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Research paper

Visual attention in 7-year-old children at familial high risk of schizophrenia or bipolar disorder: The Danish high risk and resilience study VIA 7

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ABSTRACT

Background: Attention deficits are found in children at familial high risk of schizophrenia (FHR-SZ) and bipolar disorder (FHR-BP) using assessment methods relying on motor-based response latency. This study compares visual attention functions in children at FHR-SZ or FHR-BP with controls using an unspeeded task unconfounded by motor components.

Methods: Visual attention was assessed in 133 7-year-old children at FHR-SZ (N = 56) or FHR-BP (N = 32), and controls (N = 45) using the unspeeded paradigm, TVA-based whole report. We compared four parameters of visual attention: visual processing speed, visual short-term memory, threshold for visual perception, and error rate. Further, we investigated their potential relationships with severity of psychopathology, adequacy of the home environment, and neurocognitive measures.

Results: Children at FHR-SZ displayed significant deficits in perceptual processing speed of visual attention compared with controls ($p < .001$; $d = 0.75$) as did children at FHR-BP ($p < .05$; $d = 0.54$). Visual processing speed was significantly associated with spatial working memory (β = -0.23; $t(68)$ = -3.34, $p = .01$) and psychomotor processing speed ($\beta = 0.14$, $t(67) = 2.11$, $p < .05$).

Limitations: Larger group sizes would have permitted inclusion of more predictors in the search for neurocognitive and other factors associated with the parameters of TVA-based whole report.

Conclusions: Young children at FHR-SZ and FHR-BP display significant deficits in processing speed of visual attention, which may reflect the effect of shared vulnerability risk genes. Early identification of children at FHR-SZ and FHR-BP with perceptual processing speed impairments may represent a low-cost basis for low-risk interventions.

1. Introduction

Schizophrenia and bipolar disorder are neurodevelopmental disorders with distinct neurocognitive pathways (Craddock and Owen, 2010). Neurocognitive deficits are present before the onset of clinical symptoms and although the neurocognitive impairments are more pronounced in schizophrenia they are well established in both disorders (Green, 2006; Bora et al., 2009, 2016; Reichenberg and Harvey, 2007). Moreover, neurocognitive functions are suggested as endophenotypes or risk markers for both disorders with varying degrees

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of heritability (Blokland et al., 2016; Bora et al., 2009; Glahn et al., 2010). Accordingly, neurocognitive impairments are present in both offspring of individuals with schizophrenia (Hameed and Lewis, 2016; Agnew-Blais and Seidman, 2013) and offspring of individuals with bipolar disorder (Sharma et al., 2017; Bora and Ozerdem, 2017). Specific neurocognitive deficits in visual attention have also been reported in studies of children at familial high risk of schizophrenia (Erlenmeyer-Kimling and Cornblatt, 1992; Nuechterlein, 1983) and children at familial high risk of bipolar disorder (Diwadkar et al., 2011; Klimes-Dougan et al., 2006). Hitherto, visual attention in young children at familial high risk has preferably been measured with assessment methods depending on motor-based response latency (e.g. various versions of the widely used Continuous Performance Test) (Hameed and Lewis, 2016) thus preventing the measurement of specific perceptual aspects of visual attention capacity. A measurement that circumvents a motor-based response latency however would measure attentional capacity without potential confounding from motor skills including motor speed (Vangkilde et al., 2011).

Based on Bundesen's Theory of Visual Attention (TVA) (Bundesen, 1990) the computerized experimental procedure of TVA-based whole report (Duncan et al., 1999) allows for the measurement and estimation of distinct parameters of visual attention accuracy and processing speed in one integrated and unspeeded test independent of motor functions. In TVA-based whole report, the subject gives a verbal report of all remembered targets from brief visual displays, and the capacity of visual attention is mathematically accounted for by three separate parameters: the speed of encoding information into visual short-term memory (visual processing capacity of C objects per second), the visual short-term memory span (storage capacity of K objects), and the threshold of visual perception (minimum effective exposure duration of t_0 milliseconds) (McAvinue et al., 2012; Habekost and Starrfelt, 2009). TVA-based paradigms have been applied across different clinical conditions (ADHD, dyslexia, neurodegenerative diseases, and neglect after traumatic brain injury among others) in various clinical studies (Habekost, 2015), which generally demonstrated a high degree of sensitivity, specificity, as well as a good internal and test-retest reliability of the TVA parameters (Habekost, 2015; Habekost et al., 2014). Inter-parametric correlations of a moderate magnitude between C and K have been reported in non-clinical populations (Finke et al., 2005; Vangkilde et al., 2011), which might indicate overlapping properties of these two parameters.

A handful of TVA-based studies on children have been conducted in clinical populations with neurodevelopmental disorders such as Attention-Deficit/Hyperactivity Disorder (ADHD) (McAvinue et al., 2015; Caspersen et al., 2017), dyslexia (Dubois et al., 2010; Bogon et al., 2014), and spina bifida myelomeningocele (Caspersen and Habekost, 2013). However, no previous studies have measured aspects of visual attention with a TVA-based paradigm in children at familial high risk of schizophrenia or bipolar disorder. Given that first degree relatives at familial high risk of schizophrenia show deficits in processing speed and motor functions (Agnew-Blais and Seidman, 2013; Burton et al., 2016, 2017; Hemager et al., 2018) which also applies to children at familial high risk of bipolar disorder (Bora and Ozerdem, 2017), the assessment with the TVA-based whole report may provide more accurate measures of visual attention not affected by response latency and motor speed.

Thus, the primary aim of the study was to compare aspects of visual attention measured with the TVA-based whole report paradigm in children at familial high risk of either schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) with children without familial risk of any of these disorders (controls). We hypothesized that both familial high risk groups would display significant deficits in visual attention compared with the control group and that the children at FHR-SZ would demonstrate more pronounced impairments than the children at FHR-BP. Moreover, in an exploratory approach, we investigated the associations of the TVA-parameters with intelligence, sustained attention, processing speed, and spatial working memory derived from additional testing, as well as with psychopathology and adequacy of the home environment.

