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ORIGINAL CONTRIBUTION

Formal thought disorder in autism spectrum disorder predicts future symptom severity, but not psychosis prodrome

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Abstract Formal thought disorder (FTD) is a disruption in the flow of thought, which is inferred from disorganisation of spoken language. FTD in autism spectrum disorders (ASD) might be a precursor of psychotic disorders or a manifestation of ASD symptom severity. The current longitudinal study is a seven-year follow-up of 91 individuals aged 5–12 years with ASD. We tested (1) whether childhood FTD predicted prodromal symptoms of psychosis in adolescence and (2) whether childhood FTD was associated with greater ASD symptom severity in adolescence. ASD symptom severity was assessed in childhood (T1) and 7 years later (T2), using the autism diagnostic observation schedule (ADOS). At T1, the Kiddie-Formal Thought Disorder Rating Scale (KFTDS) was used to measure symptoms of FTD. At T2, the prodromal questionnaire (PQ) was used to assess prodromal symptoms of psychosis. FTD at T1 did not predict prodromal symptoms of psychosis at T2 in children with ASD. FTD symptoms at T1, namely illogical thinking, predicted ASD symptom severity at T2 and this effect remained significant after controlling for T1 ASD symptom severity. In children with ASD, illogical thinking predicts severity of ASD symptoms in adolescence, but FTD does not predict prodromal symptoms of psychosis.

Keywords Autism spectrum disorder · Longitudinal study · Psychotic symptoms · Thought disorder · Psychopathology

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Introduction

Disordered speech is an important symptom of severe mental illnesses like schizophrenia and autism [1]. Disordered speech in these conditions can reflect a linguistic impairment, a cognitive impairment, or an abnormal integration of these functions for communication as in formal thought disorder (FTD) [1]. FTD has been defined as a disruption in the organisation and flow of thoughts, which is inferred from the disorganisation of spoken language i.e. as assessed using the Kiddie-Formal Thought Disorder rating Scale (KFTDS) [2, 3].

FTD has been viewed as an impaired ability to apply goal-directed behaviour in the language domain [4]. It has been established that FTD is associated with a wide variety of neuropsychological dysfunctions, including dysfunctions in sustained attention, working memory and sequencing [1, 5]. This association explains why FTD has been found in severe mental illness and in attention deficit and hyperactivity disorder (ADHD), as well as in neurological diseases like epilepsy [6]. Originally, based on Andreasen's scale [7], four types of FTD symptoms were discerned: illogical thinking, loose associations, poverty of content of speech and incoherence [8]. Later,

based on empirical studies, two of these types of FTD remained to be valid: loose associations and illogical thinking [9]. Loose associations were rated when the child changed the topic of conversation to a new and unrelated topic without preparing the listener for this change. Illogical thinking was rated when the child used causal utterances in an inappropriate way, and presented the listener with unfounded and inappropriate reasoning in non-causal utterances or when the child contradicted him/herself.

Formal thought disorder is regarded as a hallmark for childhood or adult onset schizophrenia [2, 5, 7, 9, 10] and as a marker of abnormal neurodevelopment in schizophrenia, indicated by the fact that school-aged children with schizophrenia show persistent high levels of illogical thinking and loose associations, whereas in typically developing school-aged children, there is a considerable decline of illogical thinking and loose associations [2]. FTD is also regarded as a manifestation of the genetic vulnerability to schizophrenia, which was underscored by the finding that subtle forms of FTD were present in first-degree relatives of patients with schizophrenia [11, 12].

However, FTD is not only restricted to patients who might develop psychosis, but it is also a symptom of autism spectrum disorders (ASD) [13]. Some older studies showed that certain forms of FTD (i.e. neologisms, idiosyncratic language or lack of cohesion) were very common in ASD [14, 15]. Moreover, high levels of FTD, as assessed by KFTDS, have been found in ASD, and were related to language abnormalities [13, 16]. In one study, half of the ASD participants showed two or more illogical utterances, and 30 % showed two or more loose associations [13]. It was found that the amount of loose associations correlated positively with total scores on the Autism Diagnostic Observation Schedule (ADOS) [13].

The relationship between ASD and schizophrenia is complicated. Historically, some authors have considered autism and schizophrenia as two independent disorders [17–19], whereas others have considered autism as an early precursor of schizophrenia [20]. Nowadays, ASD are considered to be a developmental disorder without a relation to schizophrenia or other psychotic disorders, although this remains a point of debate.

There are clear differences between core autism and core schizophrenia and the rate of comorbidity is very low [21, 22]. However, within the broader-defined autism spectrum some children go on to develop psychosis or broader-defined schizophrenia spectrum disorder. For instance, longitudinal studies revealed that 6–29 % of individuals diagnosed with ASD in childhood developed schizophrenia later in life [23, 24] and it was found that ASD were present before onset of the psychotic disorder in 25 % of a cohort of children diagnosed with early onset schizophrenia [25]. A distinct subgroup of children with ASD characterised by the presence of FTD and a high vulnerability to develop schizophrenia spectrum disorder has been suggested, referred to as multiple complex developmental disorder (MCDD). Follow-up of children diagnosed with MCDD into adulthood demonstrated that 17 % developed schizophrenia and 58 % schizotypal personality disorder [26, 27].

