S., Nelson B., & McGorry P. D. (2012b). Emotion recognition in individuals at clinical high-risk for schizophrenia. *Schizophrenia Bulletin*, 38(5), 1030–1039. <https://doi.org/10.1093/schbul/sbr015>
- APA (2000). *Diagnostic and statistical manual of mental disorders* (4th edn). Washington: American Psychiatric Association, Text Revision,
- Bech, P., Gram, L. F., Dein, E., Jacobsen, O., Vitger, J., & Bolwig, T. G. (1975). Quantitative rating of depressive states. *Acta Psychiatrica Scandinavica*, 51(0001-690X (Print)), 161–170.
- Bliksted, V., Fagerlund, B., Weed, E., Frith, C., & Videbeck, P. (2014). Social cognition and neurocognitive deficits in first-episode schizophrenia. *Schizophrenia Research*, 153(1-3), 9–17. <https://doi.org/10.1016/j.schres.2014.01.010>

- Bourgou S., Halayem S., Amado I., Triki R., Bourdel M. C., Franck N., Krebs M. O., Tabbane K., & Bouden A. (2016). Theory of mind in adolescents with early-onset schizophrenia: Correlations with clinical assessment and executive functions. *Acta Neuropsychiatrica*, 28(4), 232–238. <https://doi.org/10.1017/neu.2016.3>
- Cervellione, K. L., Burdick, K. E., Cottone, J. G., Rhinewine, J. P., & Kumra, S. (2007). Neurocognitive deficits in adolescents with schizophrenia: Longitudinal stability and predictive utility for short-term functional outcome. *Journal of the American Academy of Child and Adolescent Psychiatry*, 46(0890-8567 (Print)), 867–878.
- Chatham, C. H., Taylor, K. I., Charman, T., Liogier D'ardhuy, X., Eule, X., Fedele, E., Hardan, A.Y., Loth, E., Murtagh, L., del Valle Rubido, M., San Jose Caceres, A., Sevigny, J., Sikich, L., Snyder, L., Tillmann, J.E., Ventola, P.E., Walton-Bowen, K.L., Wang, P.P., Willgoss, T., & Bolognani, A. (2018). Adaptive behavior in autism: Minimal clinically important differences on the Vineland-II. *Autism Research*, 11(2), 270–283. <https://doi.org/10.1002/aur.1874>
- Clemmensen, L., Vernal, D. L., & Steinhausen, H. C. (2012). A systematic review of the long-term outcome of early onset schizophrenia. *BMC Psychiatry*, 12(1), 1. <https://doi.org/10.1186/1471-244X-12-150>
- Coulon, N., Godin, O., Bulzacka, E., Dubertret, C., Mallet, J., Fond, G., Brunel, L., Andrianarisoa, M., Anderson, G., Chereau, I., Denizot, H., Rey, R., Dorey, J.-M., Lançon, C., Faget, C., Roux, P., Passerieux, C., Dubreucq, J., Leignier, S., . . . & Schürhoff, F. (2020). Early and very early-onset schizophrenia compared with adult-onset schizophrenia: French FACE-SZ database. *Brain and Behavior*, 10(2), 1–13. <https://doi.org/10.1002/brb3.1495>
- Couture, S. M., Penn, D. L., & Roberts, D. L. (2006). The functional significance of social cognition in schizophrenia: A review. *Schizophrenia Bulletin* 32, 32(Suppl 1 (0586-7614 (Print))), S44–S63.
