Psychological Medicine

cambridge.org/psm

Differential effects of age at illness onset on verbal memory functions in antipsychotic-naïve schizophrenia patients aged 12–43 years

Birgitte Fagerlund[1,2,*], Christos Pantelis[1,3,*], Jens Richardt Møllegaard Jepsen[1,4], Jayachandra Mitta Raghava[1,5], Egill Rostrup[1], Marie Bjerregaard Thomas[1], Mette Ødegaard Nielsen[1,6], Kirsten Bojesen[1], Karsten Gjessing Jensen[4,6], Marie Stentebjerg-Decara[4,6], Dea Gowers Klauber[4,6], Ditte Rudå[4,6], Bjørn H. Ebdrup[1,6], Kasper Jessen[1], Anne Sigvard[1,6], Karen Tangmose[1,6], Pia Jeppesen[4,6], Christoph U. Correll[7,8,9], Anders Fink-Jensen[6,10], Anne Katrine Pagsberg[4,6,†] and Birte Yding Glenthøj[1,6,†]

[1]Center for Neuropsychiatric Schizophrenia Research (CNSR) and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Mental Health Center Glostrup, Glostrup, Denmark; [2]Department of Psychology, University of Copenhagen, Copenhagen, Denmark; [3]Department of Psychiatry, Melbourne Neuropsychiatry Centre, University of Melbourne and Melbourne Health, Carlton South, Victoria, Australia; [4]Mental Health Services, Capital Region of Denmark, Child and Adolescent Mental Health Center, Copenhagen, Denmark; [5]Functional Imaging Unit, Department of Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet Glostrup, 2600 Glostrup, Denmark; [6]University of Copenhagen, Faculty of Health and Medical Sciences, Department of Clinical Medicine, Copenhagen, Denmark; [7]The Zucker Hillside Hospital, Department of Psychiatry, Northwell Health, Glen Oaks, NY, USA; [8]Zucker School of Medicine at Hofstra/Northwell, Department of Psychiatry and Molecular Medicine, Hempstead, NY, USA; [9]Charité Universitätsmedizin Berlin, Department of Child and Adolescent Psychiatry, Berlin, Germany and [10]Mental Health Center Copenhagen, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Abstract

Background. The typical onset of schizophrenia coincides with the maturational peak in cognition; however, for a significant proportion of patients the onset is before age 18 and after age 30 years. While cognitive deficits are considered core features of schizophrenia, few studies have directly examined the impact of age of illness onset on cognition.

Methods. The aim of the study was to examine if the effects of age on cognition differ between healthy controls (HCs) and patients with schizophrenia at illness onset. We examined 156 first-episode antipsychotic-naïve patients across a wide age span (12–43 years), and 161 age- and sex-matched HCs. Diagnoses were made according to ICD-10 criteria. Cognition was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS), and IQ was estimated using subtests from the Wechsler adult- or child-intelligence scales. Multivariate analysis of covariance (MANCOVA) was used to examine linear and quadratic effects of age on cognitive scores and interactions by group, including sex and parental socioeconomic status as covariates.

Results. There was a significant overall effect of age on BACS and IQ ($p < 0.001$). Significant group-by-age interactions for verbal memory (for age-squared, $p = 0.009$), and digit sequencing (for age, $p = 0.01$; age-squared, $p < 0.001$), indicated differential age-related trajectories between patients and HCs.

Conclusions. Cognitive functions showing protracted maturation into adulthood, such as verbal memory and verbal working memory, may be particularly impaired in both early- and late-schizophrenia onset. Our findings indicate a potential interaction between the timing of neurodevelopmental maturation and a possible premature age effect in late-onset schizophrenia.

Introduction

The typical onset of schizophrenia is in late adolescence and early adulthood, with a peak age of illness onset (AIO) of 22 years (Pedersen et al., 2014), coinciding temporally with late maturational brain remodeling processes (Lebel, Treit, & Beaulieu, 2019; Moises, Zoega, & Gottesman, 2002). While pre-teen onset is very rare, as many as 18% of schizophrenia patients have their illness onset before the age of 18 years (Frangou, 2013), and a considerable proportion have an illness onset after the age of 30 and even 40 years (Harris & Jeste, 1988). Early-onset schizophrenia (EOS) in childhood and adolescence is considered phenotypically

Original Article

*Birgitte Fagerlund and Christos Pantelis have contributed equally and share first authorship.

†Birte Y. Glenthøj and Anne Katrine Pagsberg have contributed equally and share last authorship.

Cite this article: Fagerlund B *et al* (2021). Differential effects of age at illness onset on verbal memory functions in antipsychotic-naïve schizophrenia patients aged 12–43 years. *Psychological Medicine* **51**, 1570–1580. https://doi.org/10.1017/S0033291720000409

Received: 3 October 2019
Revised: 21 January 2020
Accepted: 6 February 2020
First published online: 11 March 2020

Key words:
Age of illness onset; cognition; neurodevelopmental; schizophrenia

Author for correspondence:
Birgitte Fagerlund,
E-mail: Birgitte.Fagerlund@regionh.dk

CAMBRIDGE UNIVERSITY PRESS

and neurobiologically continuous with adult-onset schizophrenia (AOS), but is characterized by more familial and premorbid risk factors, and a more insidious onset and severe course of illness (Eggers, 1999). In very EOS in childhood, a premature, excessive and progressive process of synaptic pruning has been demonstrated (Thompson et al., 2001), indicating that the timing of illness onset appears to be influenced by multiple factors, including the type, timing and severity of aberrant neurodevelopment (Gogtay, Vyas, Testa, Wood, & Pantelis, 2011). The continuity between AOS and late-onset schizophrenia (>40 years) is less clear, due to few available studies (Maglione, Thomas, & Jeste, 2014). Nevertheless, most studies support late onset as a subtype of schizophrenia (Vahia et al., 2010), with a similar symptom profile, although some suggest fewer negative symptoms in the late-onset group (Howard, Rabins, Seeman, & Jeste, 2000). The neurobiological findings in late-onset schizophrenia are similar to those in young AOS, implicating both gray and white matter abnormalities, with increased ventricle size and atrophy in frontal, temporal and subcortical areas (Van Assche, Morrens, Luyten, Van de Ven, & Vandenbulcke, 2017).

Cognitive deficits are core features of schizophrenia, the specific profile and severity of which may be impacted by the AIO, dependent on the timing of maturational processes for specific cognitive functions (Pantelis, Yucel, Wood, McGorry, & Velakoulis, 2003). If an early age of onset is a proxy measure of the severity of illness processes and implicates more disruptions of developmental processes, then earlier ages of onset should be associated with a broader range and greater severity of cognitive deficits. Most of the available evidence is indirect, comparing results from separate early-onset and adult-onset studies. These studies indicate lower levels of IQ, both premorbidly and after illness onset (Khandaker, Barnett, White, & Jones, 2011; Rajji, Ismail, & Mulsant, 2009), and more severe deficits in certain specific cognitive functions, such as executive functions, processing speed and verbal memory in EOS compared to AOS (Rajji et al., 2009). Some studies have found cognitive deficits of a similar magnitude in children and adolescents with EOS to those found in the AOS literature, indirectly suggesting a similar profile and severity of deficits (Kravariti, Morris, Rabe-Hesketh, Murray, & Frangou, 2003a, 2003b). In comparison, similar levels of deficits have been found in late-onset schizophrenia compared to young adult-onset patients regarding intelligence, processing speed, attention and some aspects of executive functions, while other aspects of executive functions, and verbal memory have been reported as less impaired (Van Assche et al., 2017). There is also evidence of some relatively preserved functions, suggesting a rather specific profile of deficits, not merely indicative of aging effects (Rajji et al., 2009).

