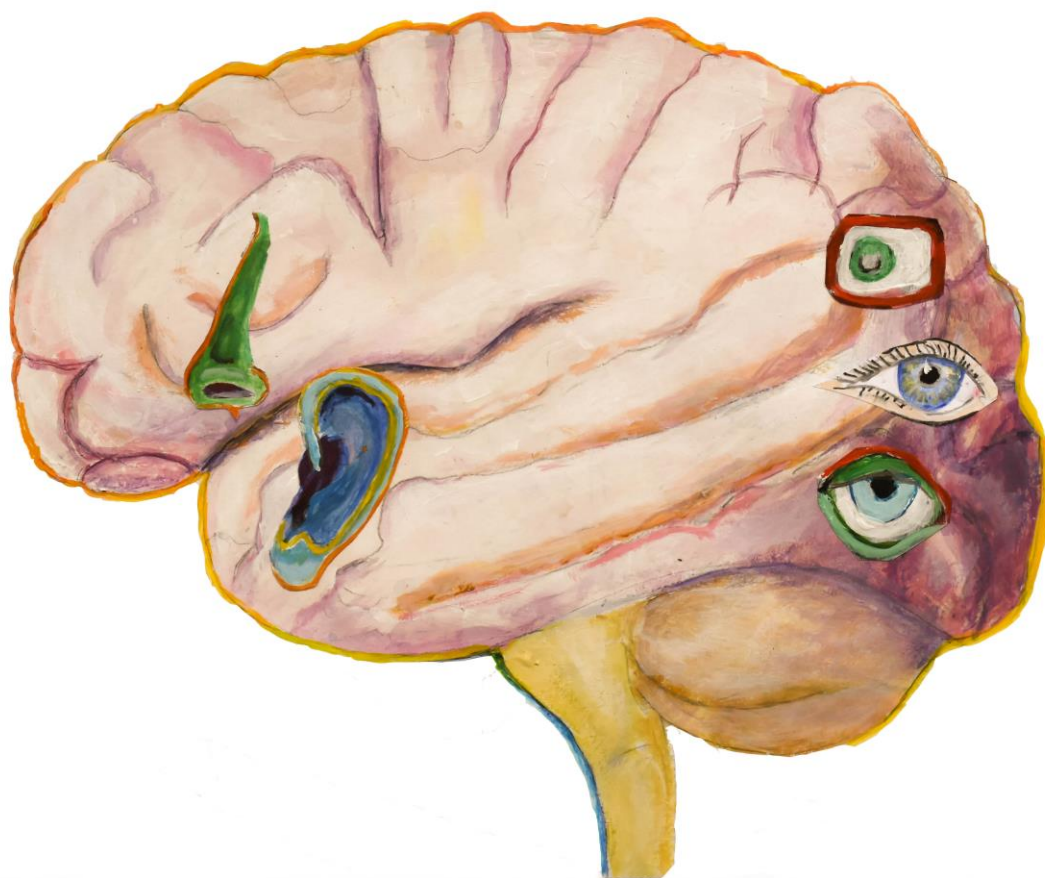


From early information processing to higher-order cognitive functioning in children with familial high risk of schizophrenia or bipolar disorder



PhD Thesis

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This thesis has been submitted to the Graduate School of Health and Medical Sciences,
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DANISH RESEARCH
CENTRE FOR
MAGNETIC RESONANCE



**Mental Health
Services**

PhD thesis

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1. Preface

The work of the present dissertation was conducted at the Child and Adolescent Mental Health Centre, Mental Health Services in the Capital Region of Denmark; the Danish Research Centre for Magnetic Resonance (DRCMR), Copenhagen University Hospital Hvidovre; Copenhagen Research Center for Mental Health (CORE), Mental Health Centre Copenhagen; and the University of Copenhagen, Denmark. The PhD scholarship was financed by the Capital Region of Psychiatry, Mental Health Services Capital Region, Denmark. The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), the Mental Health Services of the Capital Region of Denmark, The Research Fund in Capital Region of Denmark, The Innovation Foundation, and The Independent Research Fund Denmark have supported the Danish High Risk and Resilience Study - VIA 11.

The participants included in the present PhD project were part of the Danish High Risk and Resilience Study VIA 7 and VIA 11, including children born to parents diagnosed with schizophrenia or bipolar disorder and children born to parents without these diagnoses. The VIA 7 study started in 2013 and the VIA 11 study is the first follow-up of the project, which started in 2017.

This dissertation is based on four studies examining brain responses and/or cognitive functions and a study protocol that describes the rationale and methods of the electroencephalographic part of the VIA 11 study. The papers are enclosed as appendices. The work was carried out in the period from December 2016 to February 2020.

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2. List of Papers

This dissertation is based on the following five scientific papers:

1. *Normal mismatch negativity in children with familial high risk of schizophrenia or bipolar disorder*
Ver Loren van Themaat, A.H., Oranje, B., Tomasevic, L., Larsen, K.M., Korsgaard Johnsen, L., Thorup, A.A.E., Plessen, K.J., Siebner, H.R.*, Nordentoft, M.* Submitted.
2. *Behavioral performance and neural responses during a visuomotor conflict task in children with familial high risk for schizophrenia and bipolar disorder*
Ver Loren van Themaat, A.H., Larsen, K.M., Tomasevic, L., Korsgaard Johnsen, L., Eichele, H., Oranje, B., Baladi Nejad, A., Baaré, W.F.C., Thorup, A.A.E., Plessen, K.J., Nordentoft, M.*, Siebner, H.R.* Manuscript in preparation.
3. *Development of visual attention from age 7 to age 12 in children with familial high risk for schizophrenia or bipolar disorder*
Ver Loren van Themaat, A.H., Hemager, N., Korsgaard Johnsen, L., Burton, B.K., Ellersgaard, D., Christiani, C.J., Brandt, J., Gregersen, M., Falkenberg Krantz, M., Spang, K.S., Søndergaard, A., Møllegaard Jepsen, J.R., Thorup, A.A.E., Siebner, H.R., Plessen, K.J., Nordentoft, M., Vangkilde, S. Submitted.
4. *Odor Identification in 7-year-old Children at Familial High Risk of Schizophrenia or Bipolar Disorder - The Danish High Risk and Resilience Study VIA 7*
Ver Loren van Themaat, A.H., Uddin, M.J., Christiani, C.J., Hemager, N., Ellersgaard, D., Burton, B.K., Spang, K.S., Greve, A., Gantriis, D., Mors, O., Thorup, A.A.E., Plessen, K.J., Nordentoft, M., Møllegaard Jepsen, R.J. *Schizophrenia Research*. 2020 Jan 8. ppi: S0920-9964(19)30598-5.
doi: 10.1016/j.schres.2019.12.028.
5. *Event-related electroencephalographic responses in children at familial high risk for schizophrenia or bipolar disorder: a single-site EEG sub-study of the Danish High Risk and Resilience Study-VIA 11*
Ver Loren van Themaat, A.H., Larsen, K.M., Oranje, B., Tomasevic, L., Baaré, W.F.C., Baladi Nejad, A., Eichele, H., Thorup, A.A.E., Nordentoft, M., Plessen, K.J., Siebner, H.R., PsyArXiv, 11 Nov. 2019. Web.

3. Abbreviations

ACC:	Anterior Cingulate Cortex
ADHD:	Attention Deficit Hyperactivity Disorder
ADHD-RS:	Attention Deficit Hyperactivity Disorder – Rating Scale;
ANOVA:	Analysis of Variance
ASD:	Autism Spectrum Disorders
ARMS:	At-Risk Mental State
BF:	Bayes Factor
BSIT:	Brief Smell Identification Test
C:	Visual Processing Speed
CBCL:	Child Behavior Checklist
CHR:	Clinical High-Risk
CGAS:	Children’s Global Assessment Functioning
CORE:	Copenhagen Research Center for Mental Health
CV _{RT} :	Coefficient of Variation of Reaction Time
DCRS:	Danish Civil Registration System
DSM-IV or -V:	Diagnostic and Statistical manual of Mental Disorders, Fourth or Fifth Edition
DPCR:	Danish Psychiatric Central Research Register
DurMMN:	Duration MMN
EEG:	Electroencephalography
EHRS:	Edinburgh High-Risk Study
ERP:	Event-Related Potential
FDMMN:	Frequency*Duration MMN
FDR:	First-Degree Relatives
FHR:	Familial High-Risk
FHR-BP:	Familial High-Risk of Bipolar Disorder
FHR-SZ:	Familial High-Risk of Schizophrenia
fMRI:	Functional Magnetic Resonance Imaging

FreqMMN:	Frequency MMN
ICD-10:	The ICD-10 Classification of Mental and Behavioral Disorders, Clinical Description
iPSYCH:	The Lundbeck Foundation Initiative for Integrative Psychiatric Research
K:	Visual Short-Term Memory
LRP:	Lateralized Readiness Potential
MANOVA:	Multivariate Analysis of Variance
MFS:	Memory for Stories
MMN:	Mismatch Negativity
MRI:	Magnetic Resonance Imaging
NMDA:	N-methyl-D-aspartate
OCD:	Obsessive-Compulsive Disorder
OFC:	Orbitofrontal Cortex
PBC:	Population-Based Controls
PET:	Positron Emission Tomography
PREP:	Pittsburgh Risk Evaluation Program
PSP:	Personal and Social Performance
r :	Correlation Coefficient
r_s :	Spearman's Correlation Coefficient
RIST:	Reynold's Intellectual Scaling Test
RM-ANOVA:	Repeated Measures Analysis of Variance
RT:	Reaction Time
RVP:	Rapid Visual Information Processing
SD:	Standard Deviation
SMI:	Severe Mental Illness
SRS:	Social Responsiveness Scale
t_0 :	Threshold for Visual Perception
TVA:	Theory of Visual Attention
WSR:	Word Selective Reminding

4. Dansk Resumé

Baggrund

Skizofreni og bipolar sindslidelse er blandt de mest alvorlige mentale lidelser og udgør en stor byrde for patienterne selv, patienternes pårørende og samfundet som helhed. De første kliniske symptomer viser sig oftest i de sene teenageår eller i de tidlige voksenår, hvorfor patienterne som oftest også modtager diagnosen i denne alder. Patienter med skizofreni eller bipolar sindslidelse udviser en nedsat evne inden for en række forskellige kognitive, adfærdsmæssige og emotionelle domæner lang tid inden sygdommen indtræder – allerede i barndommen. Den sene forekomst af kliniske symptomer resulterer i forsinket diagnosticering, som kan have betydelige negative konsekvenser for patienterne såsom uhensigtsmæssig brug af medikamenter, øget hospitalisering, udeblivelse fra skole, uddannelse eller job og i værste tilfælde selvmord. Det er derfor vigtigt at forbedre de nuværende diagnostiske strategier ved at finde frem til sygdomsmarkører, der identificerer individer med forhøjet risiko for at udvikle skizofreni eller bipolar sindslidelse tidligere end hvad tilfældet er i dag.

Én måde at angribe det på er ved at studere børn med biologiske forældre som er diagnosticeret med skizofreni eller bipolar lidelse. Disse børn har, sammenlignet med børn af psykiatrisk raske forældre, forøget risiko for at udvikle disse lidelser selv. Formålet med denne afhandling er at undersøge funktionelle abnormiteter som ofte findes i skizofreni og bipolar lidelse, i børn med familiær risiko for skizofreni (FHR-SZ) og bipolar sindslidelse (FHR-BP). Søgningen af funktionelle abnormiteter i børn med FHR blev udført med måling af elektroencefalografi (EEG) samt kognitive opgaver. EEG blev målt under forskellige paradigmer for at undersøge neurale responser der reflekterer et mismatch på en forventning (MMN), konfliktovervågning (N200), opmærksomhed (P3b), samt motorisk forberedelse (lateralized readiness potential (LRP)). De kognitive opgaver fokuserede på kognitiv kontrol, visuel opmærksomhed og evnen til at identificere lugte (lugteidentifikation). Disse neurale responser og kognitive funktioner har vist at være nedsat i skizofreni og bipolar sindslidelse, men er ikke ofte, hvis overhovedet, blevet undersøgt i børn med FHR-SZ og FHR-BP.

Metoder

Denne afhandling er en del af The Danish High Risk and Resilience Study som i 2013 rekrutterede 522 danske 7-årige børn med 0, 1, eller 2 forældre med skizofreni eller bipolar sindslidelse, VIA 7 undersøgelsen. Fire år senere blev de samme børn opfordret til at deltage i den første opfølgning, VIA 11 undersøgelsen. Denne afhandling inkluderer fire forskellige studier, som er baseret på data fra både VIA 7 og VIA 11 undersøgelserne.

I det første studie blev EEG målt under et 'auditory oddball paradigm' til at fremkalde MMN i børn med FHR-SZ eller FHR-BP og en kontrolgruppe. I andet studie blev EEG målt under en kognitiv opgave omhandlende visuel konfliktovervågning, en såkaldt flanker opgave. Dette paradigme blev brugt til at undersøge de neurale responser N200, P3b, og LRP. Amplituder og / eller latenstider for disse neurale responser blev sammenlignet mellem grupperne. Kognitiv præstation, målt som reaktionstid og præcision i flanker opgaven, blev også sammenlignet mellem grupperne. I det tredje studie blev udviklingsbanen for visuel opmærksomhed undersøgt i et follow-up design som inkluderede data fra VIA

7 og VIA 11 undersøgelserne. Visuel opmærksomhed blev målt ved hjælp af en opgave baseret på Theory of Visual Attention (TVA). Endeligt, det fjerde studie undersøgte lugtidentifikation ved hjælp af The Brief Smell Identification Test (BSIT), som er en valideret test der vurderer evnen til at identificere lugte.

Resultater

Børn med FHR-SZ eller FHR-BP viste ingen abnormiteter i MMN sammenlignet med kontrolbørn. Desuden blev det vist, at børn med længere forsinkelser af MMN viste dårligere global funktion. Det neurale respons P3b blev målt under udførelse af flanker opgaven og her viste børn med FHR-SZ eller FHR-BP reducerede amplituder sammenlignet med kontrolgruppen. Der blev ikke fundet nogen forskelle mellem grupperne i de neurale responser der reflekterer konfliktovervågning (N200) eller motorisk forberedelse (LRP). I forhold til kognitiv præstation under flanker opgaven viste børn med FHR-SZ eller FHR-BP større intra-individuel variation i reaktionstiden. Børn med FHR-SZ eller FHR-BP var dog lige så præcise til opgaven som kontrolgruppen. Resultaterne fra opgaven omhandlende visuel opmærksomhed viste ingen tegn på ændrede udviklingsbaner, hvilket indikerer at præstationen i den visuelle opmærksomhedsopgave forbedredes ligeligt mellem børn med FHR-SZ eller FHR-BD og kontrolbørn. Slutteligt, evnen til at identificere lugte var sammenlignelig mellem de tre grupper. Ved anvendelse af en amerikansk tærskel til at skelne en unormal fra en normal evne til at identificere lugt viste det sig, at drenge med FHR-SZ var mere tilbøjelige til at have en unormal evne, men anvendelse af en dansk tærskel understøttede ikke dette fund.