In the last decade, there has been an impressive increase of research into the developmental aspects of psychosis and more specifically research aimed at the definition of criteria to identify young people at immanent risk for developing psychosis. Yung and McGorry [28] distinguished three groups, comprising children with “ultra high risk” (UHR) for psychosis, namely (1) a vulnerability group, defined as having schizotypal personality disorder or a first-degree relative with psychotic disorder, accompanied by a significant deterioration in social functioning in the last year; (2) a group with attenuated psychotic symptoms (APS) and (3) a group with brief, limited intermittent psychotic symptoms. This UHR approach has resulted in measures, including the prodromal questionnaire (PQ) [29] and the composite assessment of at risk mental states (CAARMS) [30]. The latter predicts the outbreak of psychosis with probabilities of 22 % within 1 year and 36 % within 3 years [31]. The incidence rate of first episode psychosis in the general population is about 0.09 % per year [32, 33], and therefore it can be concluded that these UHR patients have a 405-fold risk of becoming psychotic within a year relative to an average boy or girl from the same age [34]. Recently, it was shown that UHR patients who converted to psychosis showed higher rates of FTD before the onset of psychosis than a group UHR patients, who did not convert to psychosis and this latter group showed higher rates of FTD than a group of typically developing controls [3]. Using the KFTDS [8] as a measure for FTD, illogical thinking predicted conversion to psychosis in 70.5 % of the cases, whereas the scale of prodromal symptoms predicted only 35 % of the cases [3]. In other words, FTD may be an early and reliable predictor for later psychosis in UHR patients.

The presence of FTD both in ASD and in individuals, who will develop schizophrenia and the fact that some ASD patients develop psychotic disorders, raises the question, whether FTD symptoms in ASD are a sign of impending psychosis or a manifestation of language and thought problems inherent to ASD. Summarizing, FTD can be a precursor of psychosis, a symptom of ASD and might be predictive of the development of psychosis in adolescence in children with ASD.

Aims of the study

The current study is a seven-year follow-up of 91 individuals, aged 6–12 years old, diagnosed with ASD at T1, with the aims to determine whether: (1) childhood FTD predicted prodromal symptoms of psychosis in adolescence and (2) childhood FTD was associated with ASD symptom severity in adolescence. Moreover, the effects of age, IQ, and comorbid psychopathology were explored.

Method

Participants and procedure

At the first assessment (T1) participants visited the outpatient's department of child and adolescent psychiatry of Erasmus University Medical Center Rotterdam in the Netherlands. The inclusion criteria were (a) a clinical DSM-IV-TR [35] classification of ASD, and (b) parents were able to communicate in the Dutch language. Exclusion criterion was (a) the presence of severe neurological or physical problems (e.g. blindness) [36]. A total of 142 children received a DSM-IV-TR [35] clinical diagnosis of ASD, obtained by a multi-disciplinary team based on elaborate assessment of early development, semi-structured interviews and parental questionnaires, psychiatric observation of the child in a one-to-one situation, psychological assessment, medical history, and school information [36]. Seventeen individuals (12 %) met DSM-IV-TR criteria for autistic disorder, 11/142 (7.7 %) met criteria for asperger syndrome, and 114/142 (80.3 %) received a diagnosis of pervasive developmental disorder not otherwise specified (PDD-NOS); $n = 142$; mean age 8.9 years, SD 1.81 years; Boys 88.1 %; mean IQ 91.2, SD 18. How these DSM-IV-TR PDD classifications relate to the DSM 5 classification of ASD still needs to be further clarified [37, 38]. To connect to the DSM 5 recommendations as closely as possible, we combined all PDD sub classifications into one category of ASD.

Comorbid diagnoses were assessed, using the Diagnostic Interview Schedule for Children (DISC) [39]. The most common comorbid disorders were anxiety disorders ($n = 40$; 44 %); ADHD ($n = 30$; 33 %); oppositional defiant disorder (ODD) ($n = 20$; 22 %) and mood disorder ($n = 8$; 8.8 %).

All participants with a clinical diagnosis of ASD at T1 ($n = 142$) were eligible for the follow-up study (T2). Participants were then 12–19 years old. The average time to follow-up was 7.17 years. For these children, KFTDS and ADOS data on T1 were available. To assess prodromal symptoms of psychosis at T2, the PQ was completed by the participants and when they scored above the cut-off score (>=18), a complete CAARMS was performed. The ADOS was administered again to assess ASD symptoms at T2. In total, 114 children agreed to participate in the follow-up study (response rate 80.3 %) and 91 children had complete data at T2 (64.1 %).

Ethical aspects

At T1, parents/caretakers of the participating children signed informed consent forms prior to participation in the study. At Time 2, both parents and adolescents signed the informed consent forms. The Medical Ethics Committee of the Erasmus Medical Centre approved this study.

Materials

Formal thought disorder at T1

The KFTDS is considered as a reliable measure of FTD in children aged 7–18 years [8, 9]. The validity of the KFTDS has been established in children with ASD (13), with schizophrenia spectrum disorders [2, 9] and in children with ADHD [40]. Loose associations and illogical thinking have the highest clinical significance for childhood psychopathology, because they appear at high base rate in ASD and childhood-onset schizophrenia and at a much lower base rate in controls [4].

Children were presented two audio taped stories for which they were asked to answer questions in a standardized, structured way (i.e. "what did you like about this story?" or "do you think this a true story?"). Subsequently, the child was asked to make up his/her own story about one of four given topics (the incredible hulk, a witch, a disobedient child or an unhappy child). During this part of the test session, the investigator mainly made encouraging remarks, but could pose extra open-ended questions (i.e. "can you tell more?") when for instance the child was only giving limited or very short verbal responses, or when the child was hesitating to carry on. This took approximately 20–30 min, during which the speech samples were videotaped. A blind rater established the number of FTD signs. A total raw score was derived by summing frequency counts for illogical thinking and loose associations. To correct for the variability of speech elicited in different children, raw scores were divided by the number of utterances per minute, which yielded the final corrected Loose Associations and Illogical Thinking scores. Signs of FTD were scored according to KFTDS guidelines [8].

Caplan [8] determined clinical cut-off scores with optimal sensitivity and specificity. Scores above the cut-off point reflect a higher likelihood of pathology [8]. We used these dichotomized scores for the regression analyses,

because the dimensional variables Loose Associations and Illogical Thinking were not normally distributed. Continuous KFTDS scores were dichotomized as falling above or below the cut-off point. These cut-off scores are not available for children younger than 7 years, because below this age illogical thinking and loose associations appear at a much higher base rate and therefore these measures cannot be used to discriminate between normality and pathology [8, 9]. The inter-rater reliability was good: Caplan et al [8] reported a kappa of 0.77 for the total KFTDS score and in the present study, the kappa for the total KFTDS score was 0.78. One of the authors (EdB) was trained in KFTDS ratings by R. Caplan.