- Dalsgaard, S., Thorsteinsson, E., Trabjerg, B., Schullehner, B., Plana-ripoll, J., Brikell, O., Wimberley, T., Thygesen, M., Madsen, K.B., Timmerman, A., Schendel, D., McGrath, J.J., Mortensen, P.B., & Pedersen, I. (2020). Incidence rates and cumulative incidences of the full spectrum of diagnosed mental disorders in childhood and adolescence. *JAMA Psychiatry*, 77(2), 155–164. <https://doi.org/10.1001/jamapsychiatry.2019.3523>
- Driver, D. I., Thomas, S., Gogtay, N., & Rapoport, J. L. (2020). Childhood-onset schizophrenia and early-onset schizophrenia spectrum disorders: An update. *Child and Adolescent Psychiatric Clinics of North America*, 29(1), 71–90. <https://doi.org/10.1016/j.chc.2019.08.017>
- Eggers, C., & Bunk, D. (1997). The long-term course of childhood-onset schizophrenia: A 42-year followup. *Schizophrenia Bulletin*, 23(1), 105–117.
- Fett, A. K. J., Viechtbauer, W., Dominguez, M.de G., Penn, D. L., van Os, J., & Krabbendam, L. (2011). The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. *Neuroscience and Biobehavioral Reviews*, 35(3), 573–588. <https://doi.org/10.1016/j.neubiorev.2010.07.001>
- Fleischhaker, C., Schulz, E., Tepper, K., Martin, M., Hennighausen, K., & Remschmidt, H. (2005). Long-term course of adolescent schizophrenia. *Schizophrenia Bulletin*, 31(0586-7614 (Print)), 769–780.
- Fray, P. J., & Robbins, T. W. (1996). CANTAB battery: Proposed utility in neurotoxicology. *Neurotoxicology and Teratology*, 18(0892-0362), 499–504.
- Frazier, J. A., Giuliano, A. J., Johnson, J. L., Yakutis, L., Youngstrom, E. A., Breiger, D., Sikich, L., Findling, R.L., McClellan, J., Hamer, R.M., Vitiello, B., Lieberman, J.A., & Hooper, S. R. (2012). Neurocognitive outcomes in the treatment of early-onset Schizophrenia Spectrum Disorders study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 51(5), 496–505. <https://doi.org/10.1016/j.jaac.2012.02.001>
- Frazier, J. A., McClellan, J., Findling, R. L., Vitiello, B., Anderson, R., Zablotzky, B., Williams, E., Mcnamara, N., Jackson, J., Ritz, L., Hlatala, S., Pierson, L., Varley, J., Puglia, M., Maloney, A., Ambler, D., Hunt-Harrison, T., Hamer, R., Noyes, N., . . . & Sikich, L. (2007). Treatment of Early-onset Schizophrenia Spectrum Disorders (TEOSS): Demographic and clinical characteristics. *Journal of the American Academy of Child & Adolescent Psychiatry*, 46(8), 979–988. <https://doi.org/10.1097/chi.0b013e31807083fd>
- Glenne Øie, M., Ueland, T., & Sundet, K. (2011). Neurocognition and functional outcome in early-onset schizophrenia and attention-deficit / hyperactivity disorder: A 13-year follow-up. *Neuropsychology*, 25(1), 25–35. <https://doi.org/10.1037/a0020855>
- Gold, J. M. (2004). Cognitive deficits as treatment targets in schizophrenia. *Schizophrenia Research*, 72(0920-9964), 21–28.
- Goldman, R. S., Axelrod, B., Tandon, R., Ribeiro, S. C. M., Craig, K., & Berent, S. (1993). Neuropsychological prediction of treatment efficacy and one-year outcome in schizophrenia. *Psychopathology*, 26(3-4), 122–126. <https://doi.org/10.1159/000284811>
- Green, M. F., Kern, R. S., Braff, D. L., & Mintz, J. (2000). Neurocognitive deficits and functional outcome in schizophrenia: Are we measuring the “right stuff. *Schizophrenia Bulletin*, 26(1), 119–136. <https://doi.org/10.1093/oxfordjournals.schbul.a033430>
- Hamilton, M. (1960). Scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, 23(1), 56–63.