Konklusioner

Resultaterne viste sammenlignelige abnormiteter i børn med FHR-SZ eller FHR-BP med hvad der tidligere er rapporteret hos patienter med skizofreni og hos patienter med bipolar sindslidelse, nemlig P3b-amplitudereduktion og forøget intra-individuel variation i reaktionstiden. Børn med FHR-SZ eller FHR-BP viser ikke abnormiteter på de andre neurale responser (N200 og LRP) og børnene med FHR-SZ eller FHR-BP tyder heller ikke på at udvise ændrede udviklingsbaner for visuel opmærksomhed eller at have en dårligere lugtidentifikationsevne. Studierne i denne afhandling bidrager til den aktuelle viden om tidlige informationsprocesser og højere-ordens kognitiv funktion hos børn med FHR-SZ og FHR-BP. Longitudinelle studier er nødvendige for at overvåge udviklingen og modningen af disse neurale responser i forbindelse med kognitive funktioner hos børn med forøget risiko. Sådanne studier er grundlæggende for at give indsigt i, hvorvidt vores fund er et forbigående eller vedvarende træk. Ligeledes vil det give indsigt i om disse fund kan tjene som for senere sygdomsdebut eller som beskyttende faktor mod at udvikle disse lidelser.

5. English Summary

Background

Schizophrenia and bipolar disorder are among the most severe mental health illnesses which have a huge impact on patients, their family members, and society. Usually, patients receive their diagnosis during late adolescence or young adulthood, because of the late appearance of the clinical symptoms. However, patients with schizophrenia and bipolar disorder are observed with a variety of cognitive, behavior, and emotional impairments long before the illness onset - already during their childhood - suggesting that the pathology of the illness might have started earlier. The late appearance of clinical symptoms results in a delayed diagnosis, which has negative effects for patients such as inappropriate use of medication, increased hospitalizations, school dropouts, and suicide. Therefore, it is meaningful to improve our diagnostic strategies by finding markers that can identify individuals with a high risk of developing schizophrenia or bipolar disorder at an earlier stage.

One way of doing that is by studying children born to parents diagnosed with schizophrenia or bipolar disorder because they have a higher risk to develop these disorders. The present dissertation aimed at investigating several functional abnormalities that are common to schizophrenia and bipolar disorder, in children with familial high-risk of schizophrenia (FHR-SZ) or of bipolar disorder (FHR-BP). The search for functional abnormalities in children with FHR-SZ and with FHR-BP was carried out by measuring electroencephalography (EEG) as well as through the execution of cognitive tasks. EEG was recorded in paradigms to investigate the evoked neural response mismatch negativity (MMN), and those reflective of conflict monitoring (N200), attentional demand (P3b), and motor-response preparation (lateralized readiness potential (LRP)). The cognitive tasks focused on interference control, visual attention and the ability to identify smells (odor identification). These neural responses and cognitive functions are known to be impaired in schizophrenia and (although to a lesser degree) in bipolar disorder but have not often, if at all, been investigated in children with FHR-SZ or with FHR-BP.

Methods

This dissertation is part of the Danish High Risk and Resilience Study which recruited 522 Danish 7-year-old children with 0, 1, or 2 parent(s) with schizophrenia or bipolar disorder in 2013, the VIA 7 study. Four years later, children were invited to participate in the first follow-up, the VIA 11 study. This dissertation includes four studies, of which one includes data of the VIA 7 study, one contains follow-up data (of both the VIA 7 and VIA 11 studies), and two contain data of the VIA 11 study, as well as a study protocol that described our EEG-related questions and the subsequent rationales, methods, and outcome measures clearly defined beforehand.

In the first study, EEG was recorded in an auditory oddball paradigm to elicit MMN in children with FHR-SZ, FHR-BP and population-based control (PBC) children. In the second study, EEG was recorded during a cognitive task assessing interference control, i.e. the flanker task, to investigate the neural responses N200, P3b, and the LRP. All these neural responses were compared between the groups in terms of amplitudes and/or latencies. Behavioral performance on the flanker task was also compared between groups. Further, in the third study, performance at age 12 as well as the developmental trajectories of

visual attention were examined in a follow-up design including data of the VIA 7 and the VIA 11 study. Visual attention was assessed through a task based on the Theory of Attention (TVA). Lastly, the fourth study investigated odor identification using the Brief Smell Identification Test (BSIT), a validated test assessing the ability to identify odors.

Results

Children with FHR-SZ and with FHR-BP demonstrated no abnormalities in MMN as compared to PBC children. An association was found between MMN (peak latency) and global functioning in all children. Neural responses recorded during the flanker task revealed abnormalities on P3b in terms of reduced amplitudes in children with FHR-SZ and with FHR-BP. No abnormalities were found in neural responses reflecting conflict monitoring (N200) or motor-response preparation (LRP). In terms of the behavioral performance on the flanker task, children with FHR-SZ and with FHR-BP showed increased intra-subject variability of reaction time in the incongruent condition. Children with FHR-SZ and with FHR-BP were as accurate on the task as PBC children. Further, we found no altered developmental trajectories on visual attention in children with FHR-SZ and with FHR-BP, shown by a comparable improvement of distinct aspects of visual attention as compared to PBC children; also the children with FHR-SZ that initially showed deficits at age 7. Lastly, the ability to identify odors was comparable between the three groups. Although using an American-based threshold to distinguish an abnormal from a normal ability to identify odors showed that boys with FHR-SZ were more likely to have an abnormal ability, the threshold based on Danish data could not support this finding.

Conclusions

Our results showed some similar functional abnormalities that have been reported in schizophrenia and bipolar disorder, in children with FHR-SZ and with FHR-BP, namely P3b amplitude reductions and increased intra-subject variability of reaction time. Further, children with FHR-SZ and with FHR-BP did not show abnormalities on the other neural responses (N200 and LRP) and neither showed they altered developmental trajectories of visual attention or an impaired odor identification ability. These findings contribute to the current literature on early information processes and higher-order cognitive functioning in children with FHR-SZ and with FHR-BP. Longitudinal studies are warranted to monitor the development and maturation of these neural responses and cognitive functions in high-risk children. Such studies are fundamental to provide insights on whether our findings serve as transitory or persistent features and whether these may serve as a predictor for later illness onset, or possibly, may serve as protection from developing such disorders.

6. Introduction

A shift has occurred in the field of psychiatry. Whereas the former goal was to treat psychiatric patients adequately, nowadays psychiatry is, in addition, increasingly focused on the prevention of mental health illnesses. Prevention of mental health illnesses can be achieved by predicting which individuals will develop a mental health illness as well as by providing intervention as early as possible. To that end, we need clear and distinct markers that facilitate identifying individuals at-risk. Furthermore, for designing early treatments, insight into the underlying neurobiological mechanisms is warranted.

One example illustrating the current worldwide focus on prevention in psychiatry is the use of clinical staging, particularly in the area of psychosis (Kotlicka-Antczak et al., 2020; McGorry, Hickie, Yung, Pantelis, & Jackson, 2006). Staging is the traditional framework in clinical medicine to differentiate initial and milder clinical stages from severe and final stages, but it only had its first introduction in psychiatry in the early 1990s (Fava & Kellner, 1993). Since then, the concept has been constructed and extensively studied (McGorry et al., 2014; McGorry, Killackey, & Yung, 2008). The aim of clinical staging is to classify patients according to the severity of the symptoms. Clear definitions of the antecedent stages, e.g. the period preceding the illness onset, allow clinicians to intervene at an earlier stage. Intervening at earlier stages is assumed to be more effective and less harmful compared to interventions delivered later in the illness progression. The advancements in clinical staging concerning psychotic and severe mood disorders have resulted in specific criteria to identify individuals with an at-risk mental state (ARMS) or clinical high-risk (CHR) state. This has led to an increase in research that shed light on the early stages of the development of psychotic disorders, prediction of transition to psychosis, as well as on possibilities to alter this course (Fusar-Poli et al., 2013). To further improve such prediction models, it is essential to have specific identification markers that facilitate detecting vulnerability for developing psychosis, without the phenotypic manifestation of clinical symptoms.

The aim of this dissertation was to investigate different stages of information processing in children born to parents diagnosed with schizophrenia or bipolar disorder. Hereby, this dissertation aims to contribute to the question of whether early information processes and higher-order cognitive functions can be used for the early identification of vulnerability for developing schizophrenia or bipolar disorder as well as to the understanding of the underlying neurobiological mechanisms of vulnerability states of schizophrenia and bipolar disorder.

6.1 Schizophrenia and bipolar disorder

In the last decades, there has been an increasing interest within the worldwide mental health sector in investigating the etiology of SMI such as schizophrenia and bipolar disorder. The debate continues whether schizophrenia and bipolar disorder are separate entities or whether the two disorders have one essential pathological process with different manifestations (Demjaha, MacCabe, & Murray, 2012). Literature shows substantial evidence for an overlap in genetic vulnerability (Purcell et al., 2009), etiology, risk factors (Uher, 2014), and interventions between the two disorders. The clinical symptoms that are used to set the diagnosis are most commonly recognized in late adolescence or early adulthood. For schizophrenia, these clinical symptoms include hallucinations, delusions, apathy, and anhedonia. Bipolar disorder is characterized by periodically switching from a mania state to a depressed state. Despite that

the clinical symptoms of both disorders arise relatively late in life, several behavioral, emotional, mood and motor abnormalities precede these clinical symptoms during childhood and early adolescence. The presence of these early, unrecognized abnormalities that indicate a vulnerability for the disorders also suggests that schizophrenia has a neurodevelopmental nature (Lewis & Levitt, 2002; Rapoport, Giedd, & Gogtay, 2012), and perhaps also of bipolar disorder, although alternative theories also exist (Berk, 2009).

At this point, the notion of vulnerability is not clearly defined. For example, children born to parents with an SMI have a higher risk to develop a similar disorder, but it is currently unclear which factors suggest a higher probability to proceed into the disorder. Also, it is important to understand that all patients with SMI have been vulnerable to the disorder, whereas not all vulnerable individuals will develop an SMI. We need to gain insights into what vulnerability means, and how it interacts with genetic or environmental factors, to be able to improve early intervention methods.

6.1.1 Neurodevelopmental disorder

The widely accepted proposal of schizophrenia being a neurodevelopmental disorder postulates that the illness is the result of an abnormal brain development that started long before the first recognized clinical symptoms (Rapoport et al., 2012), driven by both genetic vulnerability and environmental factors (Lewis & Levitt, 2002). The overlap between schizophrenia and bipolar disorder in cognitive and neurological abnormalities has led to the assumption that bipolar disorder may also have this neurodevelopmental nature (Sanches, Keshavan, Brambilla, & Soares, 2008). However, studies have also reported that the cognitive deficits in bipolar disorder arise at the same time as the clinical symptoms, which would make the cognitive deficits in bipolar disorder rather state- than trait-dependent (Trotta, Murray, & MacCabe, 2015). Following the neurodevelopmental theory, early measurable processes of vulnerability may be present in individuals at-risk (Gottesman & Gould, 2003). These early vulnerability measures may be indicative of reflecting the unrecognized cognitive, behavioral and emotional abnormalities preceding the diagnostic illness onset and may teach us about abnormalities in brain development that may lead, or not, to the development of SMI.

6.1.2 Endophenotypes

An endophenotype reflects the actions of genes that are predisposed to a specific disorder, regardless of having the diagnosable pathology. It has been proposed that an endophenotype requires to be (1) related to the illness, (2) heritable, (3) present in active illness-states as well as in remission states (i.e. state-independent), (4) present at a higher rate in family members of affected individuals relative to the general population, (5) and reliably measurable (Gottesman & Gould, 2003). With regard to psychiatric disorders, an endophenotype can be a neurocognitive, neurophysiological, neurodevelopmental, endocrinological, biochemical, or neuroanatomical measurable feature that is stable and heritable (Braff, Freedman, Schork, & Gottesman, 2007).

In contrast to relatively simple Mendelian dominant illnesses like Huntington's Disease, in which changes in the genetic coding of the amino acid sequence are directly associated with functional changes, endophenotypes for psychiatric disorders are conceptualized as multifactorial (Braff et al., 2007). A multifactorial endophenotype is most likely reflecting the interaction of influences from genetic, epigenetic, stochastic, and nongenetic factors. Also, it is rather likely that multiple genes are affected, instead of a singular one (Braff et al., 2007). Several research groups emphasized the importance of the

use of endophenotypes in psychiatry (Bearden & Freimer, 2006; Weiser, Van Os, & Davidson, 2005), which are likely closer linked to specific genetic distortions than to diagnostic entities defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Braff et al., 2007).

A positive family history is currently the strongest predictor for schizophrenia and bipolar disorder. Children who have one or two parents with schizophrenia or bipolar disorder are at familial high-risk (FHR). Children born to parents with schizophrenia, bipolar disorder or a major depressive disorder have a 32% probability of developing a similar disorder by adulthood and approximately 55% of these children will develop any mental disorder (Rasic, Hajek, Alda, & Uher, 2014). Previous findings of FHR-studies point to clinical, neurocognitive, environmental, and neuroanatomical factors being involved in the familial transmission of schizophrenia and bipolar disorder and such studies contribute to the knowledge of distinct or shared developmental trajectories of the two illnesses.

6.1.3 Familial high-risk studies

Recently, a review reported the results of three waves of FHR-studies from over the last 70 years (Sandstrom, Sahiti, Pavlova, & Uher, 2019). They described that the first wave was schizophrenia-focused, including offspring of patients with schizophrenia, and demonstrated early impairments in the social and neurological domains. The second wave included, in addition, offspring of patients with mood disorders who were also observed with early impairments in several domains, questioning the specificity of such impairments to schizophrenia. The third wave focused on the offspring of patients with bipolar disorder and on transdiagnostic approaches. Several large-scale projects included the application of neuroimaging, fine-grained phenotypes, and molecular genetics, expanding the variety of questions that can be answered. Overall, previous FHR-studies conclude that family history is still the strongest predictor for developing an SMI. The Danish High Risk and Resilience Study is an FHR-study including both children with FHR of schizophrenia (FHR-SZ) and children with FHR of bipolar disorder (FHR-BP) and children of parents without schizophrenia or bipolar disorder (referred to as population-based control (PBC) children).

6.1.3.1 Results from the Danish High Risk and Resilience Study - VIA 7

The baseline of the Danish High Risk and Resilience - VIA 7 started investigating the development of children with FHR in 2013 when children were 7 years of age (see Figure 1 for the concept of FHR-studies with the Danish High Risk and Resilience Study as an example). The findings regarding psychopathology (Ellersgaard et al., 2018), neurocognition (Burton et al., 2018; Hemager et al., 2018; Hemager et al., 2019), social cognition (Christiani et al., 2019), motor development (Burton et al., 2017), and home environment (Gantriis et al., 2019) will shortly be described below to give an idea of the cohort's functioning at age 7.