Prodromal symptoms at T2

The PQ [29] is designed to assess the presence and the severity of prodromal symptoms of psychosis using self-report and it serves to identify young people, with a minimum (mental) age of 12 years, at UHR for psychosis in an early stage. The PQ sums up 92 true or false statements about symptoms, which may manifest in the prodromal phase of psychosis. The PQ consists of a positive scale, measuring symptoms like ideas of reference, delusional ideas and perceptual illusions and a negative scale, measuring symptoms like decline in social functioning, passivity and withdrawn behaviour. A threshold of 18 on the PQ total score (positive and negative symptoms of psychosis) predicted UHR status with 90 % sensitivity and 38 % specificity [29] and a threshold of 14 on the PQ positive score predicted UHR status with 71 % sensitivity and 81 % specificity [29]. These thresholds were used in this study to describe severity of UHR symptoms. The PQ was also used as an outcome measure at T2 and for that goal dimensional scores on the PQ positive scale were assessed. We used the PQ positive scale, because 12 out of the 17 questions that pertain to the PQ negative scale bear crucial similarities with symptoms of ASD, leading to overrating of presumed prodromal symptoms (and loss of specificity) when using the PQ total score or the PQ negative score in an ASD population. Because scores of the PQ were not normally distributed, we used a root transformation, which resulted in a normal distribution. Participants with incomplete PQ data ($n = 23$; 21 %) were excluded from these analyses.

When the PQ total score exceeded or equalled 18, the CAARMS [30] was administered.The CAARMS, which is validated for children from 14 years onwards, uses strictly defined quantitative criteria to distinguish between full threshold psychosis, attenuated psychosis and no UHR. In this study, mean age of the participants who completed the CAARMS was 15.8 years, SD 1.8 years; range 13.0–19.6 years. In the CAARMS, psychotic symptoms are described under four main headings: unusual thoughts, non-bizarre ideas, perceptual disturbances and cognitive disorganisation.

ASD severity at T1 and T2

The ADOS (41) was administered at both time points. The ADOS provides a standardized context for an elaborate observation of ASD-related behaviours in the domains of social interaction, communication, and stereotyped behaviours and restricted interests. Lord et al. [41] showed that the psychometric properties of the ADOS are good with an excellent internal consistency. In the current study, at T1 ADOS, module 3 was used and at T2 ADOS, module 4 was administered. The items are scored on a 3-point scale from 0 (no evidence of abnormality related to autism) to 2 (definite evidence of abnormality). We used the ADOS scores in a dimensional way as proposed by Volkmar et al. [42]. Mean weighted scores were computed by adding all item scores (0, 1, or 2), and subsequently dividing these scores by the total number of items; thus yielding scores ranging between 0 and 2. We did not use ADOS calibrated severity scores, because at T2, module 4 of the ADOS was administered in a substantial number of cases and currently, there are no guidelines to translate module 4 scores into ADOS calibrated severity scores. The ADOS at T1 and at T2 were performed and scored by trained and certified clinicians and researchers, who were blind for the clinical diagnosis.

Putative covariates

Age, sex, IQ, co-occurring attention problems, anxious/depressed problems and the use of anti-psychotic medication were taken into account as possible confounding covariates. Age was taken into account as a covariate, because developmental aspects play a pivotal role in the manifestation of FTD and therefore FTD scores could correlate with age. Age was included as a possible confounder since prodromal symptoms of psychosis emerge in middle or late adolescence and therefore older adolescents are more often affected with prodromal symptoms of psychosis than younger adolescents [43]. Intelligence Quotient (IQ) was taken into account as possible covariate, because FTD might be more prominent in children with lower IQ's. At T1, IQ was measured with the Wechsler's Intelligence Scale for Children-Revised version (WISC-R) [44] and at T2 with the Wechsler's Abbreviated Scale for Intelligence (WASI). Co-occurring attention problems and anxious/depressed problems were assessed with the child behaviour checklist (CBCL) [45] Attention problems and the anxious/depressed problems subscales. This was done because comorbid attention problems [46] or internalizing

problems could increase the chance of developing psychosis for a youngster with ASD. The CBCL/4–18 [45], problem items are scored on a three-point scale (0 not true, 1 somewhat or sometimes true, 2 very true or often true), and were completed by the mother. The CBCL, attention problems subscale consists of 10 items, the anxious-depressed scale consists of 13 items. The psychometric qualities of the CBCL have been well established [45, 47].

The DISC [39] was used to assess correlations between DISC- diagnoses of ADHD, ODD, anxiety disorders, depression and the outcome variables of ADOS total scores at T2 and the PQ positive scale.

To investigate whether use of medication between time 1 and 2 influenced the development of prodromal symptoms in adolescence; an additional health care questionnaire was used [48]. At T2, parents were asked if their adolescents had used medication in the past 2 weeks. Anti-psychotics use was taken into account.

Statistical analyses

To check for the effects of attrition differences in age, sex, ASD subtype and mean IQ were calculated between the groups at T1 ($n = 142$) and at T2 ($n = 91$) and between the groups with complete data on the PQ ($n = 91$) and the part of T2 group without PQ data ($n = 23$).

For descriptive purposes, means, ranges and standard deviations were calculated at T1 and T2 for age, IQ, weighted ADOS total scores and PQ scores. KFTDS scores and CBCL, Attention Problems subscale scores were only assessed at T1 and PQ scores were only assessed at T2. To provide further descriptive information regarding psychotic symptoms at T2, frequencies of CAARMS scores were computed. For children participating on PQ and/or CAARMS complete age, intelligence range and mental age were calculated, because we used these measures in relatively young children.