The very few studies that have directly examined the effects of AIO across EOS and AOS patients show conflicting results. Biswas, Malhotra, Malhotra, & Gupta (2006) found more severe deficits in younger AIO in IQ and memory, with very early onset patients (age <13 years) underperforming relative to EOS, who in turn had worse deficits than AOS. In contrast, Tuulio-Henriksson, Partonen, Suvisaari, Haukka, & Lonnqvist (2004) found an association between younger ages of onset and more severe verbal memory deficits, but without effects of AIO on IQ, processing speed, attention and working memory. That study retrospectively examined a wide range of ages of onset between 12 and 44 years in a chronic schizophrenia sample. In another direct comparison examining AIO, White, Ho, Ward, O'Leary, & Andreasen (2006) found more severe deficits in EOS than AOS when examining raw scores for language, working memory and motor skills; however, when corrected for age-related developmental differences in healthy controls (HCs), only deficits in motor skills in EOS remained significant. A study by Rhinewine et al. (2005) compared only very early-onset schizophrenia to EOS and did not find age-related differences in severity of cognitive deficits. These conflicting findings may be due to differential sample characteristics and methodological approaches in these studies, such as small sample sizes, medication status and some studies assessing AIO retrospectively, making it difficult to disentangle effects of AIO from illness progression, continued maturational processes and medication effects.

To our knowledge, no previous study has directly examined the impact of AIO on cognition in antipsychotic-naïve, early-, adult- and late-onset first-episode patients with schizophrenia or schizoaffective disorder. The aim of the study was to examine if the effects of age on cognition differ between patients with schizophrenia or schizoaffective disorder and HCs. This was examined in first-episode antipsychotic-naïve patients across a wide age span from 12 to 43 years. Based on the literature, we hypothesized EOS patients would have more severe cognitive deficits than AOS- and late-onset patients. We also expected the late-onset patients to have more circumscribed and less severe cognitive deficits than EOS and young AOS patients.

Methods

The study was approved by the Danish National committee on Biomedical Research Ethics (H-3-2009-123; H-D-2008-088 and H-3-2013-149) and the Danish Data Protection Agency (CSU-FCFS-2017-012, I-Suite no. 05787). All participants provided written informed consent, including parental consent for participants below age 18 years. The study was carried out in accordance with the Helsinki Declaration II.

Subjects

Participants were included from parallel collaborative studies in child and adolescent and adult psychiatry services in the Mental Health Services in the Capital Region, Copenhagen, Denmark. The adolescent patients and HCs were included as part of the baseline assessments in the TEA trial (Pagsberg et al., 2014), while the adult patients and HCs were included as part of the PECANS studies (Bojesen et al., 2019; Jessen et al., 2019; Nielsen et al., 2012). Adolescent patients were recruited from five child- and adolescent mental health centers throughout Denmark, the majority from the Copenhagen catchment area. Adult patients were included from mental health centers in the Copenhagen catchment area. Inclusion criteria for patients in the current study were: a diagnosis of schizophrenia or schizoaffective disorder, antipsychotic-naïve status (strictly defined, not allowing any previous antipsychotic exposure), first-episode status (defined as the first diagnosis of schizophrenia or schizoaffective disorder) and complete cognitive datasets (allowing for ⩽3 missing cognitive scores). Exclusion criteria for both patients and controls were: a current diagnosis of drug dependence, any previous or current treatment with antipsychotic compounds, serious somatic or neurological illness and a history of severe head injury. Exclusion criteria specific to HCs were: previous or current psychiatric illness or family history of psychiatric illness in first-degree relatives.

The sample included 156 antipsychotic-naïve patients with first-episode schizophrenia or schizoaffective disorder between

https://doi.org/10.1017/S0033291720000409 Published online by Cambridge University Press

the ages 12 and 43 years, and 161 age- and sex-matched HCs. Results from previously published studies partially overlap with the data included here, but did not focus on cognitive data [regarding adolescent data see Jensen et al. (2017) and Pagsberg et al. (2017), also see http://www.cinsr.dk for publications from the adult cohorts].

Demographics, diagnoses and psychopathology

Parental socioeconomic status (SES) was calculated based on a combination of scores combining the highest parental attainment of educational level and/or occupation and household income, according to criteria from the Danish Institute of Clinical Epidemiology, and resulted in three groups (high, medium, and low) of parental SES.

Diagnoses were made according to ICD-10 criteria using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990) and Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime version (K-SADS-PL) interviews. Psychopathology was rated using the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987). Duration of untreated illness (DUI) was recorded slightly differently between studies, either specifically as the patient's recollection of the onset of functional impact of either psychotic symptoms, or more generally as illness-related symptoms. These were combined into one measure of DUI.

Cognition

The Brief Assessment of Cognition in Schizophrenia (BACS) was used to assess verbal learning, working memory, motor speed, verbal fluency, processing speed and planning. The BACS battery has been validated in adult patients regarding reliability, validity and correlation with measures of functional outcome (Keefe, Poe, Walker, & Harvey, 2006, 2008).

Intelligence was estimated using four subtests from the Wechsler intelligence scales (WISC-III, WISC-IV or the WAIS-IV in adolescents, and the WAIS-III in adults) (Wechsler, 1991, 1997, 2003, 2008). The four subtests selected (vocabulary, similarities, block design and matrix reasoning) have been highly correlated with full-scale IQ (Axelrod, 2002). To enable direct comparisons across the different versions of the Wechsler scales, raw scores were standardized to *z*-scores, using the HC groups for the respective Wechsler version as a reference.

Statistical analyses

Analyses were performed using SPSS 24.0. Normality of distributions was tested using the Shapiro–Wilk test. Negatively skewed data were reflected and the square root was then used to approximate a normal distribution. Parametric statistics were used for all analyses. Nominal data (sex, parental SES and diagnostic distribution) were analyzed with Pearson's χ^2. The effect of age on PANSS scores in the patient group was examined using Pearson's bivariate correlation analysis. To examine linear and nonlinear (quadratic) effects of age on cognitive scores and interactions by group, a linear regression model with multivariate analysis of covariance (MANCOVA) was used. Parameter estimates were calculated using bootstrap sampling (10 000 samples) with a bias-corrected and accelerated bootstrap interval. Main effects of age, age-squared and interactions by group were examined, including sex and parental SES as covariates. Age and age-squared were centered in all analyses. Separate post-hoc analysis of covariance (ANCOVA) analyses (corrected for sex and SES) examined the potential impact of IQ, psychopathology scores and DUI on the relationship between age and cognitive test scores, when this relationship differed between patients and controls.

Results

Demographic data

Demographic data (age, sex and parental SES) are shown in Table 1. Patients and controls did not differ on sex ($\chi^2 = 0.021$, df = 1, $p = 0.885$), but parental SES was significantly higher in HCs ($\chi^2 = 10.871$, df = 2, $p = 0.005$) (see Table 1). Sex ratio was significantly different between adolescent and adult patients, with more females (71%) in the adolescent group than in the adult group (45%) ($\chi^2 = 9.492$, df = 1, $p = 0.002$). Parental SES was significantly higher in the adolescent patients than the adult patients ($\chi^2 = 8.055$, df = 2, $p = 0.02$).

Diagnostic distribution and psychopathology

The diagnostic distribution differed between groups, with more cases of schizoaffective disorder in the adolescent group (19%) compared to the adult group (3%) ($\chi^2 = 12.126$, df = 1, $p < 0.001$). Nine of the 10 adolescent patients with schizoaffective disorder were female, while all three adult patients with schizoaffective disorder were male. The patients were moderately ill, according to PANSS total scores (Leucht et al., 2005). Adult patients had significantly higher general PANSS symptoms than adolescent patients ($p = 0.002$), but did not differ on positive or negative symptoms. The DUI was significantly longer in the adolescent than the adult patients ($p = 0.002$).