2. Methods

2.1. Participants

The current study is part of the Danish High Risk and Resilience Study VIA 7 (hereafter referred to as the VIA 7 study), described in detail elsewhere (Thorup et al., 2015). The VIA 7 study is a multi-site, population-based cohort study of 522 7-year-old children of parents meeting the diagnostic criteria for either schizophrenia spectrum psychosis (defined as schizophrenia, delusional disorder, and schizoaffective disorder; ICD 10-codes: F20, F22 and F25 or ICD 8-codes: 295, 297, 298.29, 298.39, 298.89, 298.99) ($N = 202$), bipolar disorder (ICD 10 codes F30 and F31 or ICD 8-codes: 296.19, 296.39) ($N = 120$), or neither of these disorders ($N = 200$). The children at familial high risk were recruited through the Danish Civil Registration System (Pedersen et al., 2006) based on the diagnosis of the ill parent registered in the Danish Psychiatric Central Research Register (Mors et al., 2011). The population-based controls (referred to as controls) were matched to the children at FHR-SZ on age, sex, and municipality. The sex of the ill parent in the FHR-SZ families (the index parent) defined the index parent in the control families. Several children with two ill parents were also included. The children at FHR-BP were included as a non-matched study group (Fig. 1). All participating children had Danish as their first language. The legal guardians of the participating children received written and oral information about the study and gave written informed consent to the participation.

2.1.1. The TVA sub-study

The TVA sub-study is nested within the VIA 7 study. The TVA-based whole report was only conducted on a sub-sample of children in the total VIA 7 cohort due to limitations in the assessment capacity. Prior to inclusion we conducted a statistical power analysis for sample size estimation of the TVA sub-study. Based on the mean effect size (Cohen $d = 0.77$) of C in two earlier studies comparing children diagnosed with ADHD and controls at ages 9 to 13 years (Cohen $d = 0.57$) (McAvinue et al., 2015) and 8 to 12 years (Cohen $d = 0.96$) (Caspersen et al., 2017), and with alpha set at 0.05, and power at 0.80, the projected sample size needed was $N = 28$ in each study group for between group comparisons. The number of recruited subjects reached 143 to ensure the inclusion of 28 participants in each group in a blinded assessment with the following distribution across the three groups: FHR-SZ: $N = 60$, FHR-BP: $N = 34$, and controls: $N = 49$. Other than being the first subjects enrolled in the overall VIA 7 study, the 143 participants in this sub-study were not selected on any other criteria.

2.2. Procedures

The study was approved by The Danish Data Protection Agency. Due to the non-interventional study design of the VIA 7 study, approval by The National Ethical Research Committee was not deemed necessary by this authority. Nevertheless, all procedures followed their guidelines. The assessors were trained psychologists, medical doctors, and nurses and were all instructed, supervised, and certified by a specialist in child neuropsychology (JRMJ). Assessment with the TVA-based whole report was carried out at the research site in Copenhagen by assessors blinded to the risk status of the children.

2.3. Assessment procedure

2.3.1. Clinical measures

We assessed the current level of functioning with the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983) and problem