To check which putative covariates needed to be included in the models, correlations were computed between each of these covariates (age; sex; IQ; CBCL: attention problems, anxious/depressed problems; DISC sections: ADHD, anxiety disorders, mood disorders; use of anti-psychotic medication) and the outcome variables (PQ and ADOS symptom severity). If one of these putative covariates showed a significant correlation with the predictor and with the outcome variable, we included this covariate in the subsequent multiple linear regression.

To investigate whether FTD during childhood predicted prodromal symptoms of psychosis during adolescence (Aim 1), multiple linear regression analyses were performed with the dichotomous KFTDS loose associations and illogical thinking scores as predictors and the PQ positive symptoms scale as the outcome variable.

To investigate whether FTD during childhood was associated with higher ASD symptom severity in adolescence (Aim 2), multiple linear regression analyses were performed with the dichotomous scores regarding loose associations and illogical thinking on the KFTDS as the predictors and the ADOS symptom severity score at T2 as the outcome.

Results

Descriptives

No statistically significant differences were found between participants at T1 and T2, regarding initial age, sex and ASD subtype. The mean IQ at T1 was 94.4 (SD 16.9), range 56–128. Nine participants scored below 70 at T1. The mean IQ at T2 was 100.6 (SD 17.0), range 58–135. Four participants scored below 70 at T2. Mean IQ at T2 was higher than mean IQ of this group at T1 (mean IQ T1 94.4 (SD 16.9), mean IQ T2 100.6 (SD 17.0), mean difference 6.2; $t = -5.69$; $df = 73$; $p < 0.01$).

An attrition analysis was performed, in which the participants who did not have complete PQ data at T2 were compared to the participants with complete PQ data at T2 on several features. The groups with and without complete PQ data at T2 did not differ significantly on age, sex, IQ, ADOS, or KFTDS scores ($p > 0.05$).

On the KFTDS, 55/91 (60.4 %) of the sample scored above the diagnostic threshold for illogical thinking at T1 and 15/91 (16.5 %) scored above the threshold for loose associations.

With regard to the PQ, in 32/91 (35.2 %) of the subjects, the total score equalled or exceeded 18 and subsequently the CAARMS was administered. In 22/91 (24.2 %) of the subjects, the PQ positive score scored equalled or exceeded 14 (all of the subjects with PQ positive scores above 14 scored also more than 18 on the PQ total scores). On the CAARMS, two patients met the criteria for attenuated psychosis, high-risk state, but none of these 32 patients with high PQ scores met the criteria for full threshold psychosis. These 32 patients, however, showed quite serious attenuated psychotic symptoms. Perceptual disturbances were present in 14 of these 32 subjects, unusual thought content in 13 subjects and non-bizarre ideas in 12 subjects. Eighteen participants (19.8 %) used anti-psychotic medication at T2 (Table 1).

Correlations with putative covariates

The predictor variables illogical thinking and loose associations did not show significant bivariate correlations with any of the comorbid DISC classifications (Illogical

Table 1 Descriptive information of the total sample at T1 and at T2 ($n = 91$)

	$N = 91$ N %
Male	82 (90.1 %)
ASD subtype: AD	9 (9.9 %)
ASD subtype: AS	7 (7.7 %)
ASD subtype PDD-NOS	75 (82.4 %)
T1 KFTDS, total score above threshold	63/91 (69 %)
T1 KFTDS, loose associations above threshold	15 (16.5 %)
T1 KFTDS, illogical thinking above threshold	55 (60.4 %)
T2 PQ, total score ≥18	32/91 (35.2 %)
T2 PQ, positive score ≥14	22/91 (24.2 %)
T2 use of anti-psychotics	18 (19.8 %)

	Mean (SD)	Range
T1 chronological age (years)	8.82 (1.84)	5.08–12.64
T2 chronological age (years)	16.03 (1.97)	12.85–20.87
Total IQ T1	94.4(16.91)	56–128
Total IQ T2	100.58 (16.95)	58–135
ADOS T1 raw total scores	9.67 (5.04)	0–31
ADOS T2 weighted score per item	0.73 (0.39)	0.14–1.93
PQ total score T2	20 (16.69)	1–75

AD autistic disorder, *ADOS raw total scores* autism diagnostic observation schedule, total raw scores of the sum of social affect and restricted repetitive behaviour domain of module 3, *ADOS* weighted score total raw scores of the ADOS divided by the number of items on module 3 and module 4, *AS* asperger syndrome, *IQ* intelligence quotient, *PDD-NOS* pervasive developmental disorder not otherwise specified, *SD* standard deviation

Thinking with depression ($\rho = 0.04; p = 0.76$), with anxiety disorder ($\rho = 0.06$; $p = 0.60$), with DISC ADHD ($\rho = 0.15; p = 0.22$) and loose associations with depression ($\rho = 0.13$; $p = 0.31$), with anxiety disorder ($\rho = 0.08$; $p = 0.53$), with DISC ADHD ($\rho = 0.23; p = 0.07$)).

Only the use of anti-psychotic medication showed a significant correlation with the outcome variable PQ positive scale at T2 ($r = 0.27$; $p < 0.01$), whereas age ($r = -0.05; p = 0.69$), sex ($\rho = 0.15, p = 0.16$), IQ ($r = 0.05$, $p = 0.67$), CBCL attention problems ($r = 0.05; p = 0.67$), CBCL anxious-depressed ($r = 0.01$; $p = 0.90$), DISC depression ($\rho = 0.12$; $p = 0.28$), DISC anxiety disorder ($\rho = 0.02; p = 0.85$), DISC ADHD ($\rho = 0.09; p = 0.43$) did not show a significant correlation with the PQ positive scale at T2. Use of anti-psychotic medication at T2 did not show a significant correlation with the predictor loose associations ($r = 0.08$; $p = 0.52$) or illogical thinking ($r = 0.19$, $p = 0.11$). Therefore, in the multiple linear regression analysis with the PQ positive scale at T2 as outcome measure and KFTDS illogical thinking and loose associations as predictors, the use of anti-psychotic medication was not taken into account as a covariate.