Cognition

The main MANCOVA results indicated a significant overall effect of age on BACS and IQ measures ($F_{(7,270)} = 8.373$; $p < 0.001$; Wilk's lambda = 0.8; partial eta squared = 0.18). Highly significant group effects between patients and controls were seen on all BACS subtests and on estimated IQ (see Table 2). There were significant main effects of age on estimated IQ ($p = 0.01$), verbal memory ($p = 0.01$), digit sequencing ($p < 0.001$), token task ($p < 0.001$), verbal fluency ($p < 0.001$ for age, and $p = 0.001$ for age squared), tower of London ($p = 0.02$ for age squared) and on symbol digit ($p = 0.02$ for age squared). All linear age effects indicated overall better scores with age, while non-linear, quadratic effects indicated an inverted U-curve, with lower scores at the younger and older ages (Fig. 1*a–e*). There were significant group-by-age interactions for verbal memory ($p = 0.009$ for age squared), and digit sequencing ($p = 0.01$ for age, and $p < 0.001$ for age squared), indicating differential age-related trajectories on verbal memory and verbal working memory between patients and HCs. Separate group analyses showed that the significant group × age interactions on verbal memory were driven by highly statistically significant quadratic effects of age on verbal memory in patients ($p < 0.00001$), which was non-significant in controls. Similarly, on digit sequencing, patients showed a highly significant quadratic effect of age ($p < 0.00001$), which was non-significant in controls (see Fig. 2*a* and *b*). HCs showed significant linear effects of age on verbal memory ($p = 0.006$) and digit sequencing ($p = 0.001$) (see Table 3).

https://doi.org/10.1017/S0033291720000409 Published online by Cambridge University Press

Table 1. Demographic and clinical data for antipsychotic-naïve schizophrenia or schizoaffective patients and HCs

	Patients $N = 156$		HCs $N = 161$	Statistics
Demographic data				
Mean age in years; mean (s.d.); range	21.45 (6.18) 12–43		21.10 (5.99) 12–43	$p = 0.614$[a]
Female gender, *N* (%)	84 (54)		88 (55)	Patients *v.* controls ($\chi^2 = 0.021$, df = 1, $p = 0.885$)[b]
Parental SES (A/B/C)[c]	(53/79/21)		(84/62/14)	Patients *v.* controls ($\chi^2 = 10.871$, df = 2, $p = 0.005$)[b]
Estimated intelligence; mean *z*-score (s.d.)	−1.13 (1.46)		0.00 (1.00)	Patients *v.* controls ($F_{(1,284)} = 31.774$, $p < 0.001$)[b]
Clinical data				
Diagnosis, *N*	SCZ, 143	SCZ-AF, 13	HCs, 161	–
Duration untreated illness, weeks, mean (s.d.), range	104.4 (126.2) 0–530		–	–
PANSS positive, mean (s.d.)	19.74 (4.05)		–	–
PANSS negative, mean (s.d.)	20.00 (6.07)		–	–
PANSS general, mean (s.d.)	38.79 (8.16)		–	–
PANSS total, mean (s.d.)	78.54 (14.62)		-	–

Results from analyses of group differences.
Parental SES, parental socioeconomic status; SCZ, schizophrenia; SCZ-AF, schizoaffective disorder; PANSS, Positive and Negative Syndrome Scale.
[a]Student's *t* test.
[b]Pearson's χ^2.
[c]*N* varies due to missing data: parental SES (patient *N* = 152/control *N* = 160).
*Significant results.

Post-hoc ANCOVA analyses (with sex and parental SES as fixed factor covariates) examined the potential impact of IQ, psychopathology scores and DUI on the quadratic relationships between age and verbal memory and verbal working memory. While there was a highly significant main effect of IQ on verbal memory ($p < 0.0001$) and on digit sequencing ($p < 0.0001$) in patients, this did not change the significant quadratic relationship between age and verbal memory ($p < 0.0001$) and working memory in patients ($p = 0.001$). None of the PANSS scores changed the significant quadratic relationship between age and verbal memory and working memory, which all remained significant at $p < 0.001$; although negative and general symptoms had a significant main effect on working memory ($p = 0.002$, and $p < 0.0001$, respectively), and verbal memory ($p = 0.01$ for negative symptoms, and $p = 0.02$ for general symptoms). Positive symptoms showed a trend-level effect on working memory only ($p = 0.05$), without significant effect of general symptoms on the verbal memory model. The DUI did not have a significant impact on any of the models.

Discussion

In this study of antipsychotic-naïve first-episode schizophrenia patients aged 12–43 years who were assessed at illness onset, patients had significantly lower performance on all cognitive tasks compared with HCs. An age effect was evident on all cognitive tasks across patients and controls, with linear effects indicating better scores with increasing age on motor skills, and estimated IQ. Non-linear, quadratic age effects (indicating an inverted U-curve fit) were seen for verbal fluency, planning skills and processing speed, with evidence of a similar, parallel age-related peak in performance in early adulthood in both patients and HCs. Verbal memory and verbal working memory showed differential relationships with age in patients in comparison with HC, indicating poorer performance in patients at both younger and older ages of onset.

Thus, for most of the cognitive tasks examined, we did not find evidence for differential age effects between patients and controls, indicating that an adolescent-onset of illness was not associated with greater impairment of cognitive function than adult-onset in the domains of motor skills, verbal fluency, planning, processing speed or intelligence. This result is similar to some (e.g. Kravariti, Morris, Rabe-Hesketh, Murray, & Frangou, 2003b; Rhinewine et al., 2005; White et al., 2006) but not all (Biswas et al., 2006; Tuulio-Henriksson et al., 2004) previous studies.

In contrast, there were significant age by group interaction effects for verbal learning and memory (BACS verbal memory) and verbal working memory (BACS digit sequencing task). For these tasks, the highly significant non-linear, quadratic age effects indicated relatively poorer performance at the early and later AIO ranges compared with the cognitive deficits in patients with an illness onset in early adulthood. These non-linear effects were significant in patients, but were not present in HC. The quadratic effects were not explained by psychopathology, duration of illness or IQ. Further, while the adolescent patients had significantly longer DUI than the adult patients, similar to previous findings suggesting a more insidious onset in adolescence (e.g. Eggers, 1999), there was no impact of DUI on the relationship with age. EOS patients had fewer general symptoms than AOS patients, which does not suggest EOS to be a more clinically severe form of the illness, and the psychopathology measures did not impact the relationship between cognition and age. These findings suggest a particular, direct, inverted U-curve association between age and both verbal memory and verbal working memory in patients only, which is independent of the effects of IQ, psychopathology and DUI.

https://doi.org/10.1017/S0033291720000409 Published online by Cambridge University Press

Table 2. Bootstrap parameter estimates of age and group effects on cognition

Dependent variables	Parameter	*B* (Std. error)	Sig. (two-tailed)	BCa 95% confidence interval
Bootstrap for parameter estimates				
Verbal memory	Intercept	53.02 (2.028)	0.0001*	49.067–56.972
	Group	−3.85 (1.383)	0.005*	−6.575 to −0.963
	Sex	1.132 (1.273)	0.384	−1.355 to 3.717
	Parental SES = 1	3.999 (2.004)	0.045*	0.117–7.931
	Parental SES = 2	2.417 (1.937)	0.212	−1.302 to 6.308
	Age	0.484 (0.193)	0.011*	0.123–0.875
	Age^2	−0.02 (0.014)	0.134	−0.048 to 0.007
	Group × Age	0.454 (0.272)	0.097	−0.093 to 0.998
	Group × Age^2	−0.062 (0.024)	0.009*	−0.11 to −0.02
Digit sequencing	Intercept	22.558 (1.009)	0.0001*	20.557–24.592
	Group	−1.772 (0.619)	0.006*	−3.007 to −0.512
	Sex	−1.392 (0.487)	0.006*	−2.338 to −0.429
	Parental SES = 1	0.401 (1)	0.686	−1.491 to 2.439
	Parental SES = 2	−0.014 (0.987)	0.987	−1.889 to 1.932
	Age	0.228 (0.061)	0.0001*	0.105–0.351
	Age^2	−0.004 (0.005)	0.375	−0.014 to 0.003
	Group × Age	0.256 (0.103)	0.014*	0.05–0.463
	Group × Age^2	−0.029 (0.009)	0.001*	−0.047 to −0.013
Token test	Intercept	69.754 (2.307)	0.0001*	65.316–74.017
	Group	−8.678 (2.042)	0.0002*	−12.735 to −4.419
	Sex	2.334 (1.742)	0.179	−1.201 to 5.983
	Parental SES = 1	2.408 (2.52)	0.341	−2.548 to 7.589
	Parental SES = 2	1.263 (2.443)	0.609	−3.519 to 6.122
	Age	0.909 (0.242)	0.0001*	0.437–1.398
	Age^2	−0.025 (0.016)	0.107	−0.056 to 0.008
	Group × Age	0.283 (0.388)	0.462	−0.491 to 1.068
	Group × Age^2	−0.044 (0.028)	0.1	−0.1 to 0.001
Fluency	Intercept	61.083 (2.908)	0.0001*	55.655–66.779
	Group	−11.198 (2.027)	0.0001*	−15.162 to −7.311
	Sex	3.811 (1.667)	0.023*	0.536–7.128
	Parental SES = 1	0.973 (2.818)	0.72	−4.563 to 6.48
	Parental SES = 2	2.398 (2.781)	0.391	−3.426 to 8.088
	Age	1.388 (0.257)	0.0001*	0.896–1.874
	Age^2	−0.076 (0.02)	0.0003*	−0.117 to −0.041
	Group × Age	−0.518 (0.346)	0.135	−1.182 to 0.169
	Group × Age^2	−0.003 (0.031)	0.916	−0.063 to 0.061
Symbol digit	Intercept	63.224 (2.456)	0.0001*	58.457–68.108
	Group	−9.549 (1.84)	0.0001*	−13.294 to −5.682
	Sex	2.075 (1.586)	0.194	−1.033 to 5.226
	Parental SES = 1	4.143 (2.388)	0.081	−0.627 to 9.006
	Parental SES = 2	2.765 (2.371)	0.241	−1.799 to 7.28
	Age	0.441 (0.224)	0.05	−0.007 to 0.895