39% percent of children with FHR-SZ and 36 percent of children with FHR-BP displayed a DSM-IV Axis 1 psychiatric diagnosis (after excluding elimination disorders), which was both significantly higher than the 15 percent of the PBC children. The level of functioning of children with FHR-SZ was significantly lower compared to PBC children but also compared to children with FHR-BP, whose level of functioning was also lower than that of PBC children (Ellersgaard et al., 2018). In addition, the basic needs of a healthy home environment for 7-year-old children were not met in 21 percent of the children with FHR-SZ and in 7 percent of children with FHR-BP, which was both significantly higher than the 2 percent of the PBC children (Gantriis et al., 2019). Together, these findings show that children of the two FHR groups have

higher rates of psychopathology and would, therefore, need more support and stability from their environment. However, 21 percent of the home environments of children with FHR-SZ and 7 percent of the home environments of children with FHR-BP do not seem to be able to provide the support and stability that these children need.

At a neurocognitive level, children with FHR-SZ showed widespread impairments compared to PBC children, while the neurocognitive performance of children with FHR-BP and PBC children did not differ (Burton et al., 2018; Hemager et al., 2018). In addition, children with FHR-SZ showed deficits in receptive and pragmatic language, impaired social responsiveness (Christiani et al., 2019), deficits in fine motor function and balance (Burton et al., 2017) compared to PBC children, while children with FHR-BP did not show such deficits compared to PBC children. These findings suggest distinct neurodevelopmental manifestations of children with FHR-SZ and with FHR-BP (Burton et al., 2017; Burton et al., 2018; Christiani et al., 2019; Hemager et al., 2018).

Taken together, these findings highlight the notion that children with FHR-SZ are more affected by the genetic and/or environmental factors than children with FHR-BP. Interestingly, the most vulnerable group in several publications have been boys with FHR-SZ. Despite that children with FHR-BP did not show cognitive, motor, social, or language deficits, these children had higher rates on psychopathology and lower support from their home environment than PBC children. These findings emphasize the need for early interventions to alter or support a healthy development for these children.

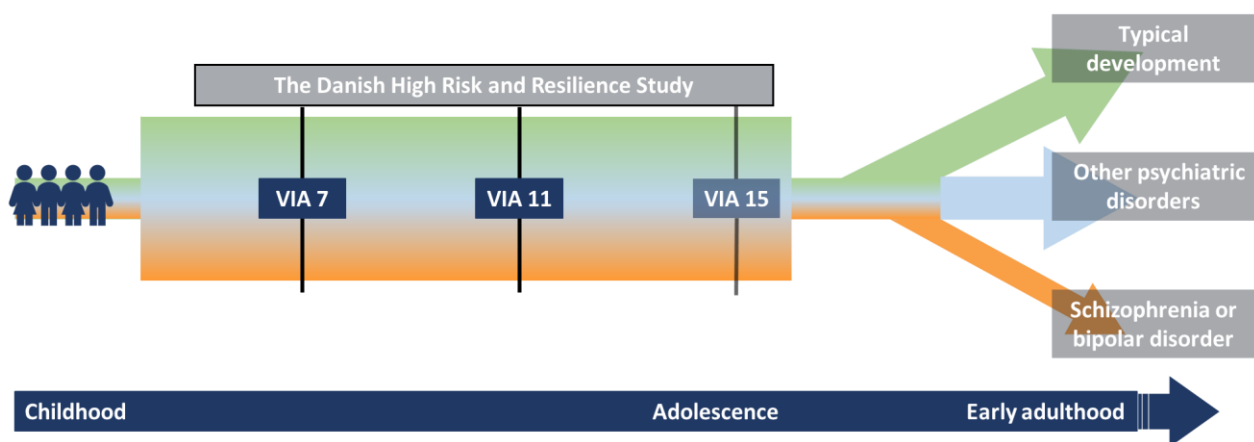


Figure 1 Principle of familial high-risk (FHR) studies with the example of the Danish High Risk and Resilience Study - VIA 7 and VIA 11. In the VIA 7 study, children were 7 years of age; in the VIA 11 study, children were 11-12 years of age; and in the planned third wave, the VIA 15 study, children will have the age of 15(-16) years.

6.1.4 Altered brain development in children with FHR

Additionally to the studies on psychopathological, neurocognitive, and behavioral domains, a few FHR-studies focused on brain development by using neuroimaging techniques. Two longitudinal prospective FHR-studies included structural magnetic resonance imaging (MRI), the Edinburgh High-Risk Study (EHRS) (Johnstone, Ebmeier, Miller, Owens, & Lawrie, 2005) and the Pittsburgh Risk Evaluation Program (PREP), which also included electroencephalography (EEG) (Keshavan, Diwadkar, Montrose, Stanley, & Pettegrew, 2004). The EHRS included 163 young adults (age: 16-25 years) having at least two relatives

with schizophrenia, and 36 controls (Johnstone et al., 2005). Reductions in grey matter density in the anterior cingulate cortex (ACC) were found in FHR individuals as compared to controls (Job et al., 2003). In a two-year follow-up, the group of the FHR individuals that had developed psychotic symptoms was compared to the group that remained resilient. The FHR individuals with psychotic symptoms showed greater reductions of temporal lobe volumes two years before the emerging symptoms as compared to those without psychotic symptoms. This decrease of the temporal lobe volume was suggested as a transitioning marker from the vulnerable to a psychotic state (Job, Whalley, Johnstone, & Lawrie, 2005). With more confirming findings, such reductions may be able to predict the onset of schizophrenia at an early stage.

The PREP included first-degree relatives (FDR) with at least one relative with schizophrenia and FDR were aged 6 to 25 years. Both younger and older FDR showed prefrontal and temporal volumetric abnormalities compared to controls, as well as volume reductions in the amygdala and hippocampus (Lawrie, McIntosh, Hall, Owens, & Johnstone, 2008; Rajarethinam, Sahni, Rosenberg, & Keshavan, 2004). Also, results on EEG demonstrated reduced amplitudes of a brain response reflecting higher levels of attention and cognitive control (P300) in the FDR of patients with schizophrenia compared to controls (Keshavan et al., 2004). The latter was also found in cross-sectional studies, not part of PREP (Friedman & Squires-Wheeler, 1994; Schreiber, Stolz, Rothmeier, Kornhuber, & Born, 1989).

A longitudinal study included non-psychotic siblings of patients with young childhood-onset schizophrenia and healthy controls, aged 8 to 28 years, in order to map the grey matter development in these non-psychotic siblings (Gogtay et al., 2007). At a young age, the non-psychotic siblings were observed with grey matter reductions in prefrontal and temporal cortices, however, these cortical reductions disappeared by the age of 20 years. Therefore, this study suggested grey matter loss as a familial/trait marker for schizophrenia, and, due to the normalization of these deficits by late adolescence, may prevent from illness onset through yet unknown protective factors.

Lastly, cross-sectional studies reported reductions in total gray matter volume in children with FHR-SZ and with FHR-BP (Sugranyes et al., 2017) and dysconnectivity in the basal ganglia network in children with FHR-SZ but not in children with FHR-BP (Sole-Padulles et al., 2016). Future longitudinal MRI studies including children with FHR-SZ and with FHR-BP are warranted to clarify potential brain abnormalities that may lead to disorders but also that may normalize over time, which would increase our understanding of the neurodevelopmental course of these disorders.

6.2 From early information processing to higher-order cognitive functioning

Several decades ago, McGhie and Chapman reported that patients with schizophrenia often complained about being “overmastered” or “overwhelmed” by sensory stimuli, as if there was too much information coming in to be able to focus on one specific aspect (McGhie & Chapman, 1961). The authors introduced that patients with schizophrenia might have a deficit in filtering relevant information, which is in need of attention, from irrelevant information, which can be ignored. Subsequently, an overload of sensory stimuli enters the brain and needs to be analyzed, which, in turn, may lead to deficits in subsequent higher-order cognitive processes (Javitt, 2009b; McGhie & Chapman, 1961). This has led to the traditional idea that schizophrenia involves attentional dysfunction due to an impaired filtering mechanism.

Attention can be conceptualized in terms of pre-attentive and attentive stages. While pre-attentive mechanisms are unlimited in capacity, attentive mechanisms operate serially and are restricted to direct attention to only one location at a time. In addition, pre-attentive processes are considered as automatic or reflexive sensory mechanisms whereas the attentive processes are suggested to be volitional and cognitive. Lastly, pre-attentive mechanisms are rather seen as stimulus-driven by sensory events while attentive processes are reflected during cognitive tasks that require attentional demands (Schwartz, Tomlin, Evans, & Ross, 2001). To illustrate, a sudden noise or motion can automatically grab our attention that is directed to that particular external event (i.e. a pre-attentive process). In contrast, in order to achieve a personal goal or to follow a specific task instruction, we can voluntarily control our attention (i.e. an attentive process) (Posner & Petersen, 1990).

An increasing realization is that, in schizophrenia, deficits are found not only in higher-order processes such as in executive functioning and working memory but also at the level of early sensory processing (Javitt & Sweet, 2015). Such deficits at the earlier sensory level are relevant for potential novel targets for treatments as well as for our understanding of underlying pathophysiological mechanisms. It has been suggested that dysfunction of the glutamatergic N-methyl-D-aspartate (NMDA) receptor plays a fundamental role in that pathophysiology of schizophrenia (Coyle, 2006; Javitt & Zukin, 1991), with negative consequences for early sensory information processing as well as for higher-order cognitive functions (Javitt & Sweet, 2015). Explaining potential reasons for NMDA receptor dysfunction is beyond the scope of this dissertation, but it is important to mention that the role of NMDA receptors has been studied well in the early auditory and visual systems and that deficits have been found from early to later processes of sensory information processing. Additionally, NMDA receptors are also present in other brain regions, including the olfactory cortices, which has been shown to be implicated in schizophrenia as well (Javitt, 2009a, 2009b). Despite that more research is needed to understand the exact role of NMDA receptor dysfunction in schizophrenia, it has often been suggested as an effective target for novel drug development (Javitt, Spencer, Thaker, Winterer, & Hajos, 2008).

Research in this field has mainly focused on processes supported by auditory and visual input. In contrast, cognitive functions related to olfactory stimuli are less studied, despite that an altered olfactory function may be indicative of brain abnormalities (Féron et al., 2006; Nguyen, Shenton, & Levitt, 2010). In the following sections, several topics within early information processes and higher-order cognitive functions will be described.

6.3 Early information processing

6.3.1 Electroencephalography (EEG)

EEG is used to study processes of sensory information processing and monitors the brain's electrical activity that floats between communicating neurons. The strength of communication between neurons is dependent on several circumstances, such as the active state (e.g. during the execution of a cognitive task) or the resting state. EEG has the potential to unravel, on a high temporal level (milliseconds), how neurons interact and how they respond to external stimuli (Niedermeyer & da Silva, 2005). Although EEG is often used in research focused on sleeping disorders or for diagnosing epilepsy, within the field of psychiatry, EEG can facilitate to provide insights into potentially affected neural mechanisms during a cognitive or a resting-state task. By using EEG in the healthy and the affected brain, knowledge has been

gained about underlying pathological mechanisms, which were meaningful for understanding the neurobiology of disorders, predicting illness progress, and designing new treatments (Begemann, Florisse, van Lutterveld, Kooyman, & Sommer, 2016; Javitt, 2015; Näätänen, Todd, & Schall, 2016). Through the years, EEG has been suggested as a tool for identifying clinical stages in psychosis spectrum and severe mood disorders (Lavoie, Polari, Goldstone, Nelson, & McGorry, 2019).

6.3.2 What does EEG measure?

EEG records electrical brain activity using electrodes that are affixed to a specific location on the scalp. Each electrode measures voltage fluctuations that are the product of large groups of neurons that are firing synchronously (Jutzeler et al., 2011). The well-aligned spatial orientation of pyramidal cells is considered to produce most of the EEG signal. Pyramidal cells are electrically charged by ions that are exchanged between the cell and the extracellular environment. When communication between neurons takes place, thousands or millions of pyramidal cells fire together and voltage fluctuations can be caught by the EEG (Niedermeyer & da Silva, 2005).

The EEG signal can be used as an observable property of large groups of neurons engaging in cortical information processing. Studying this activity can be done in two ways. One can look at different brain waves (i.e. neural oscillations) or one can look at event-related potentials (ERPs) (Koukkou, 2019). Neural oscillations can be observed in the frequency domains, where lower frequencies (i.e. delta, theta, or alpha) are suggested to indicate a resting state of the brain and higher frequencies (gamma) are suggested to be related to higher cognitive processes. Further, ERPs are representations of voltage fluctuations that are time-locked to an event, such as an auditory or visual stimulus, or to a button press. Consequently, ERPs reflect electrical brain changes related to the processing of a stimulus or an action. For this reason, ERPs are often studied in cognitive neuroscience, cognitive psychology, and psychophysiological research (Handy, 2005).

6.3.2.1 *Advantages and limitations*

The greatest advantage of EEG is the high temporal resolution of milliseconds, which allows to record neural dynamics between cortical networks within a physiological time period. Contrary, techniques such as positron emission tomography (PET) and functional MRI (fMRI) techniques offer a much lower temporal resolution (one second or more). Other advantages of EEG are the non-invasive and relatively easy use in combination with its low costs. However, PET and fMRI have a higher degree of spatial resolution compared to EEG techniques as the signal source localization of EEG lacks millimeter precision (Jutzeler et al., 2011).

6.3.3 Event-Related Potentials (ERPs)

As described in the previous section, ERPs are brief changes in electrical brain activity in reaction to an external (e.g. presentation of an auditory stimulus) or internal event (e.g. preparation of a movement). Usually, ERPs are studied in paradigms where an individual is presented with a series of similar sensory stimuli (e.g. auditory tones) or decision-based events that require a motor response. The continuous EEG signal can be cut into specific time-windows, so-called epochs, that are stimulus-locked (with respect to the stimulus of interest) or response-locked (by taking the time-window around the moment of the subject's response). Subsequently, epochs are averaged over the number of trials that reveals the averaged brain response to the stimulus (Handy, 2005).

By doing so, one can study the amplitude, a positive- or negative deflection waveform, and the latency of an ERP. The peak amplitude is defined as the voltage difference between zero and the largest positive or negative peak within a certain time window. One can also use the mean amplitude, which is the mean amplitude in a certain time window. A third option is the peak-to-peak amplitude, defined as the voltage difference between two voltage extremes (e.g. between a positive and negative peak) (Handy, 2005). Further, latency is defined as the time point of the maximum peak amplitude, measured from the stimulus onset (Polich & Kok, 1995). Typically, ERPs, e.g. N100 or P300, earn their names from the positive (P) or negative (N) electrical load as well as from the time point (in ms) of the peak amplitude, on average, measured from the stimulus onset (Handy, 2005). Four ERPs will be described in the following sections.