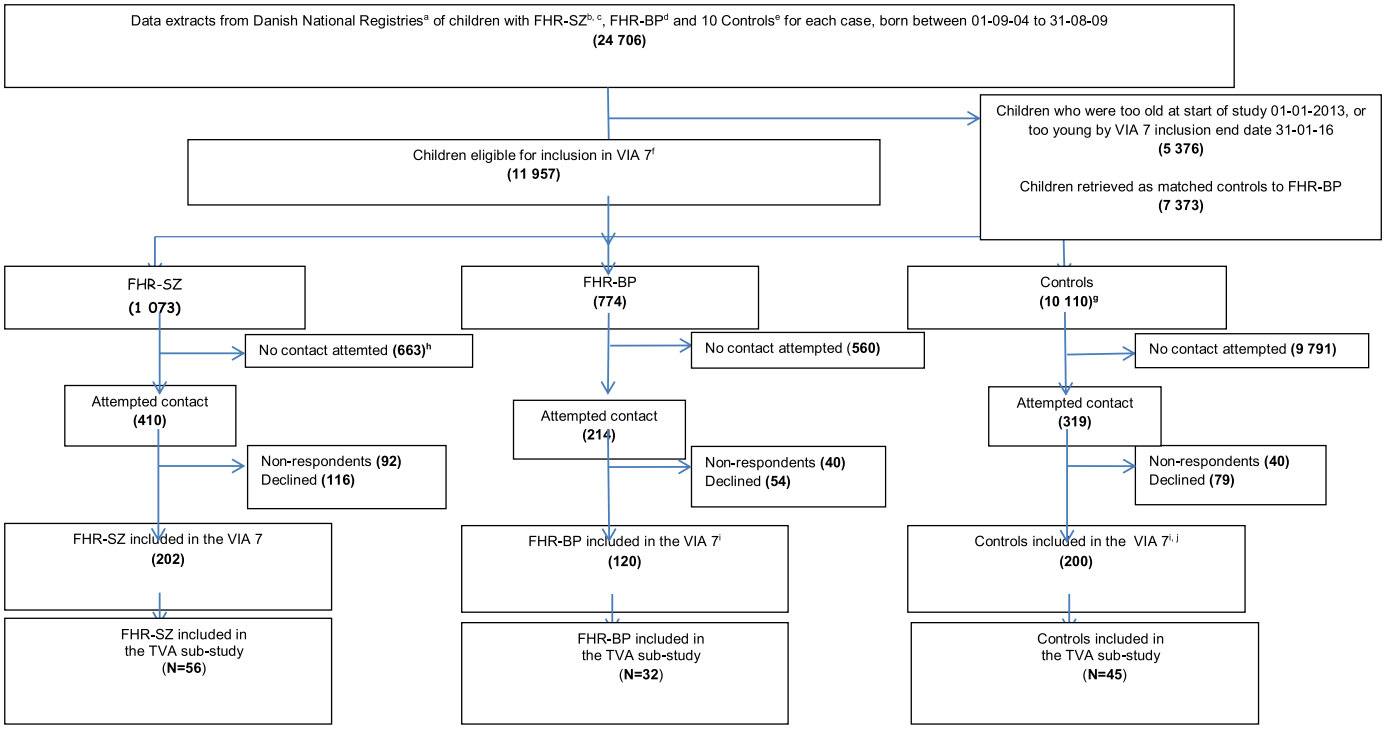

Fig. 1. Data extraction and recruitment procedure of the VIA 7 cohort.
[a]**Danish national registries:** Danish civil registration system and Danish psychiatric central research register.
[b]**FHR-SZ:** Children at familial high risk of schizophrenia
[c]**Double diagnosed parents:** In the event of a parent with a double diagnosis of schizophrenia *and* bipolar disorder the offspring was assigned to the schizophrenia familial high risk group as per the ICD-10 hierarchy.
[d]**FHR-BP:** Children at familial high risk of bipolar disorder.
[e]**Controls:** Population-based control children of parents with no diagnoses of schizophrenia spectrum disorders or bipolar disorder.
[f]**Research protection:** In May of 2011, legislation was enacted to protect individuals' phone numbers from being called for participation in scientific research. Therefore, there were eligible children who were not contacted and enrolled in the VIA 7 study.
[g]**Controls selection:** A total of 10 controls were retrieved for each child in the FHR-SZ and the FHR-BP group. Controls were matched to cases on sex, municipality and exact age. The original intent was to only select control cases that were matched to the children at FHR-SZ. However, there are 38 FHR-BP-controls among the 200 total controls.
[h]**Definition of contact:** First through letters sent to the child´s address. If the family did not respond, contact by telephone was attempted (calls and text messages), if a phone number could be found.
[i]**Re-assigned control parent:** One control parent was found to have a diagnosis of bipolar disorder made by a private doctor, therefore the diagnosis was not present/visible in the national registry extract, as private doctors do not report to the national registry. This family/parent was therefore reassigned to the bipolar disorder familial high risk group. Therefore the $N = 201$ for controls is now $N = 200$.
[j]**Control children not in the original extract:** Two younger siblings were included in the VIA 7 study by request of the parents. They were not in the original extract.

behaviour with the Child Behaviour Checklist (CBCL) School-Age Version (Achenbach and Rescorla, 2001) completed by the primary caregiver (defined as the parent/legal guardian spending the most time with the child). Symptoms of Attention Deficit/Hyperactivity Disorder (ADHD) were assessed with a modified version of the ADHD-Rating Scale (ADHD-RS) rated by the primary caregiver (Makransky and Bilenberg, 2014). Finally, we assessed the adequacy of the home environment of the children with the semi-structured interview Middle Childhood-HOME Inventory (MC-HOME) for children aged 6–10 (Bradley et al., 1988).

2.3.2. TVA-based whole report

The experimental procedure was a TVA-based whole report paradigm where all displayed stimuli are targets to be reported. It was conducted as a verbal-report procedure in a semi-darkened room on a 17″ monitor with a refresh rate of 100 Hz. The child was instructed to focus on a fixation cross and was then shown six target numbers between 0 and 9 in a notional circle centred on the fixation cross. Target size and colours are described in detail elsewhere (Vangkilde et al., 2011). Numbers were chosen as stimuli instead of letters as a pilot study showed that children at this young age were more consistent in their number identification skills compared with their letter identification skills. Further, each child's number identification skills were tested prior to assessment by asking them to name the numbers from 0 to 9 when shown a hard copy display of those numbers. Exposure times of the target stimuli varied systematically between 20, 30, 50, 80, 140 and 200 milliseconds and the stimulus display was followed by pattern masks to prevent a visual afterimage of the display prolonging the effective duration of the exposure times (Fig. 2). These exposure durations spanned approximately from the threshold of visual perception, t_0, to the longest exposure duration, in which eye movements will not improve performance, to allow for the best estimation of the TVA parameters. The child was instructed to give an unspeeded report of the numbers they were "fairly certain" to have seen but to refrain from guessing. The test procedure consisted of two practice blocks of eight trials and three experimental blocks of 30 trials. This is an abbreviated version used with children that have previously been employed (with letter stimuli) in a large scale population study with 914 participants (Vangkilde et al., 2009) and other abbreviated versions have been validated in comparable groups of children (Caspersen et al., 2017). After

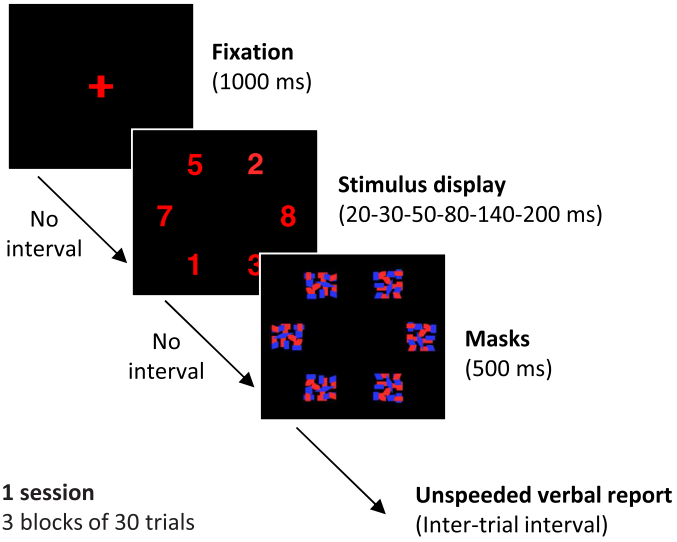

Fig. 2. TVA-based whole report trial outline.