(*Continued*)

https://doi.org/10.1017/S0033291720000409 Published online by Cambridge University Press

Table 2. (*Continued.*)

Dependent variables	Parameter	*B* (Std. error)	Sig. (two-tailed)	BCa 95% confidence interval
	Age^2	−0.035 (0.018)	0.035*	−0.072 to −0.007
	Group × Age	0.147 (0.343)	0.673	−0.526 to 0.825
	Group × Age^2	−0.034 (0.028)	0.18	−0.089 to 0.015
Tower of London	Intercept	0.46 (0.064)	0.0001*	0.325–0.586
	Group	0.108 (0.043)	0.011*	0.023–0.186
	Sex	0.008 (0.035)	0.804	−0.057 to 0.073
	Parental SES = 1	−0.05 (0.065)	0.437	−0.172 to 0.074
	Parental SES = 2	−0.013 (0.061)	0.833	−0.127 to 0.111
	Age	−0.009 (0.005)	0.089	−0.019 to 0.001
	Age^2	0.001 (0)	0.019*	6.44×10^{-05} to 0.002
	Group × Age	0 (0.007)	0.962	−0.013 to 0.014
	Group × Age^2	0 (0.001)	0.42	−0.001 to 0.002
Estimated intelligence	Intercept	−0.644 (0.284)	0.024*	−1.227 to −0.141
	Group	−0.872 (0.177)	0.0001*	−1.247 to −0.495
	Sex	−0.085 (0.145)	0.565	−0.376 to 0.216
	Parental SES = 1	1.054 (0.279)	0.0001*	0.536–1.602
	Parental SES = 2	0.56 (0.279)	0.046*	0.037–1.143
	Age	0.051 (0.02)	0.012*	0.013–0.089
	Age^2	−0.002 (0.002)	0.361	−0.006 to 0.004
	Group × Age	0.033 (0.033)	0.309	−0.032 to 0.101
	Group × Age^2	−0.003 (0.003)	0.325	−0.009 to 0.002

BCa, bias-corrected and accelerated bootstrap interval; Parental SES, parental socioeconomic status (1 = high SES, 2 = middle SES, 3 = low SES); Group, patients and controls (0 = patients; 1 = HCs); Sex (0 = female, 1 = male).
Age and age^2 were centered in all analyses.
*Significant results.

The more severe deficits in EOS patients regarding verbal memory is consistent with findings by Tuulio-Henriksson et al (2004) and the meta-analysis by Rajji et al. (2009), although other studies [reviewed by Frangou (2010)] did not find differences in verbal memory deficits between EOS and AOS. Fewer studies have examined working memory differences between early- and adult-onset patients, most pointing toward similar levels of deficits (e.g. Tuulio-Henriksson et al., 2004; White et al., 2006). The differential findings may be partly due to varying task complexity in relation to the timing of maturation of the specific measures used across studies. For example, the digit-span backward task used to assess verbal working memory (Tuulio-Henriksson et al., 2004; White et al., 2006) shows adult-level performance already in adolescence (Iverson & Tulsky, 2003), and may not be a sufficiently difficult measure of the more executive aspects of working memory (Egeland, 2015). The relatively more severe deficits in verbal memory and verbal working memory in our late-onset patients is in contrast to previous findings, which reported less severe visual and verbal memory deficits and similar deficits in working memory in late-onset compared to young adult-onset patients (Van Assche et al., 2017). Again, we suggest that differences between studies may be task-specific, reflecting different maturational trajectories.

The differential relationship of age and cognition between patients and controls on verbal memory and verbal working memory is interesting from a maturational perspective. We have previously suggested that perhaps in part due to the age-related decrease in neural plasticity, cognitive functions that mature late in the developmental process may be more impacted in schizophrenia-spectrum disorders than those maturing early (Pantelis et al., 2003, 2009b, 2015). The basic elements of working memory are established early in life, with a steady increase in working memory capacity until early puberty (Conklin, Luciana, Hooper, & Yarger, 2007; Simmonds, Hallquist, & Luna, 2017), with further maturation continuing in late adolescence into early adulthood related to increasing complexity and efficiency of information processing (De Luca et al., 2003; Diamond, 2002). In parallel with this maturation, there is a protracted development of neural networks, e.g. maturation of white matter in fronto-parietal networks, and an increased specialization of the cortical areas recruited in working memory processing (Andre, Picchioni, Zhang, & Toulopoulou, 2016; Tamnes et al., 2013). The present linear relationship between age and working memory in HCs indicates a late maturation of functioning regarding these tasks (e.g. Andre et al., 2016). Results on a non-verbal working memory task support the current findings, indicating that the onset of schizophrenia may interact with these maturational processes (Pantelis et al., 2009a, 2015).

Brain maturation may also be relevant to our findings for verbal memory. Basic episodic memory functions, such as those

https://doi.org/10.1017/S0033291720000409 Published online by Cambridge University Press