- Han W., Zhang T., Ni T., Zhu L., Liu D., Chen G., Lin H., Chen T., & Guan F. (2019). Relationship of common variants in CHRNA5 with early-onset schizophrenia and executive function. *Schizophrenia Research*, 206(2019), 407–412. <https://doi.org/10.1016/j.schres.2018.10.011>
- Harvey, P. D., & Bellack, A. S. (2009). Toward a terminology for functional recovery in schizophrenia: Is functional remission a viable concept? *Schizophrenia Bulletin*, 35(2), 300–306. <https://doi.org/10.1093/schbul/sbn171>
- Hemager, N., Plessen, K. J., Thorup, A., Christiani, C., Ellersgaard, D., Spang, K.S., Burton, B.K., Gregersen, M., Søndergaard, A., Greve, A.N., Gantriis, D.L., Poulsen, G., Seidman, L.J., Mors, O., Nordentoft, M., & Jepsen, J.R.M. (2018). Assessment of Neurocognitive Functions in 7-Year-Old Children at Familial High Risk for Schizophrenia or Bipolar Disorder The Danish High Risk and Resilience Study VIA 7. *JAMA Psychiatry*, 1–9. <https://doi.org/10.1001/jamapsychiatry.2018.1415>
- Hoaglin, D. C., & Iglewicz, B. (1987). Fine-tuning some resistant rules for outlier labeling. *Journal of the American Statistical Association*, 82(400), 1147–1149. <https://doi.org/10.1080/01621459.1987.10478551>
- Hollis, C. (1995). Child and adolescent (juvenile onset) schizophrenia. A case control study of premorbid developmental impairments. *British Journal of Psychiatry*, 166(0007-1250 (Print)), 489–495.
- Hollis, C. (2003). Developmental precursors of child- and adolescent-onset schizophrenia and affective psychoses: Diagnostic specificity and continuity with symptom dimensions. *British Journal of Psychiatry*, 182(JAN.), 37–44. <https://doi.org/10.1192/bjp.182.1.37>
- Holmén A., Juuhl-Langseth M., Thormodsen R., Ueland T., Agartz I., Sundet K., Andreassen O. A., Rund Born R., & Melle I. (2012). Executive function in early- and adult onset schizophrenia. *Schizophrenia Research*, 142(1-3), 177–182. <https://doi.org/10.1016/j.schres.2012.10.006>
- Hooper, S. R., Giuliano, A. J., Youngstrom, E.A., Breiger, D., Sikich, L., Frazier, J.A., Findling, R.L., McClellan, J., Hamer, R.M., Vitiello, B., & Lieberman, J.A. (2010). Neurocognition in early-onset schizophrenia and schizoaffective disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, 49(1), 52–60. <https://doi.org/10.1016/j.jaac.2009.11.001>
- Hsu, C. W., Lee, S. Y., & Wang, L. J. (2019). Gender differences in the prevalence, comorbidities and antipsychotic prescription of early-onset schizophrenia: A nationwide population-based study in Taiwan. *European Child and Adolescent Psychiatry*, 28(6), 759–767. <https://doi.org/10.1007/s00787-018-1242-9>
- Immonen, J., Jääskeläinen, E., Korpela, H., & Miettunen, J. (2017). Age at onset and the outcomes of schizophrenia: A systematic review and meta-analysis. *Early Intervention in Psychiatry*, 11(6), 453–460. <https://doi.org/10.1111/eip.12412>
- Jepsen, J. R. M., Rydkjaer, J., Fagerlund, B., Pagsberg, A. K., Jespersen, R. A. F., Glenthoj, B. Y., & Oranje, B. (2018). Overlapping and disease specific trait, response, and reflection impulsivity in adolescents with first-episode schizophrenia spectrum disorders or attention-deficit/hyperactivity disorder. *Psychological Medicine*, 48(4), 604–616. <https://doi.org/10.1017/S0033291717001921>
- Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., & Ryan, N. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American*

- Academy of Child and Adolescent Psychiatry*, 36(0890-8567 (Print)), 980–988.
- Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, 13(0586-7614 (Print)), 261–276.