each block the child was given visual feedback on the quality of its performance (i.e. the percentage of correctly reported targets out of all reported targets). In case a child had been either too liberal (less than 80% correct) or too conservative (more than 90% correct) in its report strategy, the child was corrected encouragingly by the assessor to aim for 80–90% correct reports. The total duration of the test procedure was approximately 18–20 min per subject. The visual attention functions were quantified by estimating three parameters for each child; *C*, perceptual processing speed of visual attention measured by elements processed per second; *K*, capacity of visual short-term memory measured by number of elements; t_0, the threshold of visual perception or the minimum effective exposure duration measured in milliseconds. The performance of the child develops as a function of the exposure duration (Fig. 3). When the child's perceptual threshold (t_0) exceeds the exposure duration, the score is zero. Once the threshold is reached, the score rises steeply. The slope of the curve at t_0 corresponds to the individual's perceptual processing speed of visual attention (*C*). Thus, the steeper the slope, the more elements can be processed per millisecond. Finally, the performance curve levels off illustrated by the horizontal asymptote of the curve corresponding to the maximum storage capacity of visual short-term memory (*K*). Thus, for each child, the observed performance across exposure durations were used to estimate the described TVA parameters; *K* (5 degrees of freedom, df[1]), *C* (1 df), and t_0 (1 df), which together with the error rate were used to describe the visual attention functions of the child. Fig. 3 illustrates the observed performance and associated estimated performance of two individual subjects (one child from the control group and one child from the FHR-SZ group). The TVA model fitting procedure is described in the supplementary text and in further detail elsewhere (Kyllingsbaek, 2006; Dyrholm et al., 2011). To ensure enough valid observations for reliable estimation of the TVA parameters and a performance reflecting adherence to the task instructions, children with an error rate above 0.35 were excluded from the modelling (see also Caspersen et al., 2017). For the present sample this corresponded to exclusion of children with an error rate above two standard deviations from the mean.

2.3.3. Other neurocognitive tests

Intelligence was assessed using the Reynold's Intellectual Screening Test (RIST) (Reynolds and Kamphaus, 2003). Processing speed was assessed with the Symbol Search test from the Wechsler Intelligence Scale for Children - fourth edition (WISC-IV) (Wechsler, 2003). Sustained attention was assessed using the Rapid Visual Information Processing (RVP) test from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Sahakian and Owen, 1992) including measures of detection sensitivity (A'), response time (Mean Latency) and motor response control (Total False Alarms). Finally, spatial working memory was assessed using the Spatial Span (SSP) test (Span Length) and Spatial Working Memory (SWM) test (Total Errors) from the CANTAB (Sahakian and Owen, 1992).

2.4. Statistical analyses

Demographic, symptom dimensional, home environmental, and neurocognitive characteristics were compared across the three study groups using parametric (univariate analysis of variance with Fisher's Least Significant Difference (LSD) post hoc tests) and non-parametric (Pearson chi-square or Kruskal–Wallis) analyses when appropriate. Log transformation was applied if necessary to approximate a normal distribution (CBCL Total Score, ADHD-RS Total Score, RVP Mean Latency, and RVP Total False Alarms). All main outcome measures as well as the measures used in the exploratory analyses were standardized into z-scores with the control group mean as reference. The z-scores were constructed so that a negative value would always reflect a poorer performance.

To compare the performance of the three study groups on the four primary outcome measures *C, K,* t_0, and error rate we conducted a multivariate analysis of variance (MANOVA). We adjusted for multiple comparisons using Scheffé post hoc tests and statistical significance was accepted at 0.05. Estimates of effect size were calculated with Cohen *d*.

To investigate whether a priori selected clinical, home environmental or neurocognitive measures were associated with each of the four TVA-variables (*C, K,* t_0, and error rate), we conducted independent multiple linear regression analyses with the respective predictor variables entered simultaneously into the model (standard method (Tabachnick and Fidell, 2007)). The number of participants allowed for applying multiple regression in that $N \geq$ the number of predictors plus 104 (Tabachnick and Fidell, 2007). Familial high risk status, intelligence (the RIST Index (Reynolds and Kamphaus, 2003)), and adequacy of the home environment (the MC-HOME (Bradley et al., 1988)) were chosen a priori as predictors across all four analyses. Further, for each of the four analyses we a priori selected three neurocognitive and/or clinical measures addressing theoretically related constructs of the respective TVA parameters. For the regression model with *C* we chose neurocognitive measures of processing speed (the Symbol Search from the WISC-IV (Wechsler, 2003)), detection sensitivity during sustained attention (the RVP A' from the CANTAB (Sahakian and Owen, 1992)), and spatial working memory (the SWM Total Errors from the CANTAB (Sahakian and Owen, 1992)) as predictors. For the regression model with *K* we chose neurocognitive measures of visual span length (the SSP Span Length), detection sensitivity during sustained attention (the RVP A'), and spatial working memory (the SWM Total Errors) from the CANTAB (Sahakian and Owen, 1992) as predictors. For the regression model with t_0 we chose neurocognitive measures of processing speed (the Symbol Search from the WISC-IV (Wechsler, 2003)), response latency during sustained attention (the RVP Mean Latency from the CANTAB (Sahakian and Owen, 1992)), and response inhibition during sustained attention (the RVP Total False Alarms from the CANTAB (Sahakian and Owen, 1992)) as predictors. Finally, for the regression model with error rate we chose a neurocognitive measure of detection sensitivity during sustained attention (the RVP A' from the CANTAB (Sahakian and Owen, 1992)) as well as clinical symptom dimensional measures of attention (the inattention subscale from the ADHD-RS (Makransky and Bilenberg, 2014)) and problem behaviour (the CBCL total score) as predictors (Achenbach and Rescorla, 2001). Potential effect modification of the predictors by high risk status was examined in

[1] The reported *K* values is the expected *K* given a particular probability distribution (i.e., the probabilities that $K = 1, 2, \ldots, 5$), where $K = 6$ accounts for the remaining probability up to a value of 1.