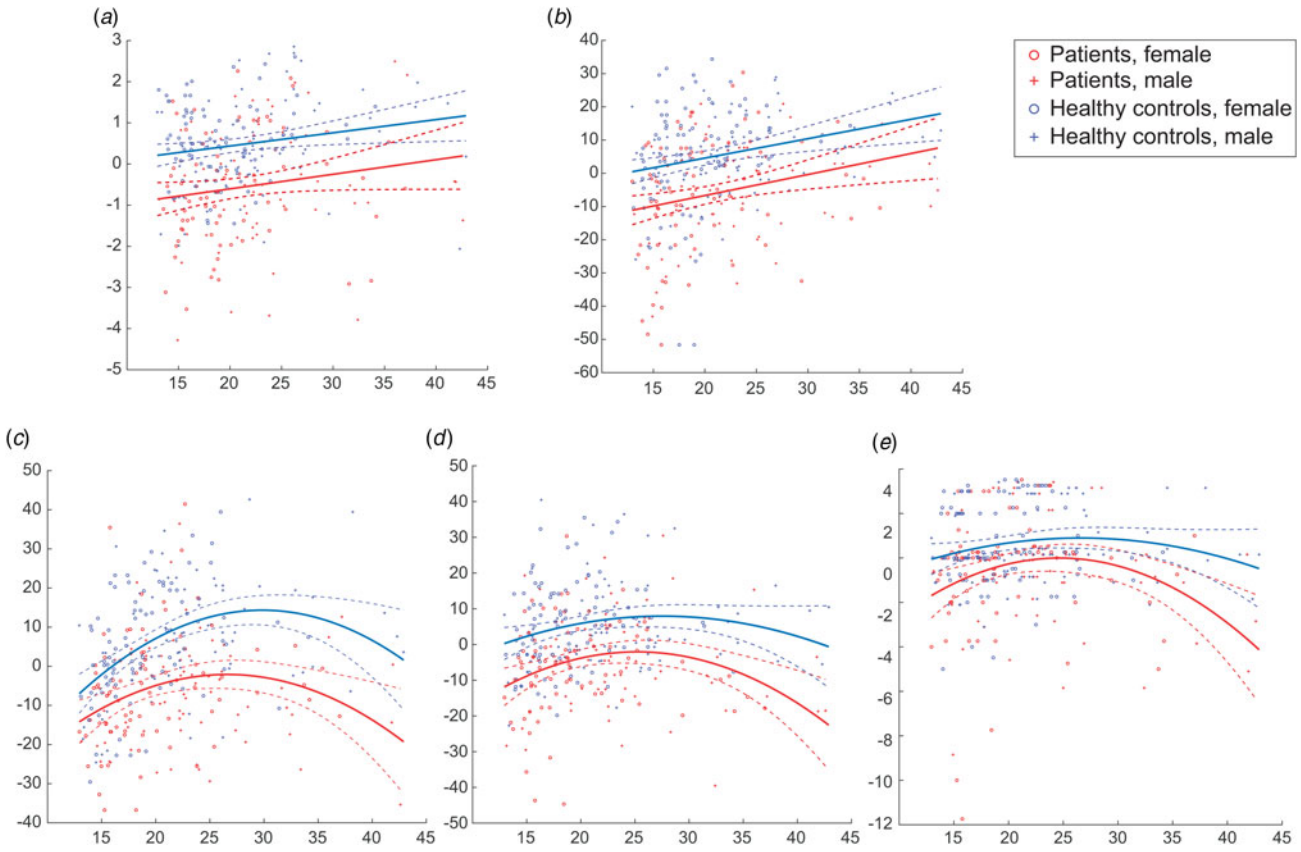

Fig. 1. Linear and non-linear (quadratic) effects of age on cognitive measures in schizophrenia patients and HCs. The panels show the corrected data (residuals after correcting for parental SES and sex) + fitted across age, in years of (*a*) estimated intelligence; (*b*) token task; (*c*) fluency; (*d*) symbol coding and (*e*) tower of London.

assessed on verbal list learning tasks, show steep development from around age 7 years and mature much earlier than the more complex aspects of working memory (Diamond, 2002; Finn et al., 2016). Nevertheless, elements of verbal memory continue to mature in early adulthood, most likely reflecting maturation of more executive aspects of cognition, when strategic learning or recall of information is required, as for the BACS verbal memory task where the memory load exceeds immediate working memory capacity. The continued, significant linear increase in performance with age in the HC indicates that performance on this test matures late, well into adulthood. This trajectory is consistent with findings that verbal memory has been associated with hippocampal volume development (Tamnes et al., 2014) (early neurodevelopment), while strategic verbal memory recall has been related to maturation of the prefrontal cortex (late neurodevelopment) (Yu et al., 2018).

The notion of an interaction between maturational stage and AIO of schizophrenia is one possible explanation for the findings of a relatively poorer performance in the EOS patients compared to the AOS patients regarding verbal memory and verbal working memory. Based on previous findings, we speculated that patients developing the illness later in life would show a relatively circumscribed profile of cognitive deficits, with relatively intact function on late-maturing abilities compared to patients with an earlier AIO (Rajji et al., 2009). However, the findings for the later-AIO patients in the current analysis are not consistent with this hypothesis, indicating that there is increased impairment on such late-developing functions of verbal memory and verbal working memory, with a greater disparity between adult-onset patients and controls with AIO beyond age 25 years. This inverted U-curve relationship between age and verbal memory and working memory in patients with schizophrenia in conjunction with a positive linear relationship in HCs requires explanation. A number of possibilities could be considered.

First, those presenting at a later age may have had a lengthy prodrome or longer DUI, during which they may have shown deterioration in cognitive ability. However, this was not the case in our sample where, consistent with the literature (Stentebjerg-Olesen, Pagsberg, Fink-Jensen, Correll, & Jeppesen, 2016), early-onset cases had a longer DUI, and where we found a relatively short DUI in the older onset patients. Further, DUI did not impact the relationship between age and verbal memory functions.

Second, it has been suggested that cognitive deficits in adulthood in schizophrenia may represent later expressions of underlying neurodevelopmental processes (Zipursky, Reilly, & Murray, 2013). For example, a relationship between early neurodevelopmental processes and later cognitive functioning in both healthy people and schizophrenia patients is demonstrated in the Northern Finland Birth Cohort study (Murray et al., 2006). The pattern of findings in this study for the EOS group is also consistent with findings from studies showing that cognitive abilities that mature late in the neurodevelopmental process may be particularly impaired at illness onset (Pantelis et al., 2003, 2015). Nevertheless, an exclusively neurodevelopmental process does not explain the lower functioning in verbal memory and

https://doi.org/10.1017/S0033291720000409 Published online by Cambridge University Press

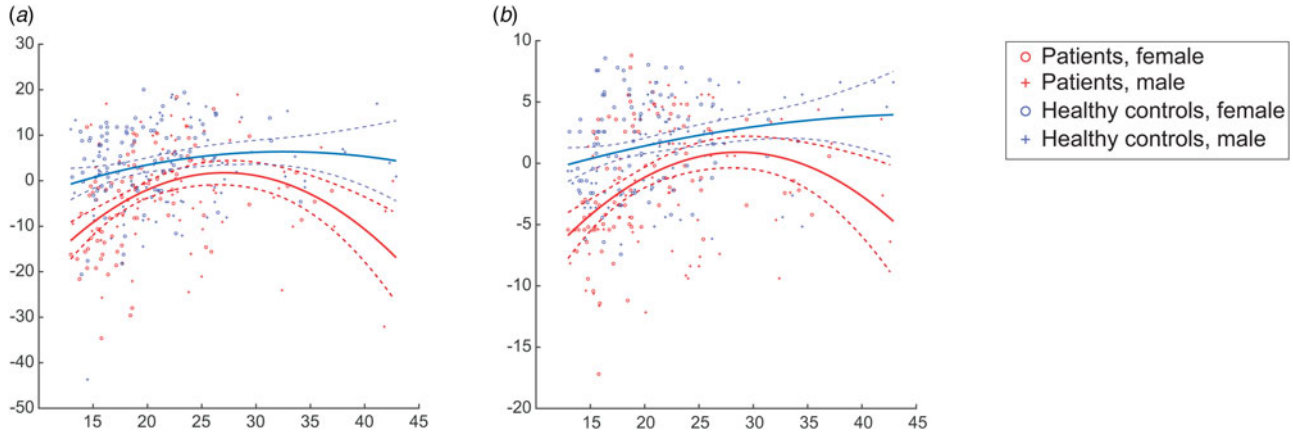

Fig. 2. Non-linear (quadratic) effects of age on verbal memory and verbal working memory in schizophrenia patients and HCs. The panels show the corrected data (residuals after correcting for parental SES and sex) + fitted across age, in years of (*a*) verbal memory and (*b*) digit sequencing. The quadratic effects were significant in patients only.

working memory in the older onset patients relative to the younger adult onset patients.

Third, the profile of deficits in the older onset patients may reflect a premature, accelerated, or exaggerated cognitive aging effect, the onset of which may have precipitated the illness presentation in patients at a later age. This is consistent with evidence of accelerated and premature cognitive and brain aging effects in schizophrenia (Harvey & Rosenthal, 2018; Koutsouleris et al., 2014). Nevertheless, if premature aging effects were affecting cognitive functions more globally, we would expect to have seen an even earlier decline in schizophrenia of the other cognitive measures that do show an age-related decline in both HCs and patients, including processing speed and verbal fluency that show parallel inverted U-curve relationships with age in both groups. Thus, aging effects alone cannot explain the specificity of the age-related trajectory with relatively poorer functioning in the late-onset group on verbal memory tasks compared to the age effects on the other cognitive tasks.