Table 2 Multiple regression using scores on prodromal questionnaire (PQ) positive symptoms scale at T2 as outcome measure and illogical thinking/loose associations as predictors ($N = 69$)

Variable	*B*	SE	*t* value	CI-L	CI-U	*p*	*R2*
Model						0.66	0.04
Illogical	0.03	0.06	0.48	−0.09	0.15	0.63	
Loose Ass.	0.04	0.07	0.67	−0.09	0.18	0.51	

B regression coefficient, *SE* standard error, *t* *t* test value, *CI-L* 95 % confidence interval lower bound, *CI-U* 95 % confidence interval upper bound, *p* significance value, *R2* multiple correlation coefficient squared

The putative covariates sex ($\rho = <0.01$; $p = 0.97$), IQ ($r = 0.17$; $p = 0.13$), comorbid CBCL attention problems ($r = -0.07$; $p = 0.57$), CBCL anxious-depressed ($r = -0.18; p = 0.11$), DISC depression ($\rho = -0.09; p = 0.43$), DISC anxiety disorder ($\rho = 0.15$; $p = 0.16$), DISC internalizing disorder ($\rho = -0.19$; $p = 0.07$), DISC ADHD ($\rho = 0.19; p = 0.08$) did not show a significant correlation with the ADOS symptom severity score at T2, whereas age did ($r = -0.21$; $p = 0.03$). Moreover, age was negatively correlated with the dichotomous predictor illogical thinking ($\rho = -0.29; p = 0.01$) and with loose associations ($\rho = -0.30$; $p = 0.01$). Therefore, in the multiple regression analyses with the ADOS symptom severity score at T2 as the outcome variable, age was entered as a covariate.

Main effects: FTD as a predictor of prodromal symptoms

As shown in Table 2, KFTDS scores on illogical thinking ($t = 0.48$, $p = 0.63$) and loose associations ($t = 0.67$, $p = 0.51$) did not significantly predict scores on the PQ positive scale. Excluding the nine participants for whom the use of PQ was not validated due to a mental age at T2 lower than 12 years old did not change the results. As found in the total sample, illogical thinking ($t = 0.06$, $p = 0.95$) and loose associations ($t = 0.53$, $p = 0.60$) did not significantly predict scores on PQ positive scale in this subsample.

When taking the covariate, use of anti-psychotics, into account, this covariate did predict scores on PQ positive scale ($t = 2.54$; $p = 0.01$; 95 % CI 0.03–0.27).

Main effects: FTD as a predictor of ASD severity

As shown in Table 3, illogical thinking at T1 significantly predicted a higher total score on the ADOS symptom severity score at T2 7 years later ($t = 2.91; p < 0.01$; 95 % CI 0.09–0.46). Other factors, in particular loose associations did not significantly predict ADOS symptom severity scores at T2 (Table 3).

Table 3 Multiple regression with total score on ADOS at T2 as outcome measure; illogical thinking and loose associations as predictors and age as a covariate ($N = 67$)

Variable	*B*	SE	*t* value	CI-L	CI-U	*p*	*R2*
Model						0.02	0.15
Illogical	0.28	0.10	2.91	0.09	0.46	<0.01	0.13
Loose Ass.	−0.05	0.11	−0.47	−0.27	0.17	0.64	
Age T1	−0.02	0.03	−0.87	−0.07	0.03	0.39	

Regression coefficient (B), standard error (SE), *t* test value (*t*), *CI-L* 95 % confidence interval lower bound, *CI-U* 95 % confidence interval upper bound, *p* significance value, *R2* multiple correlation coefficient squared

Table 4 Multiple regression with total score on ADOS at T2 as outcome measure and ADOS score at T1 and illogical thinking as predictors ($N = 73$)

Variable	*B*	SE	*t* value	CI-L	CI-U	*p*	*R2*
Model						<0.01	0.26
Illogical thinking	0.26	0.09	2.90	0.08	0.44	<0.01	0.13
ADOS T1	0.02	0.01	2.90	0.01	0.04	<0.01	

B regression coefficient, *SE* standard error, *t t* test value, *CI-L* 95 % confidence interval lower bound, *CI-U* 95 % confidence interval upper bound, *p* significance value, *R2* multiple correlation coefficient squared

Illogical thinking correlated positively with ADOS total score at T1 ($r = 0.27$; $p = 0.01$) and with ADOS total score at T2 ($r = 0.22$; $p = 0.03$). Loose associations did not correlate significantly with ADOS total scores at T1 ($r = 0.13$; $p = 0.19$) or with ADOS total score at T2 ($r = 0.06$; $p = 0.59$). As expected, ADOS T1 total scores correlated significantly with ADOS T2 total scores ($r = 0.44$; $p < 0.01$). ADOS T1 total scores were added to the multiple regression models to evaluate whether illogical thinking predicted ADOS T2 total scores independent of ADOS T1 total scores. It turned out that illogical thinking predicted ADOS T2 total scores significantly ($p < 0.01$) even if the ADOS T1 total scores ($p < 0.01$) were taken into account. Illogical thinking and ADOS T1 scores together accounted for 26 % of the total variance in the ADOS T2 scores and illogical thinking accounted for 13 % of the total variance. Cohen's f^2 was 0.15, which represents a medium effect size (Table 4).

Discussion

This study showed that illogical thinking and loose associations as forms of FTD in children with ASD did not predict prodromal symptoms of psychosis 7 years later. The presence of illogical thinking predicted the severity of autistic symptoms 7 years later, whereas loose associations did not. FTD in ASD may not be an early sign of psychosis, but it may rather be a manifestation of the social communication difficulties that are part of ASD.