6.3.3.1 Early processing of auditory information: Mismatch negativity (MMN)

Mismatch negativity (MMN) is an electrophysiological response that is considered to index pre-attentive information processing and is typically provoked in an auditory oddball paradigm. In an auditory oddball paradigm, standard auditory tones are interspersed with deviant auditory tones that are presented less frequently and that are characteristically different from the standard tone, e.g. in the frequency or duration of the tone. Brain responses towards the standard tones are subtracted from the brain responses towards the deviant tones and the difference wave is called MMN (Näätänen, 1990). MMN is maximal at frontocentral electrodes and emerges as a negative peak between 100 - 250 ms after stimulus presentation, on the condition that the stimulus was the deviant tone. There is no attention or behavioral response required to elicit MMN; MMN is also evoked in sleeping or comatose individuals (Kane, et al 1993).

6.3.3.1.1 MMN in schizophrenia and bipolar disorder

MMN is among the most widely investigated biomarkers in schizophrenia. MMN amplitude reductions are consistently found in patients with schizophrenia, with meta-analyses estimating its effect size between 0.95 (Erickson, Ruffle, & Gold, 2016) and 0.99 (Umbricht & Krljes, 2005). Moreover, MMN deficits correlated well with measures of cognitive, clinical, and psychosocial functioning in patients with schizophrenia, suggestive of a link (Light et al., 2015). Furthermore, in individuals with CHR, MMN amplitude reductions are able to distinguish individuals that will transition into full-blown schizophrenia from those that do not develop schizophrenia (Bodatsch, Brockhaus-Dumke, Klosterkötter, & Ruhrmann, 2015; Näätänen et al., 2016; Perez et al., 2014; Shaikh et al., 2012). Also, unaffected FDR of patients with schizophrenia have demonstrated MMN amplitude reductions (Michie, Innes-Brown, Todd, & Jablensky, 2002; Price et al., 2006), although not all studies found this (Bramon, 2004; Erickson et al., 2016; Magno et al., 2008). The evidence for MMN amplitude reductions in patients with bipolar disorder is less strong, with effect sizes between 0.37 and 0.45 (Chitty, Lagopoulos, Lee, Hickie, & Hermens, 2013; Erickson et al., 2016). Unaffected FDR of patients with bipolar disorder did not show MMN amplitude reductions (Hall et al., 2009; Umbricht et al., 2003). Taken together, MMN amplitude reductions are well described as a biomarker for schizophrenia, possibly for psychotic disorders, but it remains unclear whether MMN alterations can serve as a vulnerability indicator for those without psychotic symptoms.

6.3.3.2 Processing of visual information: N200

Another ERP component, N200, is observed as a negative peak between 200 - 400 ms after the stimulus presentation, usually at frontocentral electrode sites. N200 is often studied in various measures of

executive functioning, such as in the Go-Nogo task (Lamm 2006), the Dimensional Change Card Sort task (Espinet, Anderson, & Zelazo, 2012), and the Eriksen flanker task (Kopp, Rist, & Mattler, 1996; van Veen & Carter, 2002). In particular, previous studies showed that N200 amplitude is larger in trials when a prepotent response needs to be inhibited compared to trials where this is not required (Nogo versus Go trials). Furthermore, N200 amplitude is larger when it is difficult to discriminate between Nogo and Go trials and when subjects are distracted by irrelevant stimuli (i.e. in a flanker task) (Folstein & Van Petten, 2008). Additionally, by using dipole source modeling, it has been suggested that the ACC is the generating location of N200 (van Veen & Carter, 2002). These findings support the notion that N200 is involved in underlying processes of conflict monitoring and/or interference control.

6.3.3.2.1 N200 in schizophrenia and bipolar disorder

In contrast to MMN, N200 is scarcely described in schizophrenia and bipolar disorder. Few studies showed N200 amplitude reductions in patients with schizophrenia but not in those with bipolar disorder (O'Donnell, Vohs, Hetrick, Carroll, & Shekhar, 2004). Regarding the generator of N200, unaffected FDR of patients with schizophrenia showed ACC hypo-activation (Whalley et al., 2004) and hyper-activation (Callicott et al., 2003; Thermenos et al., 2004) as shown by fMRI studies. Also, unaffected FDR of patients with psychosis showed behavioral impairments in executive functioning (Bora et al., 2014), although contrary evidence also exists (Becker, Kerns, Macdonald, & Carter, 2008). Therefore, there is some reason to believe that N200 may be affected in schizophrenia or bipolar disorder, and possibly in children with FHR-SZ and with FHR-BP.

6.3.3.3 Processing of visual information: P300

The ERP P300 is a relatively large, positive peak with its latency between 300 - 550 ms after the presentation of an auditory or visual stimulus. The P300 component reflects information processing related to complex cognitive operations; it reflects the comparison process of evaluating incoming sensory events in the light of previously presented sensory events (Jeon & Polich, 2003). The P300 component can be categorized into the subcomponents P3a and P3b. Subcomponent P3a is generated by stimulus-driven frontal mechanisms and reflects an automatic shift in attention towards a deviant stimulus, while the subcomponent P3b is generated by temporal-parietal mechanisms and reflects the magnitude of attention that is directed to a stimulus as well as is involved in stimulus evaluation and categorization (Polich, 2007). Accordingly, P3b amplitude is larger in conditions of a cognitive task that require more attention, such as in the incongruent trials of a flanker task (Folstein & Van Petten, 2008). P3b latency is shorter when the task is less demanding indicating that it reflects the time to evaluate or process the stimulus (Polich, 2007). In short, P3b reflects attention, task-relevant stimulus processing and is relevant to study in children with FHR-SZ and with FHR-BP, due to demonstrated behavioral deficits in attentional functions (Bora et al., 2014; Pagliaccio et al., 2017).

6.3.3.3.1 P300 in schizophrenia and bipolar disorder

P300 amplitude reductions are repeatedly reported in patients with schizophrenia, shown by effect sizes between 0.85 and 0.89 (Bramon, Rabe-Hesketh, Sham, Murray, & Frangou, 2004; Jeon & Polich, 2003). Furthermore, individuals at CHR for psychosis show P300 impairments (Nieman et al., 2014). Unaffected FDR of patients with schizophrenia also show reduced P300 amplitudes and increased latencies compared to healthy controls (Bramon et al., 2005; Earls, Curran, & Mittal, 2016). Similar results have been found in patients with bipolar disorder as well as for the unaffected FDR of patients with bipolar

disorder (Hall et al., 2009; Schulze et al., 2008). These findings may indicate that P300 alterations can be considered as an endophenotype for psychosis-related disorders.

6.3.3.4 *Motor-response preparation: lateralized readiness potential (LRP)*

Whereas the previously described ERPs are involved in automatic processing of auditory information and attention-related stimulus processing, the lateralized readiness potential (LRP) is related to cortical motor activity. This makes the LRP an interesting measure in response inhibition tasks that require a motor response, such as a button press. The LRP is a negative-going deflection that reflects the activation of the motor cortex prior to the movement. Therefore, LRPs allow to track the initially expected incorrect motor preparation in a task that requires the inhibition of a prepotent motor response (Coles, 1989). In the case of a correct response under the experimental circumstances of response inhibition, the motor activity related to the incorrect response preparation must be followed by motor activation of the correct response preparation. Due to inefficient neural mechanisms of motor-response preparation, impaired LRP may underlie the slower response times that are consistently reported in patients with schizophrenia (Luck et al., 2009; Van Voorhis et al., 2019) and bipolar disorder (Brotman, Rooney, Skup, Pine, & Leibenluft, 2009).

6.3.3.4.1 LRP in schizophrenia and bipolar disorder

In patients with schizophrenia, LRP amplitude reductions are reported (Luck et al., 2009; Mathalon et al., 2002). Both patients with schizophrenia as with bipolar disorder showed delayed LRP latencies reflecting prolonged response selection processes under experimental circumstances where they had to inhibit a prepotent motor response (Van Voorhis et al., 2019). As Burton et al. (2017) described motor deficits in children with FHR-SZ, potentially influencing cognitive control tasks including a motor response, it is relevant to study the LRP in children with FHR-SZ and with FHR-BP.

6.4 Higher-order cognitive functions

6.4.1 Cognition and developmental trajectories of cognition

The debate on the origin and the developmental trajectories of cognitive deficits in schizophrenia and bipolar disorder is still ongoing. For schizophrenia, it is well established that cognitive deficits are already evident before the onset of psychotic symptoms (Bora et al., 2014). This may be different in bipolar disorder, in which it is proposed that cognitive functions are normal until the diagnostic onset of the disorder (Duffy, Vandeleur, Heffer, & Preisig, 2017; Goodwin, Martinez-Aran, Glahn, & Vieta, 2008). Studies have agreed that first episode patients with schizophrenia and bipolar disorder demonstrate deficits in most cognitive domains (verbal memory, processing speed, sustained attention, visual memory, and working memory), with an intermediate performance of those with bipolar disorder between controls and patients with schizophrenia (Bora & Pantelis, 2015). The cognitively underperforming of patients with schizophrenia compared to bipolar disorder continues during further illness progression (Krabbendam, Arts, van Os, & Aleman, 2005). In summary, cognitive deficits are present before the illness onset of schizophrenia, however, evidence exists that these deficits emerge together with the first clinical symptoms of bipolar disorder (Lewandowski, Cohen, & Ongur, 2011; Reichenberg et al., 2002).

As a group of children with FHR-SZ includes some individuals that will develop schizophrenia, but, more importantly, a majority that will not develop schizophrenia, it is interesting that cognitive deficits are consistently reported in numerous studies including children with FHR-SZ (de la Serna et al., 2017; Gur et al., 2007; Hemager et al., 2018; Maziade et al., 2009; Sanchez-Gutierrez et al., 2019). Such cognitive deficits are less pronounced in children with FHR-BP (Bora & Ozerdem, 2017; Klimes-Dougan, Ronsaville, Wiggs, & Martinez, 2006; Maziade et al., 2009) if present at all (Hemager et al., 2018). A lack in the current literature exists concerning the developmental trajectories of cognitive functions in children with FHR. It has been agreed upon that (some of the) cognitive deficits reported in children with FHR-SZ and with FHR-BP are part of the vulnerability state (Bora et al., 2014; Bora & Ozerdem, 2017; Maziade et al., 2009). However, it may be that worsening of some particular deficits can predict later illness onset. Otherwise, it is possible that the normalization of particular deficits occurs in those children that do not transition to psychosis. Thus, studies investigating developmental trajectories of cognitive functions may provide new insights valuable for prediction models as well as for the understanding of resilience factors. Four theoretical trajectories describe how cognitive function can follow the path of the developmental deficit (stable), developmental lag (slower growth), developmental deterioration (worsening) (Reichenberg et al., 2010), or developmental delay (delayed development) (see Figure 2 for the visualizations of these trajectories) (Dickson et al., 2018).

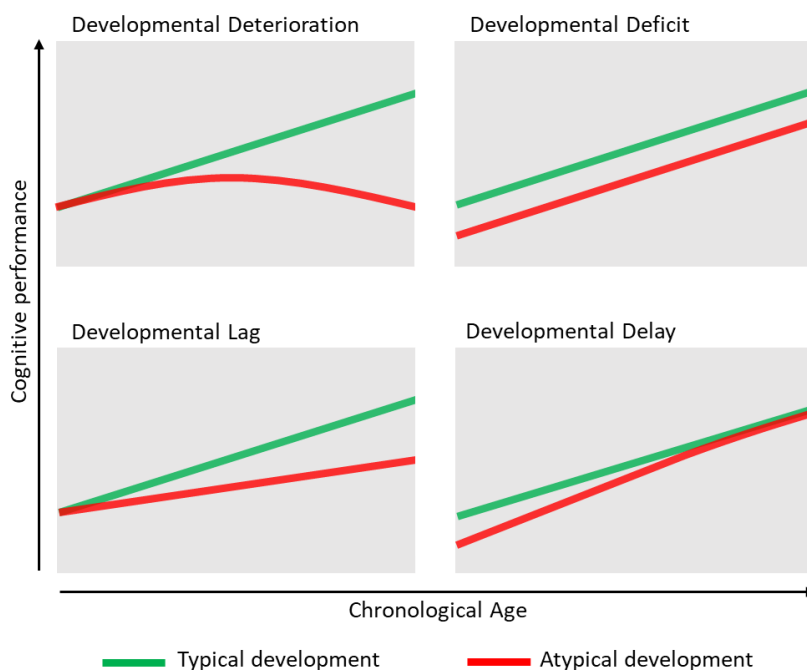


Figure 2 Visual representations of the different developmental trajectories of cognition functions. The figure is adapted from Reichenberg et al. (2010) and Dickson et al. (2018).

6.4.2 Visual attention

Often, broad extensive neuropsychological tests assess a variety of attentional and other cognitive processes rather than specific aspects of, for example, attention (Burgess, 1997). The theory of visual attention (TVA) considers distinct aspects of attention. The TVA-based task is based on Bundesen's Theory of Visual Attention (Bundesen, 1990). The strength of the TVA-based task is in its theoretical grounding and cognitive specificity, i.e. to measure distinct aspects of visual attention (Habekost, 2015), as well as it is an unspeeded, accuracy-based task unconfounded by motor components. Visual attention is defined as the competition among objects in the visual field through attentional selection. The winner of the competition is to be processed as a neural representation. Attention determines which visual object wins this competition and thus which object is to be neuronally processed (Bundesen, Habekost, & Kyllingsbaek, 2005). Using the TVA-based task in children with FHR-SZ and with FHR-BP has the potential to find specific deficits in distinct attentional processes, which may also shed light on distinct or shared deficits between the two groups.

6.4.3 Interference control

Another type of attention is selective attention, which involves focusing on one specific (relevant) aspect while ignoring other (irrelevant) aspects. Selective attention comprises a top-down process of a specific goal or requested task-demand as well as the ability to not get distracted by irrelevant stimuli. Two specific aspects of selective attention are response inhibition and interference control (Friedman & Miyake, 2004). Response inhibition is defined as the cognitive ability to override an automatic but inappropriate response with a goal-directed response. Interference control is defined as the cognitive ability to select relevant from amidst irrelevant stimuli. Among other tasks, such as the Stroop or go-Nogo-task, the flanker task is often used to assess the ability of response inhibition and interference control (Eriksen, 1995). In such tasks, children and adolescents with FHR-SZ and with FHR-BP demonstrated specific deficits in cognitive flexibility, speed of processing, and variation in reaction time (Bora et al., 2014; Brotman et al., 2009; Pagliaccio et al., 2017; Patino et al., 2013).

6.4.4 Olfaction

Of all human sensory modalities, olfaction is the only sense with direct access to the prefrontal cortex, without having the thalamus as a relay station. This means that the olfactory processing system provides a fast route between perceiving sensory information and action (Malaspina et al., 2006). Another reason why olfaction is interesting to study is that the olfactory epithelium continuously renews neurons (neurogenesis) while this process stopped earlier in the brain regions for other senses (Brewer, Castle, & Pantelis, 2006). To that end, olfaction is often evaluated as a "window to brain development" (Féron et al., 2006) and is, therefore, a powerful tool to study in neurodevelopmental or neurodegenerative disorders.