A fourth possibility is an interaction between a neurodevelopmental immaturity of these functions and related brain areas and networks with the onset of a premature aging effect. This model could explain why a decrease in late-maturing cognitive functions is seen both in early-onset patients and in late-onset patients. There is support for a relationship between early neurodevelopmental delays in childhood and later decline of cognitive functioning in adulthood in the Dunedin Birth Cohort (Reichenberg et al., 2010). The Northern Finland birth cohort also found an inverse relationship between age of attainment of motor skills in infancy and later decline in memory in schizophrenia (Murray et al., 2006). These findings suggest a coupling between early neurodevelopment and later degeneration, possibly representing temporally distinct reflections of the same underlying processes in schizophrenia (Kobayashi et al., 2014). Although our study is cross-sectional and cannot directly show evidence of decline, our results may support a model of possible premature age-related loss of specific cognitive functions that appears to be dependent on the timing of maturational processes. This result adds to the findings by Kobayashi et al (2014), suggesting that early pathogenic neurodevelopmental processes may be further linked to the timing of cognitive maturational processes in adolescence and adulthood, possibly inducing or interacting with pathogenic processes involved in a premature onset of age-related cognitive decline in schizophrenia.

Of the four possible models discussed above, only the interaction between the timing of maturational processes with premature aging effects appears to sufficiently explain the pattern of results in the current study.

Strengths and limitations

A strength of the current study was that the impact of age was determined at illness onset, and was not established post-hoc, as has been done in several previous studies (e.g. Tuulio-Henriksson et al., 2004; White et al., 2006). Importantly, all patients were antipsychotic-naïve, excluding the possible impact of medication and the sample size for this group of patients was relatively large. The age-matched HCs enabled the direct comparison of AIO trajectories on cognition in patients relative to the age trajectories in healthy people. Another strength was that the same cognitive test battery (BACS) was used to assess specific cognitive functions across the age-span from adolescence to adulthood, which has rarely been done in comparative studies of EOS and AOS patients. This uniformity was not possible regarding the IQ assessments, as age-relevant versions of the Wechsler intelligence scales were used. Nevertheless, further studies are warranted, preferably using a more specific neuropsychological test battery allowing for delineation of sub-functions that have shown maturational peaks at different ages throughout adolescence and adulthood (such as e.g. the Cambridge Neuropsychological Test Automated Battery) (De Luca et al., 2003; Luciana & Nelson, 1998).

Compared to several other relevant first-episode cohorts, the age-span was relatively large in this study, with age ranging from 12 to 43 years. Nevertheless, only a few patients presented with an illness onset after age 40 years, reflecting the distribution of AIO, but limiting the conclusions that can be drawn at that older part of the age spectrum. Despite the relatively low number of patients with an older AIO and the related risk of type-2 errors, the quadratic age effects on verbal memory tasks were highly significant, suggesting a robust effect. The diagnostic distribution of schizophrenia and schizoaffective disorder differed between adolescent and adult patients, and was strongly associated with sex. Because of collinearity with sex, diagnosis (schizophrenia or

https://doi.org/10.1017/S0033291720000409 Published online by Cambridge University Press

Table 3. Separate group analyses of effects of age on verbal memory and verbal working memory

Dependent variable	Parameter	*B*	Std. error	*t*	Sig.	95% confidence interval
Parameter estimates patients						
Verbal memory	Intercept	49.711	3.218	15.446	<0.0001*	43.349–56.073
	Age	0.897	0.195	4.605	<0.0001*	0.512–1.281
	Age^2	−0.078	0.016	−4.824	<0.0001*	−0.11 to −0.046
	(Sex = 0)	0.49	4.467	0.11	0.913	−8.341 to 9.321
	(Parental SES = 1)	4.396	4.105	1.071	0.286	−3.718 to 12.51
	(Parental SES = 2)	1.665	3.61	0.461	0.645	−5.472 to 8.801
	(Sex = 0) × (Parental SES = 1)	−1.015	5.382	−0.189	0.851	−11.654 to 9.623
	(Sex = 0) × (Parental SES = 2)	−2.286	5.018	−0.455	0.649	−12.206 to 7.635
Digit sequencing	Intercept	19.113	1.462	13.075	<0.0001*	16.223–22.002
	Age	0.43	0.088	4.858	<0.0001*	0.255–0.604
	Age^2	−0.029	0.007	−3.905	0.0001*	−0.043 to −0.014
	(Sex = 0)	2.049	2.029	1.01	0.314	−1.963 to 6.06
	(Parental SES = 1)	2.04	1.864	1.094	0.276	−1.646 to 5.725
	(Parental SES = 2)	1.473	1.64	0.898	0.37	−1.768 to 4.714
	(Sex = 0) × (Parental SES = 1)	−4.16	2.444	−1.702	0.091	−8.992 to 0.672
	(Sex = 0) × (Parental SES = 2)	−4.321	2.279	−1.896	0.06	−8.827 to 0.185
Parameter estimates HCs						
Verbal memory	Intercept	49.086	3.169	15.491	<0.0001*	42.826–55.347
	Age	0.498	0.179	2.787	0.006*	0.145–0.851
	Age^2	−0.021	0.014	−1.551	0.123	−0.048 to 0.006
	(Sex = 0)	6.485	4.828	1.343	0.181	−3.054 to 16.024
	(Parental SES = 1)	5.631	3.554	1.584	0.115	−1.391 to 12.653
	(Parental SES = 2)	7.432	3.56	2.088	0.039*	0.398–14.466
	(Sex = 0) × (S Parental SES = 1)	−1.939	5.226	−0.371	0.711	−12.265 to 8.386
	(Sex = 0) × (Parental SES = 2)	−6.222	5.342	−1.165	0.246	−16.777 to 4.332
Digit sequencing	Intercept	19.753	1.261	15.67	<0.0001*	17.262–22.243
	Age	0.228	0.071	3.208	0.002*	0.088–0.368
	Age^2	−0.005	0.005	−0.992	0.323	−0.016 to 0.005
	(Sex = 0)	2.828	1.921	1.473	0.143	−0.966 to 6.623
	(Parental SES = 1)	2.905	1.414	2.055	0.042*	0.112–5.698
	(Parental SES = 2)	3.384	1.416	2.389	0.018*	0.586–6.182
	(Sex = 0) × (Parental SES = 1)	−3.542	2.079	−1.704	0.09	−7.65 to 0.565
	(Sex = 0) × (Parental SES = 2)	−5.17	2.125	−2.433	0.016*	−9.369 to −0.971

Parental SES, parental socioeconomic status (1 = high SES, 2 = middle SES, 3 = low SES); group, patients and controls (0 = patients; 1 = HCs); sex (0 = female, 1 = male).
Age and age^2 were centered in all analyses.
*Significant results.

schizoaffective disorder) could not be included as a covariate in the analyses. Because this was a cross-sectional study, we cannot answer if the relatively lower functioning in verbal memory tasks in early- and late-onset patients was a precipitating factor in bringing about the illness onset; or if both lower verbal memory functions and clinical illness presentation may primarily be seen as reflecting the same underlying illness processes. Also, since this was a cross-sectional study, we do not know if the patients with illness onset in young adulthood will show a premature age-related decline in these verbal memory functions when they reach the same age as the older-onset patients.

Conclusions

Our findings suggest that some cognitive functions that show protracted maturation into adulthood, such as the verbal memory and verbal working memory functions assessed in this study may be particularly impaired in both early- and late-schizophrenia

https://doi.org/10.1017/S0033291720000409 Published online by Cambridge University Press

onset. Our findings also indicate a potential interaction between the timing of neurodevelopmental maturation and a possible premature age effect in late-onset schizophrenia. Based on the results of this study, future research should aim to examine how the timing of normal developmental trajectories of cognitive functions impacts the profile and severity of cognitive deficits in schizophrenia. Our results further point toward examining this issue across wide age ranges, and to examine the possible links between early neurodevelopment and later age-related decline.

Acknowledgements. We thank patients and controls for participating in the study and the participating mental health centers. We thank research staff for carrying out some of the cognitive assessments.