These data provide evidence for the hypothesis that FTD, especially illogical thinking, in children with ASD predicts a higher future severity of ASD. The fact that illogical thinking had a significant influence on ADOS T2 severity scores, even when the ADOS scores on T1 were taken into account, underscores the importance of illogical thinking as a predictor for the future severity of ASD independent of the severity of ASD at baseline. For theoretical reasons, we also examined whether illogical thinking predicted ADOS T2 scores over and above IQ. Adding IQ at T1 to the model did not change the findings, indicating that illogical thinking predicted ADOS T2 scores over and above ADOS T1 and IQ. Thus, FTD seems to be a predictor of future ASD severity rather than a predictor of positive prodromal symptoms.

A note of caution needs to be made concerning our findings that illogical thinking and loose associations do not predict (prodromal state of) psychosis. From the fact that at T1 60.4 % of this sample scored above the threshold for illogical thinking and 16.5 % for loose associations, it can be concluded that FTD is very common in childhood ASD. However, the fact that FTD is so common among ASD subjects and later conversion to psychosis is so rare has a negative impact on the predictive value of FTD. Furthermore, FTD also does not seem to influence the chance of developing psychotic symptoms.

We chose not to study the predictive value of FTD on negative prodromal symptoms, because of the close resemblance between autistic symptoms and negative symptoms.

However, recent research has pointed out that negative symptoms and cognitive disorganisation may both play an important role in the transition to psychosis [49]. Moreover, it is assumed nowadays that autism and psychosis share common pathophysiological mechanisms [25] and negative symptoms may well be the common ground for the two disorders.

The results and the design of the present study bear important similarities and also differences with the Bearden et al. [3] study. In their study, FTD was assessed in clinically referred or UHR adolescents, who were followed-up for conversion to psychosis during a mean period of 14.8 months. In the present study, FTD was assessed in ASD children, who were followed-up for 7 years, using prodromal symptoms of psychosis as outcome measure. In the Bearden [3] study illogical thinking and lack of cohesion predicted transition to psychosis. In our ASD sample, illogical thinking did not predict prodromal symptoms. In both studies, loose associations did not predict prodromal

symptoms or transition to psychosis. These different findings may be due to the inclusion of different age groups (adolescents versus children), to differences in initial diagnosis (UHR versus ASD) or to differences in the outcome measure (psychosis versus psychosis prodromal state). The percentage of adolescents on anti-psychotic medication was almost equal in both studies and in our sample this was an important covariate, whereas use of medication at baseline in their study did not differ between those who converted to psychosis and those who did not. The use of anti-psychotic medication may have masked symptoms of emerging psychosis. We found a significant positive association between use of anti-psychotics and scores on the PQ positive scale, indicating that subjects on medication showed significantly more positive symptoms of psychosis even after the administration of anti-psychotics. Whether use of anti-psychotics in this study has resulted in lower numbers of subjects with attenuated psychotic symptoms (APS) or lower numbers with full threshold psychosis remains object of speculation and should be clarified in further research.

The factors age and comorbid attention problems or internalizing problems are relevant for the interpretation of our results. The average age at first episode psychosis is 19 years for men and 22 years for women; prodromal symptoms emerge about 2 years earlier [50]. Therefore, the younger part of the adolescents in our T2 sample (ages between 12.8 and 16 years) may still be too young to display prodromal symptoms of psychosis and they might develop prodromal symptoms in the next 5 years. However, in bivariate correlations we did not find a correlation between age and PQ scores.

Other authors [46] found that FTD and attenuated psychotic experiences in samples of ASD children were associated with the presence of comorbid attention problems. However, we observed no relationship between attention problems at T1 and FTD at T1 and prodromal signs at T2. Also we did not find a correlation between attention problems and illogical thinking or between attention problems and loose associations. Because a relation between anxiety and FTD has been demonstrated [4], we examined the putative influence of comorbid anxiety and depression on our outcome measures, but we found no significant effect.

The choice to take prodromal symptoms of psychosis as an outcome measure raises three methodological issues. Firstly, when identifying individuals at risk for psychosis, the threshold should not be set too low not to compromise specificity and to avoid "false positives". Psychotic experiences are rather common in adolescents, with rates varying from 15 to 20 % [51–53]. The empirically based thresholds [29] we used (PQ total >18 and PQ positive >14) are far beyond the level of having one psychotic-like experience ever and therefore specificity is not compromised. In our analyses, we used the PQ positive score in a dimensional way, thereby avoiding the problem of the proper cut-off.

The second issue concerns the specificity of prodromal symptoms with respect to impending psychosis or to put it simply: prodromal symptoms are not always followed by a psychotic episode. A recent meta-analysis revealed that the transition rate from UHR to psychosis is 22 % over 1 year and 36 % over 3 years [31] and preliminary evidence suggests that the transition rate to psychosis is slightly lower in adolescents as compared to adults [54]. In the present study, based on the CAARMS, a rather large proportion of adolescents with ASD had quite serious attenuated psychotic symptoms, but none of the participants had made the transition to full psychosis yet. This may be due to the relatively low age of the sample and to the possibility that these participants might be in an early prodromal stage.

The third methodological issue concerns the minimum age for using the PQ. At T2, nine of our participants had a mental age below 12 years (i.e. calculated as IQ divided by 100 multiplied by chronological age). We decided not to exclude them since re-analysing results with these subjects excluded did not change the findings.

The fact that illogical thinking in this study predicted severity of autistic symptoms at T2 7 years later with a medium effect size is in line with earlier findings. In a cross-sectional study, Solomon et al. [13] found medium effect size relationships between illogical thinking and scores on the social communication questionnaire (SCQ) and medium to large effect size relationships between loose associations and ADOS symptom severity scores. We found a negative correlation between age and illogical thinking or loose associations, which is in line with the findings of van der Gaag et al. [16], who concluded that FTD reflects immature verbal skills and processing. Furthermore, our conclusions are in line with the general conclusions of the Solomon et al. [13] and the Van der Gaag et al. [16] studies, indicating that FTD in ASD is not an early sign of psychosis, but rather a manifestation of pragmatic language abnormalities in ASD. The contribution of the present study is that these findings are replicated and extended using long term follow-up data.