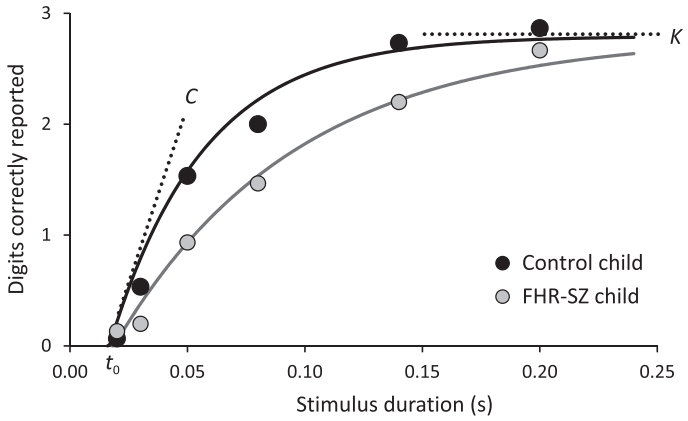

Fig. 3. TVA-based whole report performance for a typical control child and a child with FHR-SZ (FHR = Familial high risk; SZ = Schizophrenia).

all four regression models. Data were analysed using IBM SPSS Statistics, version 22 (IBM Corp., 2013) and R (R Development Core Team, 2011).

3. Results

3.1. Demographic, clinical, home environmental, and neurocognitive characteristics

Nine subjects were excluded due to an error rate above 35% (controls: $N = 4$; FHR-SZ: $N = 3$; FHR-BP: $N = 2$) and one subject (FHR-SZ) was excluded due to an insufficient amount of trials completed for the parameter estimates to be calculated. The included and excluded children did not differ significantly or substantially concerning age (Cohen $d = 0.14$), sex, or familial high risk status. The three study groups did not differ significantly on either age or sex but differed significantly on psychosocial functioning and several neurocognitive functions (Table 1).

3.2. TVA

The MANOVA showed a statistically significant effect of group on the four TVA-based attention measures (*C*, *K*, t_0, and error rate) combined ($F_{(8,\ 256)} = 3.08$, $p < .01$; Pillai's Trace = 0.18). The results of the pairwise comparisons (Table 2) revealed that both children at FHR-SZ (Cohen $d = 0.75$) and children at FHR-BP (Cohen $d = 0.53$) were significantly impaired relative to controls on processing speed of visual attention (*C*), whereas there was no statistically significant difference between the two high risk groups. The pairwise comparisons on *K*, t_0, and error rate were all rendered statistically non-significant. Noteworthy, the between-group differences on the threshold of perception were also supported at the level of observed raw scores (data not shown); when directly comparing the observed raw scores at the lower exposure durations (i.e., 20, 30 and 50 ms) no significant differences between the groups were observed.

3.3. The relationship of the TVA measures to familial high risk status, adequacy of the home environment, severity of psychopathology, and neurocognitive functions

In an explorative analysis, we investigated the potential associations between the four TVA measures and familial high risk status, adequacy of the home environment, severity of psychopathology as well as neurocognitive functions using independent multiple linear regressions analyses. The regression model for perceptual processing speed of visual attention (*C*) was highly significant ($p < .00001$) and explained 25% of the variance. Apart from being significantly negatively associated with being a child at FHR-SZ ($\beta = -0.29$, $t(146) = -1.98$, $p < .05$) and being a child at FHR-BP ($\beta = -0.42$, $t(155) = -2.69$, $p < .01$) compared with controls, perceptual processing speed of visual attention (*C*) was significantly associated with SWM Total Errors ($\beta = -0.23$, $t(68) = -3.34$, $p < .01$). The relationship was negative indicating that reduced perceptual processing speed of visual attention is accompanied by increased error proneness in spatial working memory. Finally, perceptual processing speed of visual attention (*C*) was significantly and positively associated with Symbol Search ($\beta = 0.14$, $t(67) = 2.11$, $p < .05$) indicating that reduced perceptual processing speed of visual attention is accompanied by reduced psychomotor processing speed. There were no significant interactions of group in any analyses. The remaining three regression models were rendered non-significant (Table 3).

4. Discussion

We examined perceptual aspects of visual attention in 7-year-old children at familial high risk of schizophrenia or bipolar disorder using the unspeeded, accuracy-only TVA-based whole report paradigm. We found significant deficits in perceptual processing speed of visual attention (*C*) in both familial high groups with the largest effect size among children at FHR-SZ ($d = 0.75$) compared with controls. The two familial high risk groups did not differ significantly. Thus, these impairments in perceptual processing speed of visual attention (*C*) may reflect the effect of some of the shared genetic risk factors for schizophrenia and bipolar disorder. To our knowledge this is the first study to document deficits in perceptual processing speed of visual attention in children at FHR-BP at this early age (Bora and Ozerdem, 2017). In a previous neurocognitive study, children at FHR-SZ displayed deficits in sustained attention and processing speed (with small to medium effect sizes) but not children at FHR-BP (Hemager et al., 2018). Thus, parameter *C* from the TVA-based whole report appears to be more sensitive to attention impairments in children at FHR-BP ($d = 0.54$) (Table 2) than the A' sensitivity measure of sustained attention from the RVP ($d = 0.22$) CANTAB (Sahakian and Owen, 1992) subtest (Table 1). Further, regarding children at FHR-SZ, the deficits in perceptual processing speed detected in the current study were substantially more pronounced than sustained attention deficits detected by a continuous performance test (RVP A') reflected in the markedly larger effect size reported in the present study ($d = 0.75$ for *C* in the present study vs $d = 0.22$ for RVP A' in the present study as well as $d = 0.36$ for RVP A' in a previous neurocognitive study on same-aged children at FHR-SZ (Hemager et al., 2018)). Thus, in children at FHR-SZ the visual attention processing speed measure derived from TVA-based whole report revealed a substantially greater impairment than the A' measure of sustained attention derived from RVP. Although speculative, these equivocal findings may be due to speed of attention processing measured with *C* being more closely related to early, perceptual rather than

Table 1
Demographic, clinical, and neurocognitive characteristics of 133 7-year-old children at familial high risk of schizophrenia (FHR-SZ), bipolar disorder (FHR-BP), and controls.