- Kay, S. R., Opler, L. A., & Lindenmayer, J. P. (1988). Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry Research*, (Print), 99–110.
- Keefe, R. S., Goldberg, T. E., Harvey, P. D., Gold, J. M., Poe, M. P., & Coughenour, L. (2004). The brief assessment of cognition in schizophrenia: Reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophrenia Research*, 68(0920-9964), 283–297.
- Kühl, J. O. G., Laursen, T. M., Thorup, A., & Nordentoft, M. (2016). The incidence of schizophrenia and schizophrenia spectrum disorders in Denmark in the period 2000–2012. A register-based study. *Schizophrenia Research*, 176(2-3), 533–539. <https://doi.org/10.1016/j.schres.2016.06.023>
- Landro, N. I., & Ueland, T. (2008). Verbal memory and verbal fluency in adolescents with schizophrenia spectrum disorders. *Psychiatry and Clinical Neurosciences*, 62(6), 653–661. <https://doi.org/10.1111/j.1440-1819.2008.01864.x>
- Lay, B., Blanz, B., Hartmann, M., & Schmidt, M. H. (2000). The psychosocial outcome of adolescent-onset schizophrenia: A 12-year followup. *Schizophrenia Bulletin*, 26(4), 801–816. <https://doi.org/10.1093/oxfordjournals.schbul.a033495>
- Lemvig, C. K., Jepsen, J. R. M., Fagerlund, B., Pagsberg, A. K., Glenthøj, B. Y., Rydkjær, J., & Oranje, B. (2020). Auditory sensory gating in young adolescents with early-onset psychosis: A comparison with attention deficit/hyperactivity disorder. *Neuropsychopharmacology*, 45(4), 649–655. <https://doi.org/10.1038/s41386-019-0555-9>
- Lipkovich, I. A., Deberdt, W., Csernansky, J. G., Sabbe, B., Keefe, R. S. E., & Kollack-Walker, S. (2009). Relationships among neurocognition, symptoms and functioning in patients with schizophrenia: A path-analytic approach for associations at baseline and following 24 weeks of antipsychotic drug therapy. *BMC Psychiatry*, 9(1), 1–12. <https://doi.org/10.1186/1471-244X-9-44>
- Maziade, M., Gingras, N., Rodrigue, C., Bouchard, S., Cardinal, A., Gauthier, B., Tremblay, G., Côté, S., Fournier, C., Boutin, P., Hamel, M., Roy, M., Martinez, M., & Merette, C. (1996). Long-term stability of diagnosis and symptom dimensions in a systematic sample of patients with onset of schizophrenia in childhood and early adolescence. I: Nosology, Sex and Age of Onset. *British Journal of Psychiatry*, 169(SEPT.), 361–370. <https://doi.org/10.1192/bjp.169.3.361>
- McDonald, S., Bornhofen, C., Shum, D., Long, E., Saunders, C., & Neulinger, K. (2006). Reliability and validity of The Awareness of Social Inference Test (TASIT): A clinical test of social perception. *Disability and Rehabilitation*, 28(24), 1529–1542. <https://doi.org/10.1080/09638280600646185>
- McDonald S., Flanagan S., Rollins J., & Kinch J. (2003). TASIT: A new clinical tool for assessing social perception after traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, 18(5), 219–238.
- McGlashan, T. H. (1999). Duration of untreated psychosis in first-episode schizophrenia: Marker or determinant of course? *Biological Psychiatry*, 46(7), 899–907. [https://doi.org/10.1016/S0006-3223\(99\)00084-0](https://doi.org/10.1016/S0006-3223(99)00084-0)
- Meyers, J. E., & Meyers, K. R. (1995). *Rey complex figure test and recognition trial, professional manual*. Odessa, FL: Psychological Assessment Resources, Inc.