Limitations of the study

The fact that at follow-up about twenty percent of the participants used anti-psychotics may have influenced the results on the prediction of prodromal symptoms of psychosis, because the use of these compounds may mask or mitigate symptoms of psychosis.

The second limitation concerns the age of the participants at follow-up. Although this study encompasses a

follow-up period of 7 years, the adolescents who were younger than 16 years at T2 may still be too young to display prodromal symptoms of psychosis.

Furthermore, at T2, 114/142 (80.3 %) children agreed to participate in the follow-up study and 91 children had complete data at T2 (64.1 %). In 23 (15.8 %) children, the data on the prodromal questionnaire (PQ) were not complete.

Conclusions and implications

Childhood FTD, namely illogical thinking, predicted more severe symptoms of ASD in adolescence, up and above the effect of ASD symptom severity in childhood. Because illogical thinking constitutes a significant and independent contribution to future ASD severity, it is advisable to assess illogical thinking in school-aged ASD children to get an impression of future course.

FTD does not predict prodromal symptoms of psychosis in ASD children. Although FTD in non-ASD samples predicts (prodromal symptoms of) psychosis, we could not demonstrate a clear cut relation between FTD and prodromal symptoms of psychosis in this ASD sample. FTD is common among ASD subjects and later conversion to psychosis is rare, and this negatively impacts the predictive power of FTD for psychosis in ASD children. The presence of illogical thinking seems to have an important psychopathological impact and therefore these symptoms might invite to be cautiously followed-up to see the evolution of the disorder.

Future research

It would be interesting to follow-up samples of children with ASD, especially children with PDD-NOS, for a longer period of time, long enough to enclose the total period of transition to psychosis, which lasts roughly until the age of 25. The goal of such studies would be to identify subcategories or predictors of later psychosis in samples of children with complex developmental disorders.

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Conflicts of interest The authors declare that they have no conflict of interest.

References

1. Dochterty NM, McCleery A, Divilbiss M, Schumann EB, Moe A, Shakeel MK (2013) Effects of social cognitive impairment on speech disorder in schizophrenia. Schizophr Res 39(3):608–616
2. Caplan R (1994) Thought disorder in childhood. J Am Acad Child Adolesc Psychiatry 33(5):605–615
3. Bearden CE, Wu KN, Caplan R, Cannon TD (2011) Thought disorder and communication deviance as predictors of outcome in youth at clinical high risk for psychosis. J Am Acad Child Adolesc Psychiatry 50(7):669–680
4. Ozonoff S, Pennington B, Solomon M (2006) Neuropsychological perspectives on developmental psychopathology. In: Cichetti D, Cohen D (eds) Developmental psychopathology, vol 2: developmental neuroscience, 2nd edn. John Wiley & Sons Inc, Hoboken, pp 332–380
5. Docherty NM (2012) On identifying the process of underlying schizophrenic speech disorder. Schizophr Bull 38(6):1327–1335
6. Caplan R, Guthrie D, Komo S, Siddarth P, Chayasirisobhon S, Kornblum H, Sankar R, Hansen R, Mitchell W, Shields WD (2002) Social communication in children with epilepsy. J Child Psychol Psychiatry 43(2):245–253
7. Andreasen NC (1979) Thought, language and communication disorders. Arch Gen Psychiatry 36:1315–1321
8. Caplan R, Guthrie D, Fish B, Tanguay PE, David-Lando G (1989) The Kiddie formal thought disorder rating scale: clinical assessment, reliability, and validity. J Am Acad Child Adolesc Psychiatr 28(3):408–417
9. Caplan R, Guthrie D, Tang B, Komo S, Asarnow RF (2000) Thought disorder in childhood schizophrenia: replication and update of concept. J Am Acad Child Adolesc Psychiatry 2000(39):771–778
10. Bleuler E (ed) (1950) Dementia praecox or the group of schizophrenia's. International University Press, New York
11. Docherty NM, Gottesmann II (2000) A twin study of communication disturbances in schizophrenia. J Nerv Ment Dis 2000(188):395–401
12. Docherty NM (2005) Cognitive impairments and disordered speech in schizophrenia: thought disorder, disorganization, and communication failure perspectives. J Abnorm Psychol 114:269–278
13. Solomon M, Ozonoff S, Carter C, Caplan R (2008) Formal thought disorder and the autism spectrum: relationship with symptoms, executive control, and anxiety. J Autism Dev Disord 38:1474–1484
14. Volden J, Lord C (1991) Neologisms and idiosyncratic language in autistic speakers. J Autism Dev Disord 21(2):109–130
15. Baltaxe CA, D'Angiola N (1992) Cohesion in the discourse interaction of autistic, specifically language-impaired, and normal children. J Autism Dev Disord 22(1):1–21
16. Van der Gaag R, Caplan R, van Engeland H, Loman F, Buitelaar JK (2005) A controlled study of formal thought disorder in children with autism and multiple complex developmental disorders. J Child Adolesc Psychopharmacol 15(3):465–476
17. Kanner L (1943) Autistic disturbances of affective contact. Nervous Child 1943(2):217–250
18. Rutter M (1972) Childhood schizophrenia reconsidered. J Autism Childhood Schizophrenia 2(4):315–337
19. Volkmar FR, Cohen DJ (1991) Comorbid association of autism and schizophrenia. Am J Psychiatry 148(12):1705–1707