Olfactory deficits are common to patients with neurodegenerative disorders, such as Parkinson's disease (Cramer, Friedman, & Amick, 2010; Double et al., 2003) and Alzheimer's disease (Kjelvik, Sando, Aasly, Engedal, & White, 2007), but also in neurodevelopmental disorders, such as schizophrenia (Moberg et al., 1999; Moberg et al., 2006), Obsessive-Compulsive Disorder (OCD) (Barnett et al., 1999), and autism spectrum disorders (ASD) (Tonacci et al., 2017). Olfactory deficits have been reported across a wide variety of tasks, including odor detection, odor threshold sensitivity, odor memory, odor discrimination,

and odor identification (Kamath et al., 2014). Potential explanations for olfactory deficits are processing disruptions at the level of the orbitofrontal cortex (OFC) (Barnett et al., 1999), decreased neural activity in the piriform cortex (Koehler et al., 2018), and smaller olfactory bulbs (Turetsky et al., 2000), though the precise nature of the deficits requires further research.

6.4.4.1 Olfaction in schizophrenia and bipolar disorder

Olfactory deficits are well described in patients with schizophrenia with the largest effect sizes on measures of odor identification (Moberg et al., 2014). Odor identification is the ability to smell, recognize, identify, and verbally name an odor (Stedman & Clair, 1998) and therefore relies upon prior knowledge and experience with those odors (Danthiir, Roberts, Pallier, & Stankov, 2001). Deficits in odor identification in patients with schizophrenia persist after controlling for sex (Good, Leslie, McGlone, Milliken, & Kopala, 2007; Kamath, Lasutschinkow, Ishizuka, & Sawa, 2018), age (Moberg et al., 2014), smoking (Kamath et al., 2018; Stedman & Clair, 1998), and task complexity (Kopala, Good, Martzke, & Hurwits, 1995). This olfactory deficit is less pronounced in patients with bipolar disorder as compared to those with schizophrenia (Cumming, Matthews, & Park, 2011).

Further, odor identification deficits are associated with elevated negative symptoms (Ishizuka et al., 2010; Kamath et al., 2018). A lower baseline odor identification performance was associated with poorer negative and cognitive symptoms outcomes in first-episode psychosis patients on a four-year follow-up (Good et al., 2010). Also, in a CHR sample, the odor identification performance predicted which individuals would develop schizophrenia and who would not (Brewer et al., 2003). These findings suggest that olfactory deficits early in the course of the illness may have predictive value for further progression. Owing to these findings, olfactory impairments are suggested as a vulnerability marker for psychosis (Kamath et al., 2014). This hypothesis is intuitive since the olfactory neurocircuitry that is responsible for effective olfactory functioning includes brain regions that are affected, on a structural and neurophysiological level, in schizophrenia (Turetsky, Hahn, Borgmann-Winter, & Moberg, 2009; Turetsky et al., 2000).

7. Aims and hypotheses

7.1 Overall aim and hypothesis

The overarching aim of this dissertation was to investigate early sensory information processing as well as higher-order cognitive functions in children with FHR-SZ and with FHR-BP. (See Figure 3 for an overview of the tested functions.) The overall hypothesis was that children with FHR-SZ would show deficits in processes of early information processing as well as in higher-order cognitive functions, compared to children not at FHR, while children with FHR-BP would show no deficits in information processing processes and intermediate performances (between children with FHR-SZ and children not at FHR) on the higher-order cognitive functions.

7.2 Study 1: Normal mismatch negativity in children with familial high risk of schizophrenia or bipolar disorder

The aim was to study MMN in 12-year-old children with FHR-SZ or with FHR-BP and in children not at FHR. MMN amplitude reductions are often suggested as biomarker for schizophrenia but it remains a fundamental question whether MMN alterations are part of the vulnerability for psychosis (unrelated to clinical symptoms). We hypothesized that children with FHR-SZ would show reduced MMN amplitudes, relative to PBC children, and that children with FHR-BP would not show significantly different MMN amplitudes compared to PBC children. Also, we exploratively investigated whether MMN was related to scales of global functioning, emotional and behavioral problems, and autistic traits.

7.3 Study 2: Behavioral performance and neural responses during a visuomotor conflict task in children with familial high risk for schizophrenia and bipolar disorder

The aim was to investigate interference control, by means accuracy rate, reaction time (RT), and coefficient of variation of RT (CV_{RT}), and the proposed underlying neural mechanisms N200, P3b, and LRP in a flanker task in 12-year-old children with FHR-SZ or with FHR-BP and in children not at FHR. Regarding behavioral data, we hypothesized that children with FHR-SZ relative to children not at FHR would show deficits in interference control presented by lower accuracy rates, higher RT, and higher CV_{RT} in the incongruent condition. From the EEG data, we hypothesized reduced amplitudes of N200, P3b, and LRP in children with FHR-SZ compared to children not at FHR as reflecting their impairments in interference control. As children with FHR-BP typically perform intermediate between FHR-SZ and control children, we expected that their behavioral performance and EEG measures would lie between those of FHR-SZ and children not at FHR.

7.4 Study 3: Development of visual attention from age 7 to age 12 in children with familial high risk for schizophrenia or bipolar disorder

The aim was to investigate specific aspects of visual attention in 12-year-old children with FHR-SZ and with FHR-BP and in children not at FHR, and additionally, to compare their performance between age 7 and age 12 in a follow-up design. We hypothesized that 12-year-old children with FHR-SZ and children with FHR-BP would exhibit deficits, relative to children not at FHR, on visual processing speed, with more pronounced deficits in children with FHR-SZ than in children with FHR-BP. For the follow-up analyses, we expected that children with FHR-SZ exhibited developmental lags (i.e. a slower growth) or deficits (i.e.

stable deficits) for visual processing speed compared to children not at FHR. Based on the little evidence that exists for bipolar disorder, we expected developmental deficits on visual processing speed for FHR-BP.

7.5 Study 4: Odor identification in 7-year-old children at familial high risk of schizophrenia or bipolar disorder - the Danish high risk and resilience study VIA 7

The aim was to investigate odor identification in children with FHR-SZ and with FHR-BP and in children not at FHR. We hypothesized that both FHR groups would demonstrate significant odor identification deficits compared to children not at FHR, with more pronounced deficits for children with FHR-SZ than with FHR-BP. Exploratively, this study also included demographic, psychopathological, and home environmental characteristics to provide a comprehensive identification of potential cross-sectional relations to the child's odor identification. We expected more symptomatology and a less stimulating and stable home environment to be associated with worse olfactory functioning.

7.6 Study 5: Event-related electroencephalographic responses in children at familial high risk for schizophrenia or bipolar disorder: a single-site EEG sub-study of the Danish High Risk and Resilience Study – VIA 11

The aim of this study was to set out the rationale and methodology of the EEG paradigms that are used in the Danish High Risk and Resilience Study – VIA 11. The EEG-part of the Danish High Risk and Resilience Study aims to identify potential specific and/or shared electrophysiological endophenotypes for schizophrenia and/or bipolar disorder. The secondary aim is to explore to what extent these electrophysiological measures indicate a specific electrophysiological profile (cluster of EEG deficits) that potentially distinguishes children with FHR for schizophrenia from children with FHR for bipolar disorder. In the light of the longitudinal design, the third aim is to determine predictive electrophysiological markers identifying those individuals that eventually develop schizophrenia or bipolar disorder.

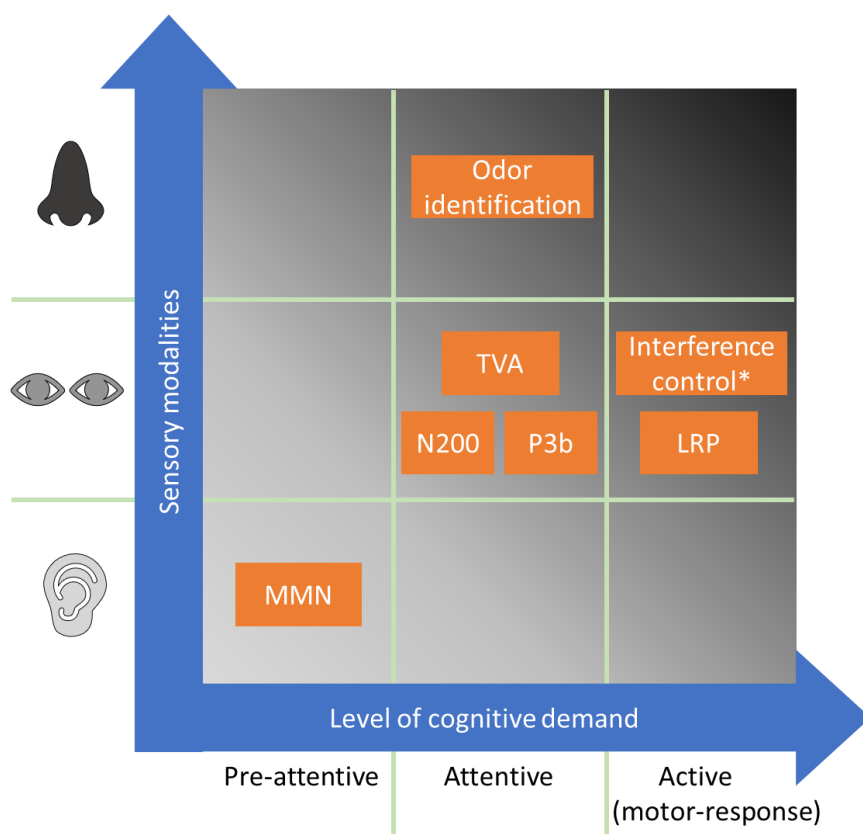


Figure 3 The tested functions in this dissertation, regarding early information processing and higher-order cognitive functioning, presented by different sensory modalities and the level of cognitive demand. *Measured by the accuracy rate, reaction time (RT) and the coefficient of variation of the reaction time (CV_{RT}).

8. Material and methods

In the following, a short overview of the material and methods is provided. Further details are explained in the corresponding manuscripts (see Appendix 1 - 4).

8.1 The Danish High Risk and Resilience Study

The Danish High Risk and Resilience Study is a prospective, longitudinal FHR-study containing children of parents diagnosed with schizophrenia, bipolar disorder, or none of these two disorders. The initial group of children for the VIA 7 study was recruited by using two registers, the Danish Psychiatric Central Research Register (DPCR) (Mors, Perto, & Mortensen, 2011) and the Danish Civil Registration System (DCRS) (Pedersen, Gøtzsche, Møller, & Mortensen, 2006). Patients from the DPCR with a diagnosis of schizophrenia spectrum psychosis (schizophrenia, delusional disorder, or schizoaffective disorder; ICD 10-codes: F20, F22, and F25 or ICD 8-codes: 295, 297, 298.29, 298.39, 298.99) or bipolar disorder (ICD 10-codes: F31 or ICD 8-codes: 296.19 and 296.36) were linked to the DCRS to identify the patients with a child of 7 years old. Parents or participants were not excluded when having other or additional psychiatric diagnoses. Follow-ups were planned every four years, in which the second wave is called the VIA 11 study; the third wave the VIA 15 study; and so forth.

8.1.1 Setting

The Danish High Risk and Resilience Study is a collaboration between the Mental Health Services of the Capital Region of Denmark and the Psychosis Research Unit, University of Aarhus. In the VIA 7 study, a large assessment battery was conducted at both research sites. In the VIA 11 study, the project was extended with brain research, using MRI techniques at both research sites as well as EEG at the research site in Copenhagen. The EEG-part was conducted at the Danish Research Centre for Magnetic Resonance (DRCMR) at the Copenhagen University Hospital Hvidovre, Denmark. Additionally, the TVA-based task was only conducted at DRCMR in Copenhagen, Denmark.

8.1.2 Participants

The initial cohort (the VIA 7 study) consisted of 522 7-year-old Danish children, of which 202 children had a parent diagnosed with schizophrenia, 120 children had a parent diagnosed with bipolar disorder, and 200 children had parents without the diagnosis of schizophrenia or bipolar disorder, who were assessed between December 2012 and March 2016. In March 2017, data collection of the VIA 11 study started. Due to the deadline of this dissertation, the manuscripts including data of the VIA 11 study contain data that were collected between March 2017 and July 2019 as well as only of children that have been assessed at DRCMR in Copenhagen, Denmark. For clarification in the following chapters of this dissertation, I will refer to this subgroup as the Copenhagen-subgroup of the VIA 11 study. (See Figure 4 for an overview of the study designs of the four studies.) It should be noted that data collection for the entire project is still ongoing and that other studies of the VIA 11 study may refer to the Copenhagen-subgroup after the inclusion of more children.

8.1.3 Ethics

Both in the VIA 7 and VIA 11 studies, parents of the children gave written informed consent. Testers and support were blinded to the risk status of the parent. Children were verbally informed about the procedures, especially regarding the EEG. The Danish Data Protection Agency approved the study

protocol. The Danish Ministry of Health gave permission to retrieve data from the Danish registers. We obtained a general evaluation from the Danish Committee on Health Research Ethics on the study protocol, but ethical approval was not necessary due to the absence of any intervention. In the VIA 11 study, families received an invitation letter by post about participation in the VIA 11 study. If families did not respond to the letter, they were contacted by email, text message, or telephone.

8.2 Study designs of four studies

In study 1, MMN was compared across the three groups of the Copenhagen-subgroup of the VIA 11 study (N=136). In study 2, behavioral as well as electrophysiological data during a flanker task was compared across the three groups of the Copenhagen-subgroup of the VIA 11 study (N=149). Study 3 is a cross-sectional study of the TVA-based task in 133 children at age 12 as well as a follow-up study of a smaller subgroup (N=89) of the cohort, comparing results on a visual attention task between age 7 and age 12 (the VIA 7 and VIA 11 studies). In study 4, odor identification is compared across the three groups as part of the VIA 7 study (N=476).