- Mohamed, S., Rosenheck, R., Swartz, M., Stroup, S., Lieberman, J. A., & Keefe, R. S. E. (2008). Relationship of cognition and psychopathology to functional impairment in schizophrenia. *American Journal of Psychiatry*, 165(8), 978–987. <https://doi.org/10.1176/appi.ajp.2008.07111713>
- Mucci, A., Galderisi, G., Gibertoni, D., Rossi, A., Rocca, P., Bertolino, A., Aguglia, E., Amore, M., Bellomo, A., Biondi, M., Blasi, G., Brasso, C., Bucci, P., Carpiniello, B., Cuomo, A., Dell'Osso, L., Giordano, G.M., Marchesi, C., Monteleone, P., . . . , & Maj, M. (2021). Factors associated with real-life functioning in persons with schizophrenia in a 4-year follow-up study of the Italian network for research on psychoses. *JAMA Psychiatry*, 1-10(5), 550. <https://doi.org/10.1001/jamapsychiatry.2020.4614>
- Nieto, R. G., & Castellanos, F. X. (2011). A meta-analysis of neuropsychological functioning in patients with early onset schizophrenia and pediatric bipolar disorder. *Journal of Clinical Child & Adolescent Psychology*, 40(1537-4424 (Electronic)), 266–280.
- Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., Essock, S., Fenton, W.S., Frese, F.J., Gold, J.M., Goldberg, T., Heaton, R.K., Keefe, R.S.E., Kraemer, H., Mesholam-Gately, R., Seidman, L.J., Stover, E., Weinberger, D.R., Young, A., . . . , & Marder, S.R. (2008). The MATRICS consensus cognitive battery, Part 1: Test selection, reliability, and validity. *American Journal of Psychiatry*, 165(2), 203–213. <https://doi.org/10.1176/appi.ajp.2007.07010042>
- Okkels, N., Vernal, D. L., Jensen, S. O. W., Mcgrath, J. J., & Nielsen, R. E. (2012). Changes in the diagnosed incidence of early onset schizophrenia over four decades. *Acta Psychiatrica Scandinavica*, 127(1), 62–68. <https://doi.org/10.1111/j.1600-0447.2012.01913.x>
- Parellada, M., Fraguas, D., Bombín, I., Otero, S., Castro-Fornieles, J., Baeza, I., Gonzalez-Pinto, A., Graell, M., Soutullo, C., Paya, B., & Arango, C. (2009). Insight correlates in child- and adolescent-onset first episodes of psychosis: Results from the CAFEPS study. *Psychological Medicine*, 39(9), 1433–1445. <https://doi.org/10.1017/S0033291708004868>
- Pedersen C. B.øcker, Mors O., Bertelsen A., Waltoft B. L., Agerbo E., McGrath J. J., Mortensen P. B., & Eaton W. W. (2014). A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. *JAMA Psychiatry*, 71(5), 573–581. <https://doi.org/10.1001/jamapsychiatry.2014.16>
- Perlick, D. A., Rosenheck, R. A., Kaczynski, R., Bingham, S., & Collins, J. (2008). Association of symptomatology and cognitive deficits to functional capacity in schizophrenia. *Schizophrenia Research*, 99(1-3), 192–199. <https://doi.org/10.1016/j.schres.2007.08.009>
- Perneger, T. V. (1998). What's wrong with Bonferroni adjustments. *British Medical Journal*, 316(7139), 1236–1238. <https://doi.org/10.1136/bmj.316.7139.1236>
- Pilowsky, T., Yirmiya, N., Arbelle, S., & Mozes, T. (2000). Theory of mind abilities of children with schizophrenia, children with autism, and normally developing children. *Schizophrenia Research*, 42(2), 145–155. [https://doi.org/10.1016/S0920-9964\(99\)00101-2](https://doi.org/10.1016/S0920-9964(99)00101-2)