Variables	Controls[a]	FHR-SZ[b]	FHR-BP[c]	*P*-value	*P*-values pairwise comparisons		
					FHR-SZ vs Controls	FHR-BP vs Controls	FHR-SZ vs FHR-BP
Children, *N*	45	56	32	–	–	–	–
Female, *N* (%)	22 (48.9)	25 (44.6)	18 (56.3)	0.58[d]	–	–	–
Age - years at inclusion, Mean (SD)	7.7 (0.2)	7.8 (0.2)	7.8 (0.2)	.18[e]	–	–	–
Child Behavior Checklist, Total score, Mean (SD) (Total *N* = 126; Controls *N* = 43; FHR-SZ *N* = 55; FHR-BD *N* = 28)	19.2 (14.8)	20.8 (17.3)	19.6 (18.0)	.61[e]	–	–	–
Children's Global Assessment Scale, Mean (SD) (Total *N* = 132; Controls *N* = 45; FHR-SZ *N* = 56; FHR-BD *N* = 31)	79.4 (12.6)	72.4 (14.3)	80 (12.4)	**.01**[f]	**.05**[f]	1.0[f]	**.04**[f]
Attention Deficit/Hyperactivity Disorder – Rating scale, inattention subscale (item 1–9), Mean (SD) (Total *N* = 127; Controls *N* = 42; FHR-SZ *N* = 56; FHR-BD *N* = 29)	5.7 (4.1)	6.0 (5.0)	5.6 (5.6)	.60[e]	–	–	–
Middle Childhood-HOME inventory, Mean (SD) (Total *N* = 128; Controls *N* = 44; FHR-SZ *N* = 53; FHR-BD *N* = 31)	49.4 (4.5)	44.9 (6.8)	47.8 (4.4)	.07[e]	–	–	–
Reynold's Intellectual Screening Test Index (IQ Estimate), Mean (SD) (Total *N* = 131; Controls *N* = 44; FHR-SZ *N* = 56; FHR-BD *N* = 31)	104.8 (10.2)	104.6 (9.2)	105.2 (8.8)	.97[e]	–	–	–
Symbol Search, Mean (SD) (Total *N* = 130; Controls *N* = 44; FHR-SZ *N* = 55; FHR-BD *N* = 31)	18.4 (5.5)	15.7 (5.1)	17.5 (5.0)	**.03**[e]	**.01**[e]	.44[e]	.13[e]
Spatial Working Memory, Total errors, Mean (SD) (Total *N* = 129; Controls *N* = 44; FHR-SZ *N* = 54; FHR-BD *N* = 31)	47.0 (17.2)	51.9 (16.0)	41.5 (16.5)	**.02**[e]	.14[e]	.16[e]	**.01**[e]
Spatial Span, Span length, Mean (SD) (Total *N* = 129; Controls *N* = 44; FHR-SZ *N* = 54; FHR-BD *N* = 31)	4.6 (1.2)	4.3 (1.3)	5.1 (1.4)	**.001**[f]	1.00[f]	**.02**[f]	**.001**[f]
Rapid Visual Information Processing, A' (A prime), Mean (SD) (Total *N* = 124; Controls *N* = 43; FHR-SZ *N* = 50; FHR-BD *N* = 31)	0.92 (0.05)	0.89 (0.06)	0.91 (0.04)	**.002**[e]	<**0.001**[e]	.34[e]	**.03**[e]
Rapid Visual Information Processing, Mean latency (seconds), Mean (SD) (Total *N* = 124; Controls *N* = 43; FHR-SZ *N* = 50; FHR-BD *N* = 31)	0.45 (0.11)	0.54 (0.15)	0.51 (0.14)	**.02**[e]	**.005**[e]	.09[e]	.39[e]
Rapid visual information processing, Total false alarms, Mean (SD) (Total *N* = 129; Controls *N* = 44; FHR-SZ *N* = 54; FHR-BD *N* = 31)	5.0 (10.1)	8.1 (10.8)	9.0 (10.6)	**.03**[e]	.07[e]	**.01**[e]	.30[e]

[a] Controls, population-based control group.
[b] FHR-SZ, children at familial high risk of schizophrenia.
[c] FHR-BP, children at familial high risk of bipolar disorder.
[d] Pearson Chi-square.
[e] One-Way ANOVA across the three study groups with Fisher's Least Significant Difference (LSD) post hoc tests.
[f] Kruskal–Wallis Test with Dunn-Bonferroni post hos tests.

Table 2
Visual attention as measured by the TVA-based whole report in 133 7-year-old children at familial high risk of schizophrenia (FHR-SZ), bipolar disorder (FHR-BP), and controls.

TVA outcome variables	1. Controls[a] N = 45 Mean (SD)		2. FHR-SZ[b] N = 56 Mean (SD)		3. FHR-BP[c] N = 32 Mean (SD)		Pairwise comparisons[d] FHR-SZ vs Controls		FHR-BP vs Controls		FHR-SZ vs FHR-BP	
	Estimated value	**Z score[e]**	**Estimated value**	**Z score[e]**	**Estimated value**	**Z score[e]**	***P***	**d[f]**	***P***	**d[f]**	***P***	**d[f]**
Processing speed of visual attention (*C*), Elements per second	36.23 (19.45)	0.00 (1.00)	24.63 (10.16)	−0.60 (0.52)	27.20 (13.63)	−0.46 (0.70)	**<0.001**	0.75	**.03**	0.54	.73	0.21
Visual short-term memory span (*K*), Number of elements	2.84 (0.67)	0.00 (1.00)	2.80 (0.92)	−0.06 (1.37)	2.45 (0.68)	−0.57 (1.01)	.97	0.05	.11	0.58	.14	0.43
Threshold of visual perception (t_0), Milliseconds	19.45 (15.61)	0.00 (1.00)	15.74 (12.65)	−0.24 (0.81)	16.37 (16.03)	−0.20 (1.03)	.45	0.26	.66	0.20	.98	0.04
Error rate	0.17 (0.07)	0.00 (1.00)	0.17 (0.09)	−0.04 (1.22)	0.17 (0.07)	−0.02 (0.97)	.98	0.04	.10	0.02	.99	0.02