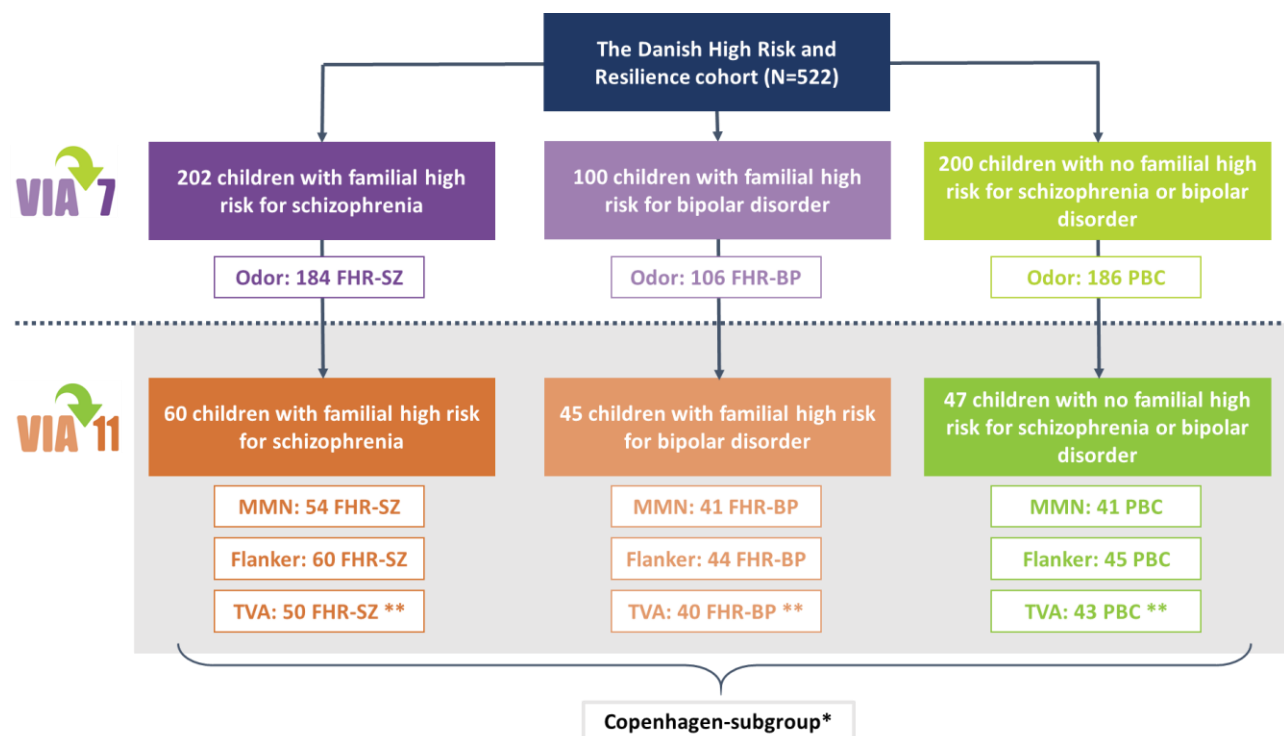


Figure 4 Number of included children per group concerning the studies of the current dissertation. Initially, the Danish High Risk and Resilience Study – VIA 11 included 522 children. In the first follow-up, the VIA 11 study, part of the entire cohort is assessed again. Due to the deadline of the current dissertation, it was not possible to include the entire cohort. *The Copenhagen-subgroup as referred to in this dissertation included participants that visited the Copenhagen research site before July 2019, i.e. the research site for clinical testing and the Danish Research Centre for Magnetic Resonance (DRCMR) for EEG recordings and the TVA-based task. It should be noted that data collection for the entire project is still ongoing and that other studies of the VIA 11 study may refer to the Copenhagen-subgroup after the inclusion of more children. **The deadline for the TVA-based task was earlier (May 2019) and therefore it contains fewer children.

8.3 Techniques and assessments

8.3.1 Electroencephalography (EEG)

For the EEG recordings, the BioSemi system was used to record electrical brain activity using 128 active electrodes. Six external electrodes were used to measure facial movements and the heartbeat, and two electrodes were placed on the mastoids as reference points. After a thorough explanation about the EEG procedure, children were seated in a comfortable chair in a quiet room. Accompanying parents were allowed in the room during the preparation of the cap but were asked to leave the room during recordings. If requested, the parents could stay during recordings.

8.3.2 Auditory oddball paradigm for MMN (study 1)

MMN is elicited in an auditory oddball paradigm in which standard auditory tones are interspersed by deviant auditory tones. The paradigm consisted of 1800 stimuli that were binaurally presented through earphones. Four types of stimuli were presented, one standard tone and three types of deviant tones. The standard tone was presented 76% of the time, with a frequency of 1000 Hz, intensity of 75 dB, and a duration of 50 ms. The three deviants were presented in 8% of the time each, with the frequency deviant (FreqMMN) having a frequency of 1200 Hz, the duration deviant (DurMMN) a duration of 100 ms, and combination deviant (FDMMN) with a frequency of 1200 Hz and a duration of 100 ms (Figure 5) (Düring, Glenthøj, & Oranje, 2016). During the MMN paradigm, children could watch a muted video to withdraw attention from the task, as MMN is best elicited in the absence of attention. The paradigm took approximately 16 minutes.

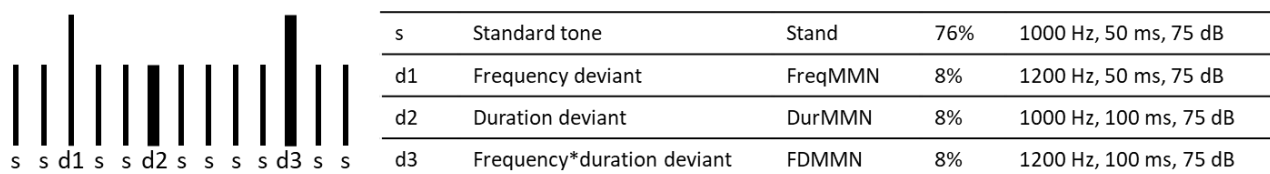


Figure 5 Auditory stimuli in the auditory oddball paradigm to measure mismatch negativity (MMN); one type of standard tone (s) and three types of deviant tones (d1, d2, and d3).

8.3.3 Eriksen flanker task (study 2)

The Eriksen flanker task measures interference control (Eriksen, 1995). The task horizontally presented seven arrows on a computer screen, three on both sides and one arrow in the middle (see Figure 6). The middle arrow was the target arrow that could point to the right or to the left and required a, respectively, right or left button press on a button box. The six flanking arrows could point to the same direction as the target arrow, resulting in the congruent condition (e.g. <<< < <<<), or to the opposite direction of the target arrow, resulting in the incongruent condition (e.g. <<< > <<<). 50% of the trials were incongruent and balanced between left and right responses. Children were asked to respond as accurate and fast as possible to the target arrow by pressing the button box using their thumbs. Children had to respond within a time window of 1000 ms. The task started with a practice round of 20 trials, to assure the children's understanding. Then, children continued with two blocks of 200 trials with a fixed-order between subjects. To keep the children alert, an exclamation mark appeared when their responses were too slow compared to an individual-based threshold, based on 1.5 times the SD of the mean RT during

the practice round. The task took six minutes per block (12 minutes in total). EEG was recorded simultaneously.

Before evaluating the behavioral performance of the task, single trials were excluded when children responded within 200 ms after the presentation of the target stimulus (considered as anticipatory response) as well as when children did not respond at all (omission error). In addition, children with more than 30% commission errors were considered to be inadequately engaged with the task and were thus excluded. Evaluation of the behavioral performance was based on accuracy rate per condition (i.e. number of correct trials divided by the number of total trials (excluding anticipatory and omission trials)); RT per condition (i.e. time between target presentation and the first button press response); and CV_{RT} per condition (i.e. SD divided by mean RT per individual).

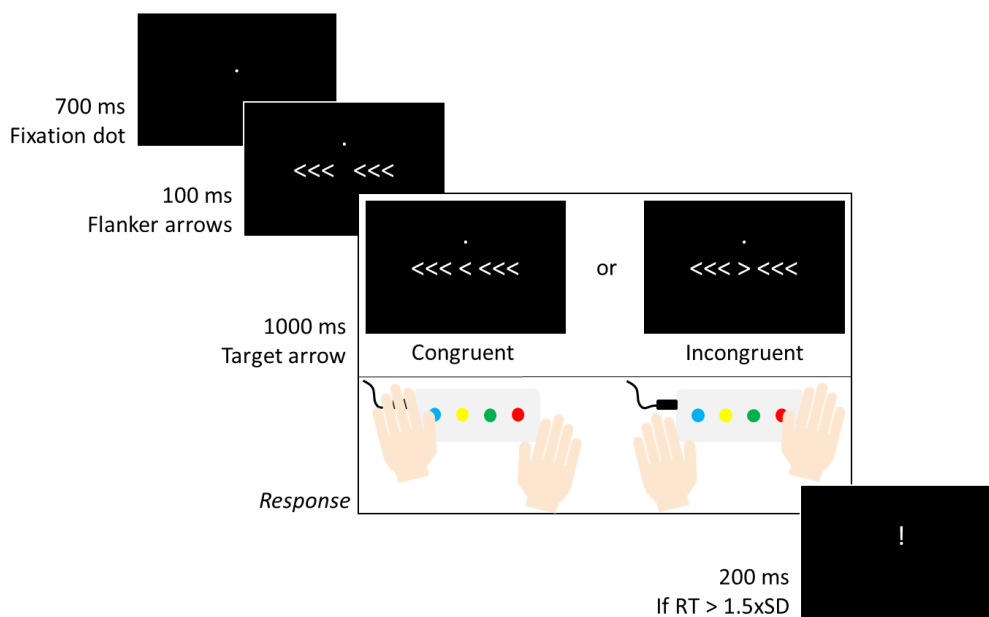


Figure 6 Visualization of the Eriksen flanker task (Eriksen, 1995), simultaneously assessed during EEG recordings. The flanker task started with a fixation dot (700 ms) that was followed by a brief appearance (100 ms) of flanking arrows. The middle arrow, the target stimulus, was then presented and required a button press corresponding to the direction of the target stimulus. Children were instructed to respond as fast and accurate as possible. When their response was too slow, compared to an individual-based threshold, they would see an exclamation mark.

8.3.4 Theory of Visual Attention (TVA) (study 3)

In the TVA-based task, children were instructed to watch a computer screen where they were first presented with two practice rounds of 10 trials, which was followed by 90 trials divided over three blocks. Each trial started with a fixation cross, which was followed by six digits (numbers) that appeared briefly. Children were instructed to remember as many numbers as they could and to verbally recall these numbers once these disappeared from the screen. The assessor that was sitting next to the child entered these numbers into the computer. The exposure durations of the numbers were 10 ms, 20 ms, 30 ms, 50 ms, 80 ms, 140 ms, or 200 ms. (See Figure 7 for the outline of the TVA-based task.) The TVA-based task took approximately 20 minutes.

The computational framework of the TVA-based task provides three estimates of parameters of visual attention, i.e. visual short-term memory capacity (K), visual processing speed (C), the threshold for visual perception (t_0), as well as the error rate. (See Appendix 3 for more details on the computational modelling.)

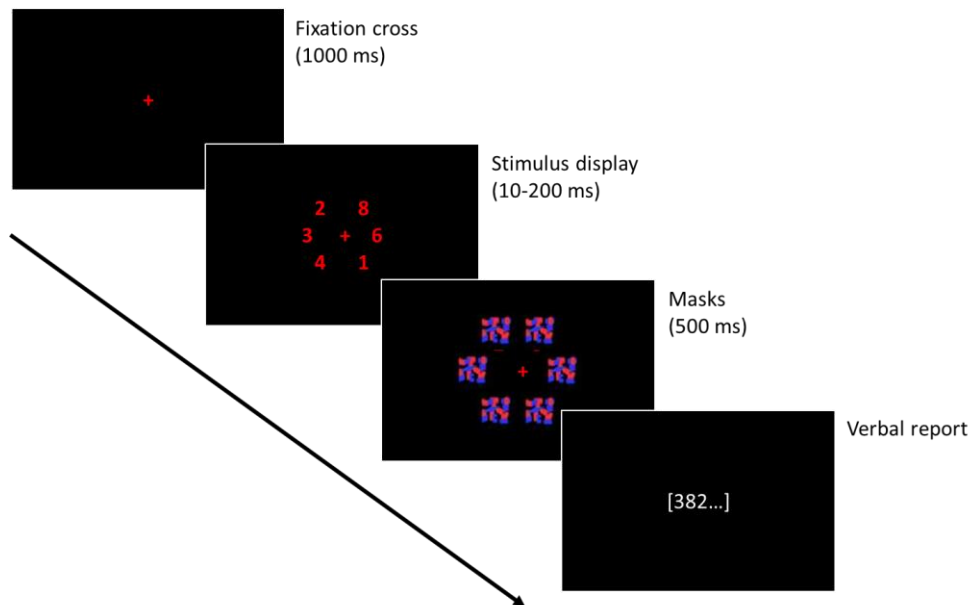


Figure 7 Trial outline of the TVA-based task in the VIA 7- and in the VIA 11 study. After the fixation cross (1000 ms), children would see six numbers for a variable brief time (10 – 200 ms) and were instructed to verbally report as many numbers as they could. These numbers were entered into the computer by the assessor.

8.3.5 Brief Smell Identification Task (BSIT) (study 4)

The Brief Smell Identification Test (BSIT, Version A, Danish version) assessed the ability to identify odors (odor identification) and was used in the VIA 7 study. The BSIT is a validated, standardized, non-invasive and quantitative test appropriate for people with the age between 5 and 99 years. The BSIT is a shorter version of the University of Pennsylvania Smell Identification Test in which 12 items out of the original 40 items are chosen based on a cross-cultural criterium. Twelve items were presented as micro-encapsulated odorant strips in a “scratch ‘n sniff” format. BSIT is a multiple-choice task with four possible odors for each item, of which one correctly corresponds to the sniffed odor. The tester read the odors out loud and the child sniffed and verbally reported his or her choice. Children were allowed to hear the four possible options again. This version of the BSIT contained the following odors: menthol, soap, gasoline, rose, cherry, cloves, leather, strawberry, lilac, pineapple, smoke, and lemon. The BSIT took approximately 5 minutes to finish.

8.4 Pre-processing EEG data

8.4.1 Mismatch negativity

We used BESA version 5.2.4 (MEGIS Software GmbH, Grafelfing, Germany) to analyze and process the EEG signals. EEG signals from the frontal/midline electrodes Fz, FCz, and Cz (Wienberg, Glenthøj, Jensen, & Oranje, 2010) were checked since the amplitude was expected to reach its maximum on those

electrodes. Electrode Fz showed the greatest amplitudes and was further analyzed. Our first step was to resample the data from 4096 Hz to 250 Hz. Then, we removed eye-artifacts from the data by using an adaptive method of BESA. This was followed by defining the epochs, from 100 ms pre-stimulus to 900 ms post-stimulus. Movement artifacts, which were epochs with an amplitude difference of more than 60 microvolts in the time period 0 – 400 ms post-stimulus (the period of time when MMN is expected), were removed. Then, we filtered the data between 1 – 40 Hz. MMN was then calculated for each deviant type by subtracting the average ERP of the standard tone from the average ERP to each of the deviant types. This resulted in FreqMMN, DurMMN, and FDMMN. The grand average waveforms for each group and deviant type were used for visual display as well as for deciding the latency windows to score MMN peak amplitude and latency. Lastly, peak amplitude and latency were extracted and used in the analyses. The scoring window for FreqMMN was 130 – 250 ms, for DurMMN 150 – 265 ms, and for FDMMN 140 – 230 ms.

8.4.2 N200, P3b, and LRP during a flanker task

We used the toolbox FieldTrip (Oostenveld, Fries, Maris, & Schoffelen, 2011) to process the EEG signal. Only correctly responded trials were used. Data were recorded at a sampling frequency of 4096 Hz. Data were referenced to the mastoids and were then filtered between 0.5 and 45 Hz using a finite impulse response filter. Then we segmented EEG data in stimulus-locked epochs (between -0.5 ms and +1.5 ms). Detection of artifacts (eye movements, muscle tension, speaks/jumps) was done through an in-house script. When amplitudes of epochs exceeded 100 microvolts, we removed these epochs. Then, every bad channel per trial was interpolated using the triangulation method (i.e. a triangle of nearby electrodes was built around the bad channel). Data were baseline-corrected to a 500 - 10 ms window pre-stimulus.