- Puig O., Penadés R., Baeza I., Sánchez-Gistau V., De la Serna E., Fonrodon L., Andrés-Perpiñá S., Bernardo M., & Castro-Fornieles J. (2012). Processing speed and executive functions predict real-world everyday living skills in adolescents with early-onset schizophrenia. *European Child and Adolescent Psychiatry*, 21(6), 315–326. <https://doi.org/10.1007/s00787-012-0262-0>
- Puig, O., Penadés, R., Baeza, I., De La Serna, E., Sánchez-Gistau, V., Bernardo, M., & Castro-Fornieles, J. (2014). Cognitive remediation therapy in adolescents with early-onset schizophrenia: A randomized controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry*, 53(8), 859–868. <https://doi.org/10.1016/j.jaac.2014.05.012>
- Rajji, T. K., Ismail, Z., & Mulsant, B. H. (2009). Age at onset and cognition in schizophrenia: Meta-analysis. *British Journal of Psychiatry*, 195(4), 286–293. <https://doi.org/10.1192/bjp.bp.108.060723>
- Rispaud, S. G., Rose, J., & Kurtz, M. M. (2016). The relationship between change in cognition and change in functional ability in schizophrenia during cognitive and psychosocial rehabilitation. *Psychiatry Research*, 244(2016), 145–150. <https://doi.org/10.1016/j.psychres.2016.07.033>
- Röpcke, B., & Eggers, C. (2005). Early-onset schizophrenia: A 15-year follow-up. *European Child and Adolescent Psychiatry*, 14(6), 341–350. <https://doi.org/10.1007/s00787-005-0483-6>
- Rydkjær, J., Møllegaard Jepsen, J. R., Pagsberg, A. K., Fagerlund, B., Glenthøj, B. Y., & Oranje, B. (2017). Mismatch negativity and P3a amplitude in young adolescents with first-episode psychosis: A comparison with ADHD. *Psychological Medicine*, 47(02), 377–388. <https://doi.org/10.1017/S0033291716002518>
- Sahakian, B. J., & Owen, A. M. (1992). Computerized assessment in neuropsychiatry using CANTAB: Discussion paper. *Journal of the Royal Society of Medicine*, 85(7), 399–402. <https://doi.org/10.1177/014107689208500711>
- Schmidt, S. J., Mueller, D. R., & Roder, V. (2011). Social cognition as a mediator variable between neurocognition and functional outcome in schizophrenia: Empirical review and new results by structural equation modeling. *Schizophrenia Bulletin*, 37(SUPPL 2), S54. <https://doi.org/10.1093/schbul/sbr079>

- Seiferth, N. Y., Pauly, K., Kellermann, T., Shah, N. J., Ott, G., Herpertz-Dahlmann, B., Habel, U., & *et al.* (2009). Neuronal correlates of facial emotion discrimination in early onset schizophrenia. *Neuropsychopharmacology*, 34(2), 477–487. <https://doi.org/10.1038/npp.2008.93>
- Smelror, R. E., Johannessen, C., Wedervang-Resell, K., Jørgensen, K. N., Barth, C., Andreou, D., Ueland, T., Andreassen, O.A., Myhre, A.M., Rund Børn, R., & Agartz, I. (2021). Cognitive impairment profile in adolescent early-onset psychosis using the MATRICS Battery: Age and sex effects. *Neuropsychology*, 35(3), 300–309. <https://doi.org/10.1037/neu0000723>
- Sparrow, S. S., Cicchetti, D. V., & Balla, D. A. (2011). *Vineland adaptive behavior scales. Danish version* (2nd edn). Stockholm, Sweden: Pearson Education, Inc.
- Stenstrom, A. D., Christiansen, E., Dehlholm-Lambertsen, B., Nøhr-Jensen, P., & Bilenberg, N. (2010). Stigende incidensrate af skizofreni hos børn og unge. *Ugeskrift for Læger*, 172(31), 2131–2135.