20. Bender L (1974) Psychopathic behaviour disorders in children. In: Lindner RM, Seliger RV (eds) Handbook of correctional psychology. Oxford Philosophical Library, Oxford, pp 360–377
21. King BH, Lord C (2011) Is schizophrenia on the autism spectrum ? Brain Res 1380:34–41
22. Rapaport J, Chavez A, Greenstein D, Addington A, Gogtay N (2009) Autism spectrum disorders and childhood onset schizophrenia: clinical and biological contributions to a relation revisited. J Am Acad Child Adolesc Psychiatry 48:10–18
23. Wolff S (1991) 'Schizoid' personality in childhood and adult life. I: the vagaries of diagnostic labelling. III: The childhood picture. B. J Psychiatry 159(615–20):634–645
24. Wolff S, McGuire RJ (1995) Schizoid personality in girls: a follow-up study–what are the links with Asperger's syndrome. Child Psychol Psychiatry 36(5):793–817
25. Sporn AL, Addington AM, Gogtay N et al (2004) Pervasive developmental disorder and childhood-onset schizophrenia: comorbid disorder or a phenotypic variant of a very early onset illness? Biol Psychiatry 55(10):989–994
26. Van der Gaag RJ, Buitelaar J, Van den Ban E, Bezemer M, Njio L, Van Engeland H (1995) A controlled multivariate chart review of multiple complex developmental disorder. J Am Acad Child Adolesc Psychiatry 34(8):1096–1106
27. Van Engeland H, Van der Gaag RJ (1994) MCDD in childhood: a precursor of schizophrenic spectrum disorder. Schizophr Res 11(2):197
28. Yung AR, McGorry PD (2007) Prediction of psychosis: setting the stage. B J Psychiatry 191(suppl. 51):s1–s8
29. Loewy RL, Bearden CE, Johnson JK, Raine A, Cannon TD, Tyrone D (2005) The prodromal questionnaire (PQ): preliminary validation of a self-report screening measure for prodromal and psychotic syndromes. Schizophr Res 77:141–149
30. Yung AR, Yuen HP, McGorry PD et al (2005) Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. Aust N Z J Psychiatry 39(11–12):964–971
31. Fusar-Poli P, Bonoldi I, Yung AR et al (2012) Predicting psychosis. Meta-analysis of transition outcomes in individuals at high clinical risk. Arch Gen Psychiatry 69:220–229
32. Yung AR, Phillips LJ, Yuen HP et al (2003) Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. Schizophr Res 60(1):21–32
33. Yung AR, Phillips LJ, Yuen HP, McGorry PD (2004) Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. Schizophr Res 67(2–3):131–142
34. Cannon TD, Cadenhead K, Comblatt B et al (2008) Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Arch Gen Psychiatry 65:28–37
35. American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders, fourth edition, text revision. Author, Washington DC
36. De Bruin EI, De Nijs PF, Verheij F, Hartman CA, Ferdinand RF (2007) Multiple complex developmental disorder delineated from PDD-NOS. J Autism Dev Disord 37(6):1181–1191
37. Mandy W, Charman T, Skuse D (2012) Testing the construct validity of proposed criteria for DSM-5 autism spectrum disorder. J Am Acad Child Adolesc Psychiatry 51:41–50
38. Skuse DH (2012) DSM-5′s conceptualization of autistic disorders. J Am Acad Child Adolesc Psychiatry 51:344–346
39. Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME (2000) NIMH diagnostic interview schedule for children version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. J Am Acad Child Adolesc Psychiatry 39(1):28–38
40. Caplan R, Guthrie D, Tang B, Neuchterlein KH, Asarnow RE (2001) Thought disorder in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 40(8):965–972
41. Lord C, Rutter M, DiLavore PC, Risi S (1999) Autism diagnostic observation schedule-WPS (ADOS-WPS). Western Psychological Services, Los Angeles
42. Volkmar FR, State M, Klin A (2009) Autism and autism spectrum disorders: diagnostic issues for the coming decade. J Child Psychol Psychiatry 50(1–2):108–115
43. Klosterkotter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F (2001) Diagnosing schizophrenia in the initial prodromal phase. Arch Gen Psychiatry 58:158–164
44. WISC-R Projectgroep: Van Haasen, PP, De Bruyn EEJ, Pijl YJ, et al (1986) WISC-R. Wechsler Intelligence Scale for Children-Revised, Dutch version. Swets & Zeitlinger, Lisse
45. Achenbach TM (1991) Manual for the child behavior Checklist/4-18 and 1991 profiles. Department of Psychiatry, University of Vermont, Burlington
46. Gadow KD (2012) Schizophrenia spectrum and attention-deficit/hyperactivity disorder symptoms in autism spectrum disorder and controls. J Am Acad Child Adolesc Psychiatry 51(10):1076–1084
47. Verhulst FC, van der Ende J, Handleiding ASEBA (2013) Vragenlijsten voor leeftijden 6 tot en met 18 jaar. ASEBA Nederland, Rotterdam
48. Amone-P'Olak K, Ormel J, Oldehinkel A, Reijneveld SA, Verhulst FC, Burger H (2010) Socioeconomic position predicts special mental health service use independent of clinical severity: the TRAILS study. J Am Acad Child Adolesc Psychiatry 49(7):647–655
49. Demjaha A, Valmaggia L, Stahl D, Byrne M, McGuire P (2012) Disorganization/cognitive and negative symptom dimensions in the at-risk mental state predict subsequent transition to psychosis. Schizophr Bull 38(2):351–359
50. Armenteros JL, Davies M (2006) Anti-psychotics in early onset schizophrenia. Systematic review and meta-analysis. Eur Child Adolesc Psychiatry 15:141–148
51. Van Os J, Hanssen M, Bijl RV, Volleberg W (2001) Prevalence of psychotic disorder and community level of psychotic symptoms: an urban-rural comparison. Arch Gen Psychiatry 58:663–668
52. Poulton R, Caspi A, Moffitt TE, Cannon M, Murray RM, Harrington H (2000) Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. Arch Gen Psychiatry 57:1053–1058
53. Arango C (2011) Attenuated psychotic symptoms syndrome: how it may affect child and adolescent psychiatry. Eur Child Adolesc Psychiatry 20:67–70
54. Ziermans TB, Schothorst PF, Sprong M, van Engeland H (2001) Transition and remission in adolescents at ultra high-risk for psychosis. Schizophr Res 126(1–3):58–64