To extract the ERPs of interest, congruent and incongruent trials were separately averaged. We calculated the mean amplitude for N200 (for electrode FCz) and P3b (for electrode Pz) as this method is robust against noise (compared to peak amplitude) (Handy, 2005). To determine the time window that was used for calculating the mean amplitude, we took 40 ms around the peak value of the grand average of all children. This resulted in the following time windows, 190 - 230 ms for the mean N200 amplitude and 360 - 400 ms for the mean P3b amplitude.

The LRP was obtained by taking the difference in EEG activity between the C3 and C4 electrodes (placed on the motor cortices). For example, for the right responses, the EEG activity of the ipsilateral side (right motor cortex; electrode C4') was subtracted from the contralateral side (left motor cortex; electrode C3') and vice versa (Coles, 1989). In order to obtain one LRP for each condition, we averaged the left-hand and right-hand responses for each condition. Then, the LRP was calculated using the peak-to-peak amplitude method. With the peak-to-peak method, the amplitude is quantified as the difference between two consecutive opposite-polarity peaks. This method is relevant to analyze the LRP because of its large distribution and the effect of the earlier positive peak (i.e. the Gratton dip (Gratton, Coles, Sirevaag, Eriksen, & Donchin, 1988)). Accordingly, time windows were based on the positive and negative peak values and we took 100 ms around the peak to capture the entire peak. To correct for potential differences in RT between the groups, the time windows were specific for each group and condition (see Appendix 2 for the exact time windows per group per condition).

8.5 Statistical analyses

8.5.1 Study 1: Normal mismatch negativity in children with familial high risk of schizophrenia or bipolar disorder

Statistical analyses were performed using SPSS (version 25.0) (Corp, 2013). First, normal distributions were checked with the Kolmogorov-Smirnov test. In the case of normally distributed data, a repeated-measures analysis of variance (RM-ANOVA) was conducted with the three types of MMN as within-subject factors (3 levels: FreqMMN, DurMMN, FDMMN) and group as between-subject factors (3 levels: FHR-SZ, FHR-BP, PBC). In the case of non-normal distributions, we used the Kruskal-Wallis test with three groups. JASP (JASP Team 2018) was used to compute the Bayes factor (BF) with the intention to estimate the likelihood of the alternative hypothesis H_1 (e.g. different MMN peak amplitude in the three groups) over the null hypothesis H_0 (e.g. similar MMN peak amplitude in the three groups) (Dienes, 2016). Additionally, Pearson's and Spearman's correlations were used to explore potential correlations between FreqMMN, DurMMN, and FDMMN and global functioning (CGAS; Children's Global Assessment Functioning (Shaffer et al., 1983), emotional and behavioral problems (CBCL; Child Behavior Checklist (Bilenberg, 1999)), and autistic traits (SRS; Social Responsiveness Scale (Constantino & Gruber, 2005)).

8.5.2 Study 2: Behavioral performance and neural responses during a visuomotor conflict task in children with familial high risk for schizophrenia and bipolar disorder

Statistical analyses were performed using SPSS (version 25.0) (Corp, 2013). Behavioral performance on the flanker task was based on the accuracy rate, RT, and CV_{RT} for each condition. RM-ANOVA's were conducted with either accuracy rate, RT, or CV_{RT} as dependent variable, condition as within-subject (congruent and incongruent) and FHR group as between-subject (FHR-SZ, FHR-BP, and PBC). Additionally, congruency effects of accuracy rate and RT were calculated by subtracting the accuracy rate or RT of the congruent condition from the incongruent condition. The two congruency effects were compared across groups with an analysis of variance (ANOVA). Additionally, distributional analyses of RT were conducted to analyze the RT in more detail, as such analyses allow us to distinguish between fast (automatic) responses and slow (deliberate) responses. According to (Ridderinkhof, 2002), four separate time bins were created based on the RT distributions per individual. Accuracy rate, mean RT, as well as the congruency effect of RT were calculated for each time bin and compared across the three groups with an RM-ANOVA with either accuracy rate, mean RT, or the congruency effect as dependent variable and group as between-subject factor (FHR-SZ, FHR-BP, PBC). Post hoc multiple comparisons by means of Bonferroni corrections were performed.

The electrophysiological data were analyzed using a RM-ANOVA with amplitudes of either N200, P3b, or LRP as dependent variable, condition as within-subject factor (congruent and incongruent), and groups as between-subject factor (FHR-SZ, FHR-BP, PBC). Post hoc multiple comparisons by means of Bonferroni corrections were performed.

Potential correlations between ERPs and clinical scales (CBCL and ADHD-RS) were exploratively investigated with Pearson's or Spearman's correlations when appropriate.

8.5.3 Study 3: Development of visual attention from age 7 to age 12 in children with familial high risk for schizophrenia or bipolar disorder

Statistical analyses were performed using SPSS (version 25.0) (Corp, 2013). First, for the cross-sectional analyses, we compared the TVA performance between the groups of 12-year-old children with a multivariate analysis of variance (MANOVA) on the four TVA measures visual short-term memory (K), visual processing speed (C), the threshold for visual perception (t_0), and error rate. As some of these children had done the TVA-based task in the VIA 7 study while others did not, we checked whether there was an effect by comparing the TVA performance between children that did the task for the first time and children that did the task for the second time. Second, the performance on the TVA-based task was compared across groups (FHR-SZ, FHR-BP, PBC) and across time points (VIA 7 and VIA 11) using four separate RM-ANOVA's. We conducted post hoc analyses of within-group differences of performance on the two test sessions with paired sampled t-tests. Furthermore, characteristics and TVA performance at age 7 were compared between children that remained in the study (i.e. were assessed again in the VIA 11 study) and those that did not. This analysis was done to investigate the potential effects of attrition bias (Ahern & Le Brocque, 2016). Also, we checked post hoc whether deficits at age 7 were still present in the smaller group that we assessed in the follow-up analyses.

8.5.4 Study 4: Odor identification in 7-year-old children at familial high risk of schizophrenia or bipolar disorder - the Danish high risk and resilience study VIA 7

Statistical analyses were performed using SPSS (version 25.0) (Corp, 2013). Odor identification was analyzed using (1) the BSIT total score with a two-way ANOVA, with sex and FHR group as fixed factors, to examine potential between-group differences, and (2) the categorical BSIT outcome with a chi-square test of independence to examine the distribution of normosmic versus microsmic. For the exploratory regression analyses, we included psychopathological, cognitive, and home environmental variables as predictors. Additionally, a hierarchical multiple regression analysis, with the BSIT total score as dependent variable, was conducted with risk status, sex, and age entered in the first step (Model 1), psychopathological and cognitive variables in the second step (Model 2), and home environmental variables in the third step (Model 3). For the categorical outcome, a sex-specific multiple logistic regression analysis was conducted with "normosmic" and "microsmic" as dependent variable. Due to lack of power, only three predictors that were theoretically most relevant were selected in the logistic multiple regression: verbal memory, social reciprocity, and verbal working memory.

9. Results

9.1 Study 1: Normal mismatch negativity in children with familial high risk of schizophrenia or bipolar disorder

The aims were to investigate MMN in children with FHR-SZ and with FHR-BP and in children not at FHR (PBC) as well as to study how MMN correlates with clinical variables (global functioning (CGAS), emotional and behavioral problems (CBCL), and the severity of ASD symptoms (SRS)) in these children. We recorded EEG during an auditory oddball paradigm with three types of deviant tones (frequency, duration, frequency*duration) to investigate MMN. MMN was quantified by peak amplitude and peak latency.

9.1.1 Participants

We included 54 children with FHR-SZ, 41 children with FHR-BP, and 41 PBC. Based on EEG quality, we excluded three datasets (1 FHR-SZ and 2 PBC) because the data were too noisy.

Groups did not differ on age, gender, handedness, or lifetime prevalence of ADHD (Attention-Deficit/Hyperactivity Disorder) or ASD diagnoses. Children with FHR-SZ and with FHR-BP had higher ratings on problem behavior and autistic traits than PBC children. Further, children with FHR-SZ and with FHR-BP had worse global functioning than PBC children. (See Table 1 for the characteristics of the children.)

9.1.2 EEG results

Peak amplitude data of FreqMMN, DurMMN, and FDMMN were non-normally distributed and therefore analyzed with non-parametrical tests. The Kruskal-Wallis tests showed no significant group differences on FreqMMN ($p = 0.510$), DurMMN ($p = 0.938$), and FDMMN ($p = 0.472$). (See Figure 8 and 9 for the grand average waveforms and the peak amplitude and latency of MMN across the three study groups.) We calculated BF to give the strength of evidence for the hypothesis that the MMN peak amplitude was similar between the groups (H_0). The Bayesian repeated-measure ANOVA showed $BF_{10} = 0.231$, which indicated strong evidence for H_0 , i.e. strong evidence that MMN peak amplitude was similar between the three groups.

Peak latency data of DurMMN were normally distributed and further analyzed with ANOVA, FreqMMN and FDMMN were analyzed non-parametrically. ANOVA with DurMMN as dependent variable revealed no significant differences across the three groups ($F(2,130) = 2.528$, $p = 0.084$). Kruskal-Wallis test with FreqMMN as dependent variable showed a trend towards significance ($p = 0.053$) and further Mann-Whitney tests showed a significantly prolonged latency for FHR-SZ relative to PBC ($p = 0.012$). No significant difference was found comparing FHR-BP with PBC ($p = 0.435$) nor FHR-SZ ($p = 0.197$). Kruskal-Wallis test with FDMMN as dependent variable was non-significant across the three groups ($p = 0.704$). The Bayesian repeated-measure ANOVA showed $BF_{10} = 0.083$, indicative for decisive evidence that MMN peak latencies were similar between the three groups.

9.1.3 Correlations

Due to non-normally distributed data, Spearman's correlations were used to exploratively investigate relations between MMN (FreqMMN, DurMMN, and FDMMN) and clinical variables (CBCL-total, SRS, and

CGAS). We found a significant negative correlation between CGAS (global functioning) and FreqMMN peak latency ($r_s = -0.177$, $p = 0.046$) in all children (see Figure 10). We did not find significant correlations between other MMN amplitudes or latencies and scales of CBCL-total, SRS, or CGAS, nor in the separate groups.

Table 1 Characteristics of children with familial high-risk of schizophrenia (FHR-SZ), children with familial high-risk of bipolar disorder (FHR-BP), and population-based controls (PBC)

	FHR-SZ	FHR-BP	PBC	Statistics (p-value)	FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
Number of children, N	53	41	39	0.162 ^a			
Age, years (s.d.)	12.09 (0.24)	12.13 (0.24)	12.16 (0.29)	0.459 ^b			
Male, N (%)	25 (47.2)	22 (53.7)	18 (46.2)	0.759 ^a			
Handedness, N right-handed (%)	46 (86.8)	36 (87.8)	36 (92.3)	0.693 ^a			
	N	N	N				
ADHD ¹ , N (%)	52 8 (15.4)	41 2 (4.9)	39 4 (10.3)	0.262 ^a			
ASD ¹ , N (%)	52 2 (3.9)	41 3 (7.3)	39 1 (2.6)	0.566 ^a			
RIST total IQ ² , mean (s.d.)	53 97.30 (9.72)	41 99.37 (8.26)	39 99.03 (8.82)	0.489 ^b			
CBCL total score ² , mean (s.d.)	51 19.78 (17.41)	40 17.03 (15.30)	39 10.95 (11.47)	0.025 ^c	0.012 ^d	0.034 ^d	0.554 ^d
SRS ² , mean (s.d.)	52 30.46 (25.83)	40 27.30 (21.70)	39 16.64 (11.96)	0.005 ^c	0.004 ^d	0.005 ^d	0.762 ^d
CGAS ² , mean. (s.d.)	50 66.80 (15.06)	39 69.80 (14.55)	37 76.50 (14.07)	0.005 ^c	0.002 ^d	0.018 ^d	0.407 ^d

¹Lifetime prevalence of ADHD or ASD diagnoses derived from the VIA 7 study; see Ellersgaard et al. (2018) for the psychopathology on the total cohort at age 7; ²Data was derived from the VIA 11 study. ^aPearson chi-square test of independence; ^bOne-way ANOVA; ^cKruskal-Wallis test; ^dMann-Whitney U test. Abbreviations: ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorders; CBCL, Child Behavior Check-List; CGAS, Children's Global Assessment Scale; FHR-BP, familial high-risk for bipolar disorder; FHR-SZ, familial high-risk for schizophrenia; N, number; PBC, population-based control; RIST, Reynold's Intellectual Screening Test; s.d., standard deviation; SRS, Social Responsiveness Scale.

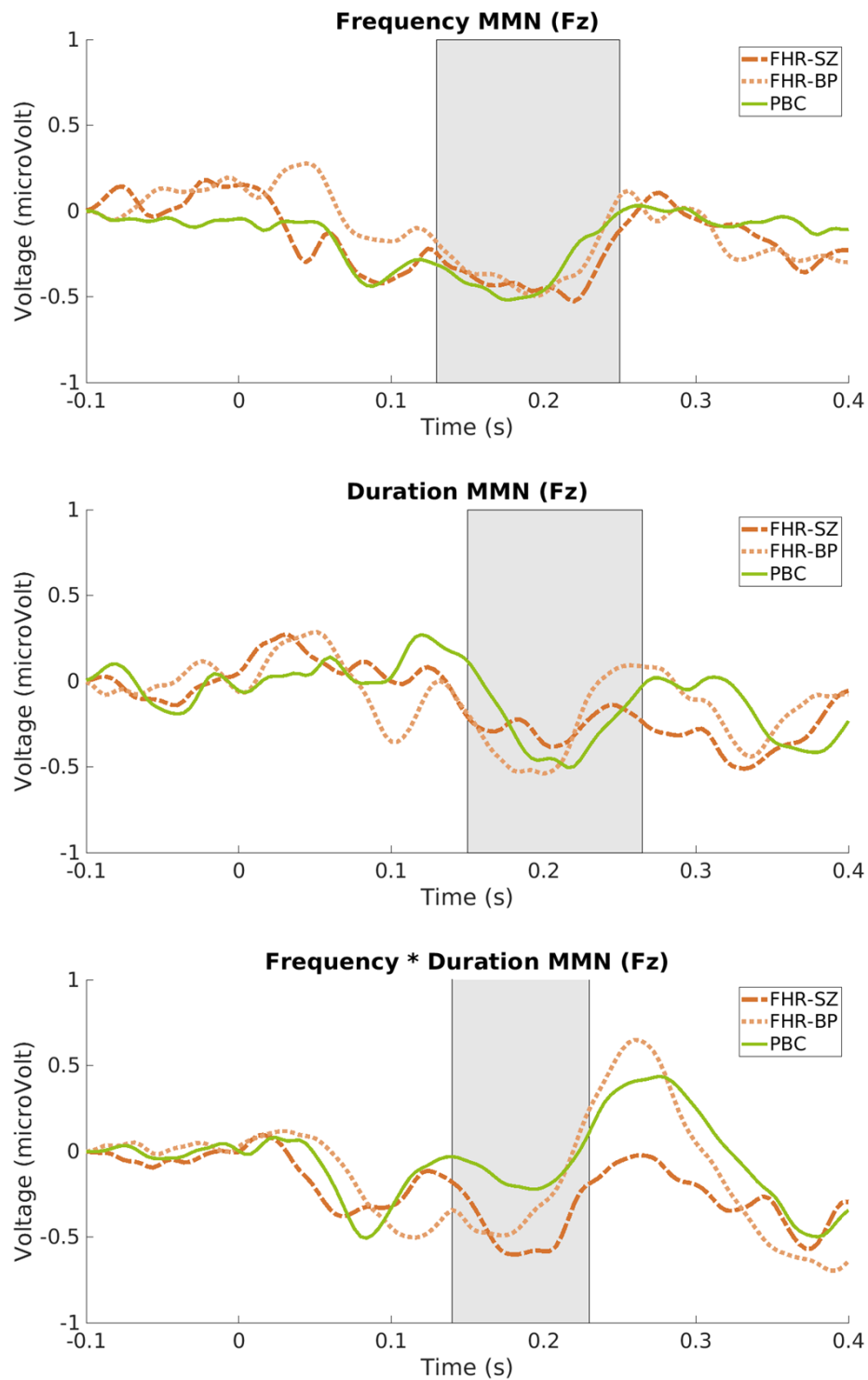


Figure 8 Mismatch negativity (MMN) of three types of deviants (Frequency MMN, Duration MMN, and Frequency*Duration MMN) of children with familial high-risk for schizophrenia (FHR-SZ), familial high-risk for bipolar disorder (FHR-BP), and population-based controls (PBC). Grey rectangles represent the time windows in which mean amplitudes were calculated.