- Stentebjerg-Olesen, M., Pagsberg, A. K., Fink-Jensen, A., Correll, C. U., & Jepsen, P. (2016). Clinical characteristics and predictors of outcome of schizophrenia-spectrum psychosis in children and adolescents: A systematic review. *Journal of Child and Adolescent Psychopharmacology*, 26(5), 410–427. <https://doi.org/10.1089/cap.2015.0097>
- Swartz, M. S., Perkins, D. O., Stroup, T. S., Davis, S. M., Capuano, G., Rosenheck, R. A., Reimherr, F., McGee, M.F., Keefe, R.S.E., McEvoy, J.P., Hsiao, J.K., & Lieberman, J. A. (2007). Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: Findings from the NIMH CATIE study. *American Journal of Psychiatry*, 164(3), 428–436. <https://doi.org/10.1176/ajp.2007.164.3.428>
- Teigset, C. M., Mohn, C., Brunborg, C., Juuhl-Langseth, M., Holmén, A., & Rund, B. R. (2018). Do clinical characteristics predict the cognitive course in early-onset schizophrenia-spectrum disorders? *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 59(9), 1012–1023. <https://doi.org/10.1111/jcpp.12896>
- Timmerby, N., Andersen, J. H., Søndergaard, S., Østergaard, S. D., & Bech, P. (2017). A systematic review of the clinimetric properties of the 6-item version of the Hamilton Depression Rating Scale (HAM-D6). *Psychotherapy and Psychosomatics*, 86(3), 141–149. <https://doi.org/10.1159/000457131>
- Ueland, T., & Rund, B. R. (2004). A controlled randomized treatment study: The effects of a cognitive remediation program on adolescents with early onset psychosis. *Acta Psychiatrica Scandinavica*, 109(1), 70–74. <https://doi.org/10.1046/j.0001-690X.2003.00239.x>
- Ventura, J., Helleman, G. S., Thames, A. D., Koellner, V., & Nuechterlein, K. H. (2009). Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: A meta-analysis. *Schizophrenia Research*, 113(1573-2509 (Electronic)), 189–199.
- Vernal, D. L., Boldsen, S. K., Lauritsen, M. B., Correll, C. U., & Nielsen, R. E. (2020). Long-term outcome of early-onset compared to adult-onset schizophrenia: A nationwide Danish register study. *Schizophrenia Research*, 220(123-129), 123–129. <https://doi.org/10.1016/j.schres.2020.03.045>
- Vourdas, A., Pipe, R., Corrigall, R., & Frangou, S. (2003). Increased developmental deviance and premorbid dysfunction in early onset schizophrenia. *Schizophrenia Research*, 62(0920-9964 (Print)), 13–22.
- Vyas, N. S., Hadjulic, M., Vourdas, A., Byrne, P., & Frangou, S. (2007). The Maudsley early onset schizophrenia study: Predictors of psychosocial outcome at 4-year follow-up. *European Child and Adolescent Psychiatry*, 16(7), 465–470. <https://doi.org/10.1007/s00787-007-0621-4>
- Wechsler, D. (2002). Wechsler adult intelligence scale - 3rd edition. In *Wechsler memory scale - 3rd Ed. Technical Manual*. USA: The Psychological Corporation. A Harcourt Assessment Company.
- Wechsler, D. (2003). Manual for the Wechsler intelligence scale for children. In *Technical and interpretative manual* (4th ed. San Antonio, TX: Psychological Corporation.
- WHO (1992). *The ICD-10 classification of mental and behavioural disorders. Clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization.
- Wykes, T., Newton, E., Landau, S., Rice, C., Thompson, N., & Frangou, S. (2007). Cognitive remediation therapy (CRT) for young early onset patients with schizophrenia: An exploratory randomized controlled trial. *Schizophrenia Research*, 94(0920-9964 (Print)), 221–230.
- Xu, L., Guo, Y., Cao, Q., Li, X., Mei, T., Ma, Z., Tang, X., Ji, Z., Yang, L., & Liu, J. (2020). Predictors of outcome in early onset schizophrenia: A 10-year follow-up study. *BMC Psychiatry*, 20(1), 1–9. <https://doi.org/10.1186/s12888-020-2484-x>