[a] Controls = Population-based control group.
[b] FHR-SZ = Children at familial high risk of schizophrenia spectrum psychosis.
[c] FHR-BP = Children at familial high risk of bipolar disorder.
[d] To reduce the risk of type I errors, a multivariate analysis of variance (MANOVA) was conducted and significance for the mean comparisons were corrected using Scheffé's method and set at $P < .05$.
[e] Negative z scores always reflect a poorer performance than the control group mean.
[f] d = Cohen d.

more complex cognitive or output control functions (Habekost, 2015). Surprisingly, parameter K did not prove sensitive to deficits in visual short-term memory span. This is in contrast to earlier findings of impairments in the theoretically related visual working memory functions as reflected in the SWM Total Errors (d = 0.29) and SSP Span Length (d = 0.32) outcome measures observed in children at FHR-SZ (Hemager et al., 2018). This difference may be due to parameter K reflecting a more passive short-term memory function, whereas SWM Total Errors and SSP Span length also reflects working memory components.

Although some aspects of visual-perceptual functions are associated with attention (Silverstein and Keane, 2011) the current findings suggest deficits in attentional processing capacity in children with FHR-SZ and FHR-BP that do not seem to be explained by or related to deficits in visual-perceptual input.

Regarding the effects of masking, the masking used here can be classified as backward Type-A masking (Skottun and Skoyles, 2009) or more specifically high-energy masking (Green et al., 2002). This type of masking has been compared in a large group of individuals with schizophrenia and a healthy, matched control group, where the groups only differed at longer stimulus durations (i.e. when masking occurred >50 ms after stimulus onset) (Green et al., 2003). These previous findings are comparable to the current results. Further, Green and colleagues conclude that visual processing deficits in schizophrenia cannot be explained by a "simple perceptual input problem" (p. 893) (Green et al., 2003), which is in line with our interpretation that attentional processing capacity is limited in children at FHR-SZ.

While the TVA paradigm is inspired by the seminal work by George Sperling (Sperling, 1960) it is important to keep in mind the distinction between whole and partial report, both of which Sperling employed. Whole report paradigms allow for the estimation of attentional capacity (be it processing capacity, C, or storage capacity, K), whereas partial report paradigms assess attentional selectivity. As the paradigm used in this study is a whole report paradigm, it enables us to parametrically disentangle the contributions of a deficit in the perceptual threshold (t_0), a deficit in attentional processing speed (C), and of a decrease in short term storage (K), whereas the whole report paradigm does not estimate selective attention. When looking at the graph in the example of Fig. 3, the performance of the child belonging to the FHR-SZ group may be interpreted as reflecting the need for more time to "see" the presented digits. This pattern may come about in two distinct ways; both a higher perceptual threshold and decreased processing speed may result in worse performance at the lower stimulus durations. In this case, the estimated attentional parameters for the two children shown in Fig. 3 point to a substantial difference in processing speed (Control: C = 53.80 digits/second; FHR-SZ: C = 29.60 digits/second) and no difference in thresholds (Control: t_0 = 18.75 ms; FHR-SZ: t_0 = 16.74 ms) nor attentional storage capacity (Control: K = 2.89 digits; FHR-SZ: K = 2.79 digits). This is also reflected at the group level as mentioned above.

In a multiple linear regression model of the associations between perceptual aspects of visual processing speed (C) and a priori selected predictors including (1) neurocognitive functions thought to be theoretically related, (2) severity of psychopathology, and (3) adequacy of the home environment, we found several significant associations as well as non-significant associations. First, reduced perceptual processing speed (C) is associated with increased error proneness in visuospatial sketchpad functions (Baddeley, 2000) of working memory functions (SWM Total Errors). Thus, the slower the processing speed the more difficulties with retaining elements in working memory (or vice versa), or the association is mediated by a third underlying component. Second, increased perceptual processing speed of visual attention (C) is positively associated with increased psychomotor processing speed (Symbol Search). These associations add to the convergent validity of the TVA parameter C and were independent of risk status. Also, the latter association supports existing evidence of significant correlations

Table 3
Multiple linear regression models[a,b] examining the potential relationships of familial high risk status, home environmental, neurocognitive, and psychopathological characteristics to the TVA-based parameters of visual attention in 7-year-old children at familial high risk of schizophrenia (FHR-SZ), bipolar disorder (FHR-BP), and controls.

Predictors	Processing speed of visual attention (*C*), Elements per second		Visual short-term memory span (*K*), Number of elements		Threshold of visual perception (t_0), Milliseconds		Error rate	
	β (95% CI)	*P*[c,d]	*β* (95% CI)	*P*[c,e]	*β* (95% CI)	*P*[c,e]	*β* (95% CI)	*P*[c,e]
Familial high risk of schizophrenia	−0.29 (−0.57;−0.00)	.05*	−0.04 (−0.55;0.47)	.88	−0.03 (−0.45;0.39)	.89	−0.01 (−0.04;0.03)	.75
Familial high risk of bipolar disorder	−0.42 (−0.72;−0.11)	.008*	−0.54 (−1.10;0.01)	.06	−0.07 (−0.52;0.37)	.75	−0.01 (−0.05;0,03)	.66
Reynold's Intellectual Screening Test Index (IQ Estimate)	−0.04 (−0.18;0.09)	.55	0.02 (−0.21;0.26)	.84	0.03 (−0.17;0.23)	.79	−0.01 (−0.03;0.00)	.08
Middle Childhood-HOME Inventory	0.03 (−0.07;0.12)	.56	0.05 (−0.12;0.22)	.58	0.10 (−0.04;0.24)	.16	0.01 (−0.00;0.02)	.14
Symbol Search	0.14 (0.01;0.27)	.04*	NA	NA	0.11 (−0.08;0.30)	.25	NA	NA
Rapid Visual Information Processing, A' (A Prime)	0.09 (−0.03;0.20)	0.15	−0.02 (−0.22;0.18)	.82	NA	NA	−0.01 (−0.03;−0.00)	.04
Spatial Working Memory, Total errors	−0.23 (−0.36;−0.09)	.001*	−0.11(−0.36;0.14)	.39	NA	NA	NA	NA
Spatial Span, Span length	NA	NA	−0.02(−0.24;0.20)	.87	NA	NA	NA	NA
Rapid Visual Information Processing, Mean latency (seconds)	NA	NA	NA	NA	0.03 (−0.12;0.17)	.74	NA	NA
Rapid Visual Information Processing, Total false alarms	NA	NA	NA	NA	−0.09 (−0.27;0.09)	.32	NA	NA
Attention Deficit/Hyperactivity Disorder – rating scale, Total score	NA	NA	NA	NA	NA	NA	0.01 (−0.01;0.03)	.19
Child Behavior Checklist, Total score	NA	NA	NA	NA	NA	NA	–0.00 (−0.00;0.00)	.53

Abbreviations: NA, Not applicable (means that the respective predictors were not included in the model for the respective TVA-measures).