Financial support. PECANS1 and 2 studies were funded by independent grants from the Lundbeck Foundation (R25-A2701; R13-A1349 and R155-2013-16337), and partially financed by the Mental Health Services in the Capital Region of Denmark, the University of Copenhagen; Marie and Krogh Fund (726290); Wørzner Foundation, Gangsted Foundation and a Gerhard Lind scholarship (726261). Prof. Pantelis was supported by an NHMRC Senior Principal Research Fellowship (1105825) and by a grant from the Lundbeck Foundation (R246-2016-3237). The TEA trial was funded by the following public and private funds: The National Research Council for Health and Disease Foundation for Health Promotion (271-07-0066); Tryg Foundation (7-09-02020; 7-11-0899; 7-12-0848 and 110905); AP Møller Foundation; Rosalie Petersens Foundation; Stevn and Rindom Foundation; Foundation for the Promotion of Medical Science; The Capital Region Psychiatric Research Foundation; Region of Southern Denmark Research Foundation; Danish Psychiatric Research Educational Fund; Psychiatry Foundation; Foundation of 17-12-1981; Psychiatric Research Foundation Region Zealand; Capital Region Strategic Research Foundation; Knud og Dagny Andresens Foundation; Psychiatric Research Foundation of 1967; The Capital Region Research Foundation; Dr Sofus Carl Emil Friis and Hustru Olga Friis Scholarship; Tømrerhandler Johannes Fogs Foundation; Brdr Hartmanns Foundation; Aase and Ejnar Danielsens Foundation; Jacob Madsen and wife Olga Madsens Foundation; CC Klestrup and wife Scholarship; Lundbeck Foundation Scholarship and Tømrermester Jørgen Holm and wife Elisas Scholarship (48709/pov).

Conflict of interest. The authors report no conflicts of interest relevant to this work.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

Andre, J., Picchioni, M., Zhang, R., & Toulopoulou, T. (2016). Working memory circuit as a function of increasing age in healthy adolescence: A systematic review and meta-analyses. *NeuroImage. Clinical*, *12*, 940–948.

Axelrod, B. N. (2002). Validity of the Wechsler abbreviated scale of intelligence and other very short forms of estimating intellectual functioning. *Assessment*, *9*, 17–23.

Biswas, P., Malhotra, S., Malhotra, A., & Gupta, N. (2006). Comparative study of neuropsychological correlates in schizophrenia with onset in childhood, adolescence and adulthood. *European Child & Adolescent Psychiatry*, *15*, 360–366.

Bojesen, K. B., Ebdrup, B. H., Jessen, K., Sigvard, A., Tangmose, K., Edden, R. A. E., … Glenthøj, B. Y. (2019). Treatment response after 6 and 26 weeks is related to baseline glutamate and GABA levels in antipsychotic-naïve patients with psychosis. *Psychological Medicine*, 1–12.

Conklin, H. M., Luciana, M., Hooper, C. J., & Yarger, R. S. (2007). Working memory performance in typically developing children and adolescents: Behavioral evidence of protracted frontal lobe development. *Developmental Neuropsychology*, *31*, 103–128.

De Luca, C. R., Wood, S. J., Anderson, V., Buchanan, J. A., Proffitt, T. M., Mahony, K., & Pantelis, C. (2003). Normative data from the CANTAB. I: Development of executive function over the lifespan. *Journal of Clinical and Experimental Neuropsychology*, *25*, 242–254.

Diamond, A. (2002). Normal development of prefrontal cortex from birth to young adulthood: Cognitive functions, anatomy, and biochemistry. In D. T. Stuss and R. T. Knight (Eds.), *Principles of frontal lobe function* (pp. 466–503). Oxford: Oxford University Press.

Egeland, J. (2015). Measuring working memory with digit span and the letter-number sequencing subtests from the WAIS-IV: Too low manipulation load and risk for underestimating modality effects. *Applied Neuropsychology: Adult*, *22*, 445–451.

Eggers, C. (1999). Some remarks on etiological aspects of early-onset schizophrenia. *European Child and Adolescent Psychiatry*, *8*(Suppl 1), I1–I4.

Finn, A. S., Kalra, P. B., Goetz, C., Leonard, J. A., Sheridan, M. A., & Gabrieli, J. D. E. (2016). Developmental dissociation between the maturation of procedural memory and declarative memory. *Journal of Experimental Child Psychology*, *142*, 212–220.

Frangou, S. (2010). Cognitive function in early onset schizophrenia: A selective review. *Frontiers in Human Neuroscience*, *3*, 79.

Frangou, S. (2013). Neurocognition in early-onset schizophrenia. *Child and Adolescent Psychiatric Clinics of North America*, *22*, 715–726.

Gogtay, N., Vyas, N. S., Testa, R., Wood, S. J., & Pantelis, C. (2011). Age of onset of schizophrenia: Perspectives from structural neuroimaging studies. *Schizophrenia Bulletin*, *37*, 504–513.

Harris, M. J., & Jeste, D. V. (1988). Late-onset schizophrenia: An overview. *Schizophrenia Bulletin*, *14*, 39–55.

Harvey, P. D., & Rosenthal, J. B. (2018). Cognitive and functional deficits in people with schizophrenia: Evidence for accelerated or exaggerated aging? *Schizophrenia Research*, *196*, 14–21.

Howard, R., Rabins, P. V., Seeman, M. V., & Jeste, D. V. (2000). Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: An international consensus. *The American Journal of Psychiatry*, *157*, 172–178.

Iverson, G. L., & Tulsky, D. S. (2003). Detecting malingering on the WAIS-III. Unusual digit span performance patterns in the normal population and in clinical groups. *Archives of Clinical Neuropsychology*, *18*, 1–9.

Jensen, K. G., Correll, C. U., Rudå, D., Klauber, D. G., Stentebjerg-Olesen, M., Fagerlund, B., … Pagsberg, A. K. (2017). Pretreatment cardiometabolic status in youth with early-onset psychosis: Baseline results from the TEA trial. *Journal of Clinical Psychiatry*, *78*, e1035–e1046.

Jessen, K., Rostrup, E., Mandl, R. C. W., Nielsen, MØ, Bak, N., Fagerlund, B., … Ebdrup, B. H. (2019). Cortical structures and their clinical correlates in antipsychotic-naïve schizophrenia patients before and after 6 weeks of dopamine D2/3 receptor antagonist treatment. *Psychological Medicine*, *49*, 754–863.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*, 261–276.

Keefe, R. S., Harvey, P. D., Goldberg, T. E., Gold, J. M., Walker, T. M., Kennel, C., & Hawkins, K. (2008). Norms and standardization of the Brief Assessment of Cognition in Schizophrenia (BACS). *Schizophrenia Research*, *102*, 108–115.

Keefe, R. S., Poe, M., Walker, T. M., & Harvey, P. D. (2006). The relationship of the Brief Assessment of Cognition in Schizophrenia (BACS) to functional capacity and real-world functional outcome. *Journal of Clinical and Experimental Neuropsychology*, *28*, 260–269.

Khandaker, G. M., Barnett, J. H., White, I. R., & Jones, P. B. (2011). A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. *Schizophrenia Research*, *132*, 220–227.

Kobayashi, H., Isohanni, M., Jääskeläinen, E., Miettunen, J., Veijola, J., Haapea, M., … Murray, G. K. (2014). Linking the developmental and degenerative theories of schizophrenia: Association between infant development and adult cognitive decline. *Schizophrenia Bulletin*, *40*, 1319–1327.

Koutsouleris, N., Davatzikos, C., Borgwardt, S., Gaser, C., Bottlender, R., Frodl, T., … Meisenzahl, E. (2014). Accelerated brain aging in schizophrenia and beyond: A neuroanatomical marker of psychiatric disorders. *Schizophrenia Bulletin*, *40*, 1140–1153.

https://doi.org/10.1017/S0033291720000409 Published online by Cambridge University Press

Kravariti, E., Morris, R. G., Rabe-Hesketh, S., Murray, R. M., & Frangou, S. (2003a). The Maudsley Early-Onset Schizophrenia Study: Cognitive function in adolescent-onset schizophrenia. *Schizophrenia Research*, *65*, 95–103.

Kravariti, E., Morris, R. G., Rabe-Hesketh, S., Murray, R. M., & Frangou, S. (2003b). The Maudsley early onset schizophrenia study: Cognitive function in adolescents with recent onset schizophrenia. *Schizophrenia Research*, *61*, 137–148.