[a] Only main effects presented due to non-significant interactions with familial high risk status.

[b] The control group was used as reference in the multiple linear regression model.

[c] Significant beta coefficients ($p < .05$) are indicated with an asterisk provided that the model was significant.

[d] The model for *C* was statistically significant ($p < .05$).

[e] The models for *K*, *t*0, and error rate respectively were rendered non-significant ($p > .05$).

between parameter *C* and neurocognitive tests of simple motor-dependent response time (suggesting that faster processing speed is accompanied by shorter response latency) (Finke et al., 2005). Noteworthy, our findings suggest that the reduced perceptual processing speed of visual attention (*C*) in children at FHR-SZ and FHR-BP cannot be explained by deficits in sustained attention (RVP A'), intelligence (RIST Index), or adequacy of the home environment (MC-HOME). A few previous studies have investigated the association of TVA parameters with general intelligence (Finke et al., 2005; Caspersen, 2016). In a study of a non-clinical adult population only non-significant correlations of *K* and *C* with intelligence were found (Finke et al., 2005). Similarly, in a group of 57 normally developing children between 8–12 years there were no significant correlations between general intelligence and the TVA parameters *C* and *K* (Caspersen, 2016). These findings suggest that visual attention functions as measured by the TVA paradigm appear independent of intelligence level, which is corroborated by the current results.

In contrast to a previous finding of significant correlations between the capacity of visual short-term memory (*K*) and visual working memory (visual memory span in a backwards version) (Finke et al., 2005), we did not find the capacity of visual short-term memory (*K*) to be significantly associated with theoretically related neurocognitive functions. Previous findings of significant correlations between parameter K and motor-dependent visual scanning speed (suggesting that larger visual short-term memory span is accompanied by faster visual scanning speed) (Finke et al., 2005) was not investigated in the current study. However, we found no significant association to the adequacy of the home environment. Similarly, the threshold of visual perception (t_0) in children at FHR-SZ or FHR-BP at this age was surprisingly not associated with any of the preselected neurocognitive functions. Again, we found no significant association to the adequacy of the home environment.

This is the first study comparing perceptual aspects of visual attention in young children at FHR-SZ and FHR-BP using a task independent of motor-based response latency. Additionally, it is a strength that the participating children were examined within a narrow age range, because it allows for a reliable characterization of aspects of attention functions at this neurocognitive stage. Finally, to our knowledge this is the largest study to date measuring visual attention in children (clinical or non-clinical) using the TVA paradigm. Nevertheless, larger group sizes would have permitted inclusion of more predictors in the search for neurocognitive and other factors associated with the parameters of the TVA-based whole report. Another limitation is the smaller sample size in the group of children at FHR-BP compared to the other groups. Thus, a larger sample size in the FHR-BP group could potentially have detected significant deficits in visual short-term memory span compared to the control group ($d = 0.58$; $p = .11$). Further, owing to the cross-sectional nature of this study the predictive value of the current results regarding transition to psychosis or any mental illness is yet to be investigated in ongoing and planned follow-up studies of this cohort. Finally, if any of the participating children had a specific disorder of mathematical skills this potentially may have affected their processing speed in a negative direction.

5. Conclusions

The TVA-based whole report paradigm identified deficits in the perceptual processing speed of visual attention in children at FHR-SZ as well as in children at FHR-BP at seven years of age, which may reflect the effect of shared vulnerability risk genes. TVA measures reflecting storage capacity of visual short-term memory, threshold of visual perception, and rate of error did not differentiate between children at FHR-SZ, FHR-BP, and controls and thus appear independent of risk status at this young age. Perceptual visual processing speed was associated with risk status. Thus, both being at risk of FHR-SZ and being at risk of FHR-BP (versus control) must be associated with components other than spatial working memory and psychomotor speed that are not identified in this study. Neither the storage capacity of visual short-term memory (*K*), threshold of visual perception (t_0), nor rate of error, when measured with the TVA-based whole report, were associated with other neurocognitive functions, adequacy of the home environment, or symptom dimensions. Early identification of children at FHR-SZ and FHR-BP with decreased perceptual processing speed of visual attention may represent a relatively low-cost effort and a potential basis for low risk interventions.

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Conflict of interest

All authors declare that they have no conflicts of interest.

CRediT authorship contribution statement

Nicoline Hemager: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Signe Vangkilde:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Anne Thorup:** Conceptualization, Data curation, Writing - review & editing, Funding acquisition. **Camilla Christiani:** Data curation, Writing - review & editing. **Ditte Ellersgaard:** Data curation, Writing - review & editing. **Katrine Søborg Spang:** Data curation, Writing - review & editing. **Birgitte Klee Burton:** Data curation, Writing - review & editing. **Aja Neergaard Greve:** Data curation, Writing - review & editing. **Ditte Lou Gantriis:** Data curation, Writing - review & editing. **Ole Mors:** Conceptualization, Writing - review & editing, Funding acquisition. **Jens Richardt Møllegaard Jepsen:** Conceptualization, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Merete Nordentoft:** Conceptualization, Writing - review & editing, Funding acquisition. **Kerstin Jessica Plessen:** Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing, Funding acquisition.

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Supplementary materials

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