Lebel, C., Treit, S., & Beaulieu, C. (2019). A review of diffusion MRI of typical white matter development from early childhood to young adulthood. *NMR in Biomedicine*, *32*, e3778.

Leucht, S., Kane, J. M., Kissling, W., Hamann, J., Etschel, E., & Engel, R. R. (2005). What does the PANSS mean? *Schizophrenia Research*, *79*, 231–238.

Luciana, M., & Nelson, C. A. (1998). The functional emergence of prefrontally-guided working memory systems in four- to eight-year-old children. *Neuropsychologia*, *36*, 273–293.

Maglione, J. E., Thomas, S. E., & Jeste, D. V. (2014). Late-onset schizophrenia: Do recent studies support categorizing LOS as a subtype of schizophrenia? *Current Opinion in Psychiatry*, *27*, 173–178.

Moises, H. W., Zoega, T., & Gottesman, I. I. (2002). The glial growth factors deficiency and synaptic destabilization hypothesis of schizophrenia. *BMC Psychiatry*, *2*, 8.

Murray, G. K., Jones, P. B., Moilanen, K., Veijola, J., Miettunen, J., Cannon, T. D., & Isohanni, M. (2006). Infant motor development and adult cognitive functions in schizophrenia. *Schizophrenia Research*, *81*, 65–74.

Nielsen, M. O., Rostrup, E., Wulff, S., Bak, N., Lublin, H., Kapur, S., & Glenthoj, B. (2012). Alterations of the brain reward system in antipsychotic naive schizophrenia patients. *Biological Psychiatry*, *71*, 898–905.

Pagsberg, A. K., Jeppesen, P., Klauber, D. G., Jensen, K. G., Ruda, D., Stentebjerg-Olesen, M., … Fagerlund, B. (2014). Quetiapine versus aripiprazole in children and adolescents with psychosis – protocol for the randomised, blinded clinical Tolerability and Efficacy of Antipsychotics (TEA) trial. *BMC Psychiatry*, *14*, 199.

Pagsberg, A. K., Jeppesen, P., Klauber, D. G., Jensen, K. G., Rudå, D., Stentebjerg-Olesen, M., … Fink-Jensen, A. (2017). Quetiapine extended release versus aripiprazole in children and adolescents with first-episode psychosis: The multicentre, double-blind, randomised tolerability and efficacy of antipsychotics (TEA) trial. *The Lancet Psychiatry*, *4*, 605–618.

Pantelis, C., Wannan, C., Bartholomeusz, C. F., Allott, K., & McGorry, P. D. (2015). Cognitive Intervention in Early Psychosis – Preserving abilities versus remediating deficits. *Current Opinion in Behavioural Sciences*, *4*, 63–72.

Pantelis, C., Wood, S. J., Proffitt, T. M., Testa, R., Mahony, K., Brewer, W. J., … McGorry, P. D. (2009a). Attentional set-shifting ability in first-episode and established schizophrenia: Relationship to working memory. *Schizophrenia Research*, *112*, 104–113.

Pantelis, C., Yücel, M., Bora, E., Fornito, A., Testa, R., Brewer, W. J., … Wood, S. J. (2009b). Neurobiological markers of illness onset in psychosis and schizophrenia: The search for a moving target. *Neuropsychology Review*, *19*, 385–398.

Pantelis, C., Yucel, M., Wood, S. J., McGorry, P. D., & Velakoulis, D. (2003). Early and late neurodevelopmental disturbances in schizophrenia and their functional consequences. *Australian and New Zealand Journal of Psychiatry*, *37*, 399–406.

Pedersen, C. B., Mors, O., Bertelsen, A., Waltoft, B. L., Agerbo, E., McGrath, J. J., … Eaton, W. W. (2014). A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. *JAMA Psychiatry*, *71*, 573.

Rajji, T. K., Ismail, Z., & Mulsant, B. H. (2009). Age at onset and cognition in schizophrenia: Meta-analysis. *The British Journal of Psychiatry*, *195*, 286–293.

Reichenberg, A., Caspi, A., Harrington, H., Houts, R., Keefe, R. S. E., Murray, R. M., … Moffitt, T. E. (2010). Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: A 30-year study. *The American Journal of Psychiatry*, *167*, 160–169.

Rhinewine, J. P., Lencz, T., Thaden, E. P., Cervellione, K. L., Burdick, K. E., Henderson, I., … Kumra, S. (2005). Neurocognitive profile in adolescents with early-onset schizophrenia: Clinical correlates. *Biological Psychiatry*, *58*, 705–712.

Simmonds, D. J., Hallquist, M. N., & Luna, B. (2017). Protracted development of executive and mnemonic brain systems underlying working memory in adolescence: A longitudinal fMRI study. *NeuroImage*, *157*, 695–704.

Stentebjerg-Olesen, M., Pagsberg, A. K., Fink-Jensen, A., Correll, C. U., & Jeppesen, 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*, 410–427.

Tamnes, C. K., Walhovd, K. B., Engvig, A., Grydeland, H., Krogsrud, S. K., Østby, Y., … Fjell, A. M. (2014). Regional hippocampal volumes and development predict learning and memory. *Developmental Neuroscience*, *36*, 161–174.

Tamnes, C. K., Walhovd, K. B., Grydeland, H., Holland, D., Østby, Y., Dale, A. M., & Fjell, A. M. (2013). Longitudinal working memory development is related to structural maturation of frontal and parietal cortices. *Journal of Cognitive Neuroscience*, *25*, 1611–1623.

Thompson, P. M., Vidal, C., Giedd, J. N., Gochman, P., Blumenthal, J., Nicolson, R., … Rapoport, J. L. (2001). Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. *Proceedings of the National Academy of Sciences of the USA*, *98*, 11650–11655.

Tuulio-Henriksson, A., Partonen, T., Suvisaari, J., Haukka, J., & Lonnqvist, J. (2004). Age at onset and cognitive functioning in schizophrenia. *British Journal of Psychiatry*, *185*, 215–219.

Vahia, I. V., Palmer, B. W., Depp, C., Fellows, I., Golshan, S., Kraemer, H. C., & Jeste, D. V. (2010). Is late-onset schizophrenia a subtype of schizophrenia? *Acta Psychiatrica Scandinavica*, *122*, 414–426.

Van Assche, L., Morrens, M., Luyten, P., Van de Ven, L., & Vandenbulcke, M. (2017). The neuropsychology and neurobiology of late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: A critical review. *Neuroscience and Biobehavioral Reviews*, *83*, 604–621.

Wechsler, D. (1991). *Manual for the Wechsler intelligence scale for children – third edition* (*WISC-III*). San Antonio, Texas: The Psychological Corporation.

Wechsler, D. (1997). *Manual for the Wechsler adult intelligence scale – third edition* (*WAIS-III*). San Antonio, Texas: The Psychological Corporation.

Wechsler, D. (2003). *WISC-IV: Administration and scoring manual*. San Antonio, Texas: Psychological Corporation.

Wechsler, D. (2008). *WAIS-IV administration and scoring manual*. San Antonio, Texas: Psychological Corporation.

White, T., Ho, B. C., Ward, J., O'Leary, D., & Andreasen, N. C. (2006). Neuropsychological performance in first-episode adolescents with schizophrenia: A comparison with first-episode adults and adolescent control subjects. *Biological Psychiatry*, *60*, 463–471.

Wing, J. K., Babor, T., Brugha, T., Burke, J., Cooper, J. E., Giel, R., … Sartorius, N. (1990). SCAN: Schedule for clinical assessment in neuropsychiatry. *Archives of General Psychiatry*, *47*, 589–593.

Yu, Q., McCall, D. M., Homayouni, R., Tang, L., Chen, Z., Schoff, D., … Ofen, N. (2018). Age-associated increase in mnemonic strategy use is linked to prefrontal cortex development. *NeuroImage*, *181*, 162–169.

Zipursky, R. B., Reilly, T. J., & Murray, R. M. (2013). The myth of schizophrenia as a progressive brain disease. *Schizophrenia Bulletin*, *39*, 1363–1372.