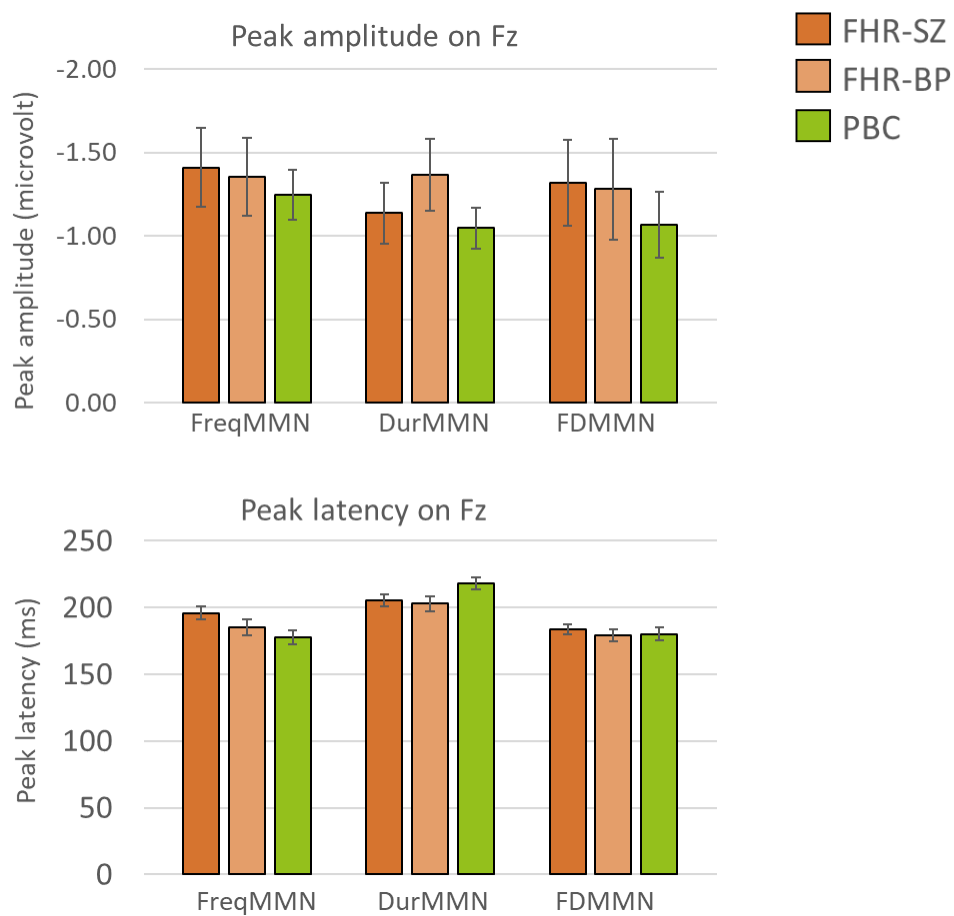


Figure 9 Peak amplitude and peak latency measured on Fz, of Frequency mismatch negativity (FreqMMN), Duration mismatch negativity (DurMMN) and Frequency*Duration mismatch negativity (FDMMN) in children with familial high-risk for schizophrenia (FHR-SZ), familial high-risk for bipolar disorder (FHR-BP) and population-based controls (PBC).

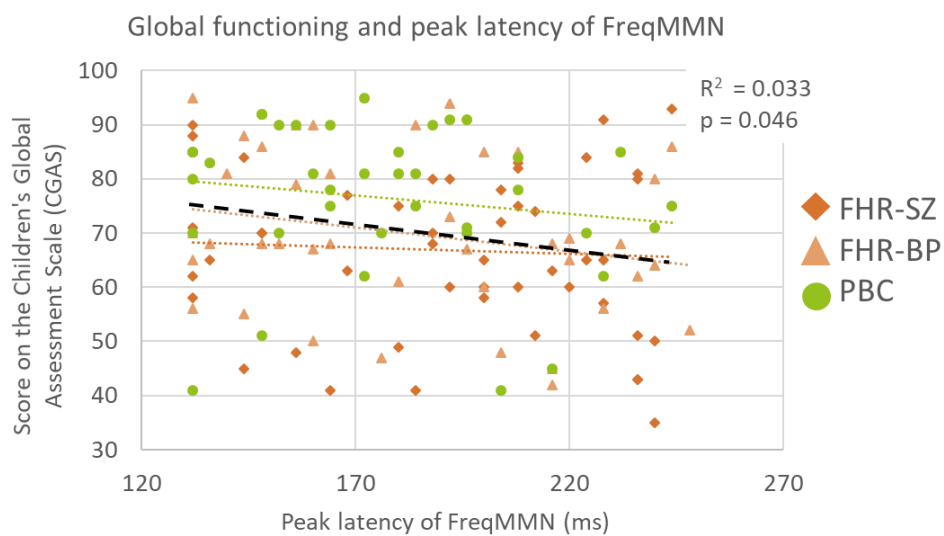


Figure 10 The correlation between global functioning, measured with CGAS, and the peak latency of frequency MMN. The black dashed line represents the negative correlation in the whole group (N=140).

9.2 Study 2: Behavioral performance and neural responses during a visuomotor conflict task in children with familial high risk for schizophrenia and bipolar disorder

The aims were to investigate electrophysiological activity during interference control (flanker task) in children with FHR-SZ and with FHR-BP and in PBC. We recorded EEG during the execution of a flanker task. Behavioral performance was evaluated based on accuracy rates, RTs and CV_{RT}. We measured the ERPs reflective of conflict monitoring (N200), attended, task-relevant stimulus processing (P3b), and motor-response preparation (LRP). Additionally, we correlated the ERPs of interest with clinical variables (emotional and behavioral problems (CBCL) and severity of ADHD symptomatology (ADHD-RS)).

9.2.1 Participants

We included 60 children with FHR-SZ, 44 children with FHR-BP, and 45 PBC. Based on behavioral data, four datasets (1 FHR-SZ and 3 PBC) were excluded and based on EEG data, another five datasets (2 FHR-SZ and 3 PBC) were excluded (due to bad EEG quality).

Children with FHR-SZ and with FHR-BP had higher ratings on problem behavior than PBC children. Further, children with FHR-SZ had higher ratings on ADHD-symptoms than PBC children. (See Table 2 for the children's characteristics.)

Table 2 Characteristics of children with familial high-risk for schizophrenia (FHR-SZ), children with familial high-risk for bipolar disorder (FHR-BP) and population-based controls (PBC)

	FHR-SZ	FHR-BD	PBC	<i>p</i> -value	FHR-SZ vs. PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
Children, N.	59	44	42				
Age, mean (s.d.)	12.10 (0.23)	12.12 (0.22)	12.19 (0.30)	0.162 ^a			
Gender, N boys (%)	26 (44)	24 (55)	22 (52)	0.527 ^b			
Handedness, N right-handed (%)	51 (86)	39 (89)	40 (95)	0.347 ^b			
Variable, mean (s.d.)	N	N	N				
RIST, total IQ (General intelligence)	59 96.54 (10.52)	44 99.73 (8.19)	42 98.55 (8.44)	0.215 ^a			
CBCL total score (Emotional and behavioral problems)	57 20.28 (17.83)	43 17.00 (15.41)	41 10.49 (9.74)	0.020 ^c	0.008 ^d	0.040 ^d	0.458 ^d
ADHD-RS (without conduct; severity of ADHD symptoms)	58 10.81 (9.43)	43 8.37 (6.64)	42 6.12 (4.75)	0.045 ^c	0.017 ^d	0.109 ^d	0.323 ^d

^aOne-way ANOVA; ^bPearson chi-square test of independence; ^cKruskal-Wallis test; ^dMann-Whitney U test; Abbreviations: ADHD-RS, Attention-Deficit/Hyperactivity Disorder – Rating Scale; CGAS, Children's Global Assessment Functioning; FHR-BP, familial high-risk for bipolar disorder; FHR-SZ, familial high-risk for schizophrenia; N, number; PBC, population-based controls; RIST, Reynold's Intellectual Scaling Test; s.d., standard deviation.

9.2.2 Behavioral results

Accuracy rates differed by condition ($F(1,142) = 317.746, p < 0.001$) shown by higher accuracy rates in congruent than in incongruent trials, but we found no significant effect of group nor an interaction effect. RTs differed by group ($F(2,142) = 4.121, p = 0.018$) such that children with FHR-SZ and with FHR-BP were significantly slower than PBC (FHR-SZ versus PBC: $p = 0.045$; FHR-BP versus PBC: $p = 0.032$), but no significant interaction effect. Regarding the CV_{RT} , we found an interaction effect of group by condition ($F(2,142) = 3.456, p = 0.034$), such that children with FHR-SZ and with FHR-BP had increased CV_{RT} in incongruent trials compared to PBC children (FHR-SZ versus PBC: $p = 0.019$; FHR-BP versus PBC: $p = 0.044$), which was not the case in congruent trials (see Figure 11).

Further, distributional analyses allowed us to distinguish between fast errors, indicating global inhibiting problems, and slow, deliberate errors, indicating inefficiency of cognitive control. MeanRT for each time bin differed by group ($F(6,282) = 2.642, p = 0.017$) such that children with FHR-SZ and with FHR-BP were significantly slower on their most deliberate responses (fourth time bin) relative to PBC (FHR-SZ versus PBC: $p = 0.008$; FHR-BP versus PBC: $p = 0.014$), without a significant effect on the accuracy rates. Children with FHR-BP were also significantly slower in the third time bin, relative to PBC ($p = 0.049$). In addition, we did not find a significant effect of group on the congruency effect of RT within each time bin ($F(6,282) = 1.269, p = 0.272$) (see Figure 12).

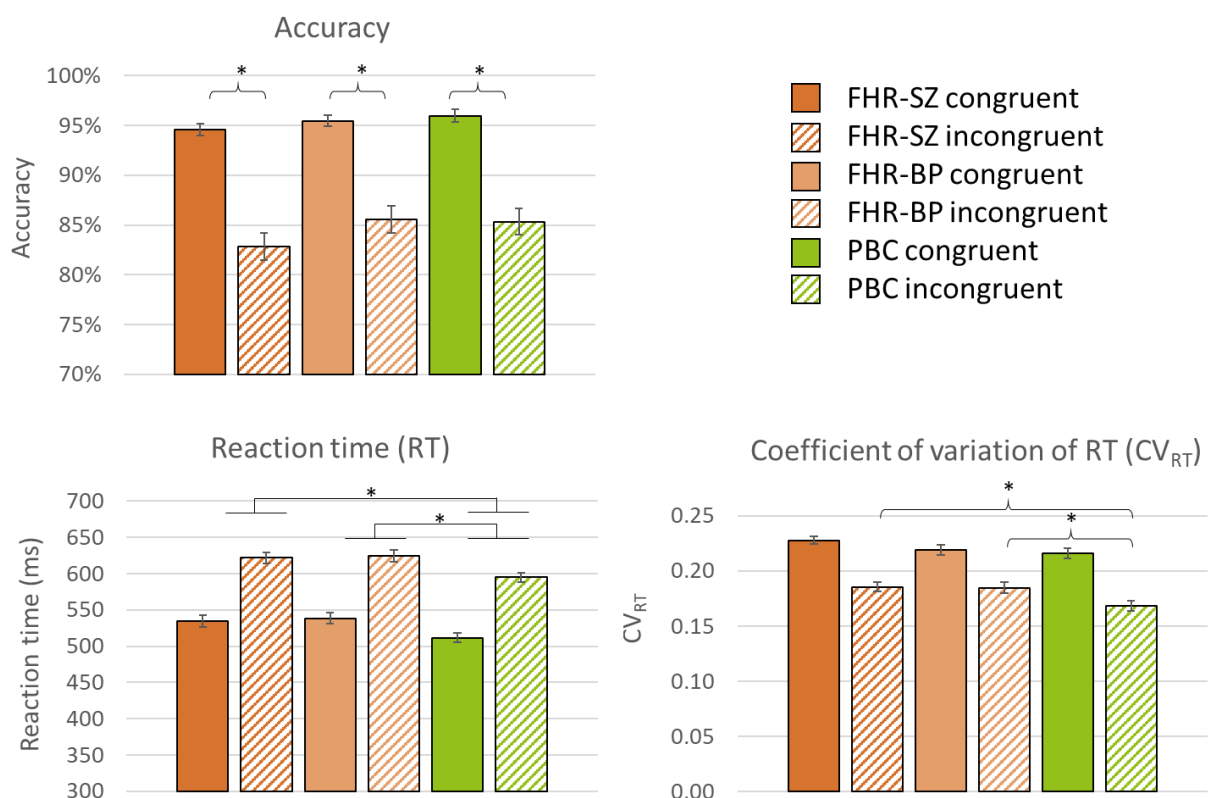


Figure 11 Performance on the flanker task, evaluated using the accuracy rate, reaction time (RT), and the coefficient of variation of the RT (CV_{RT}), in children with familial high-risk for schizophrenia (FHR-SZ), familial high-risk for bipolar disorder (FHR-BP), and population-based controls (PBC). *Indicates significance $p < .05$.

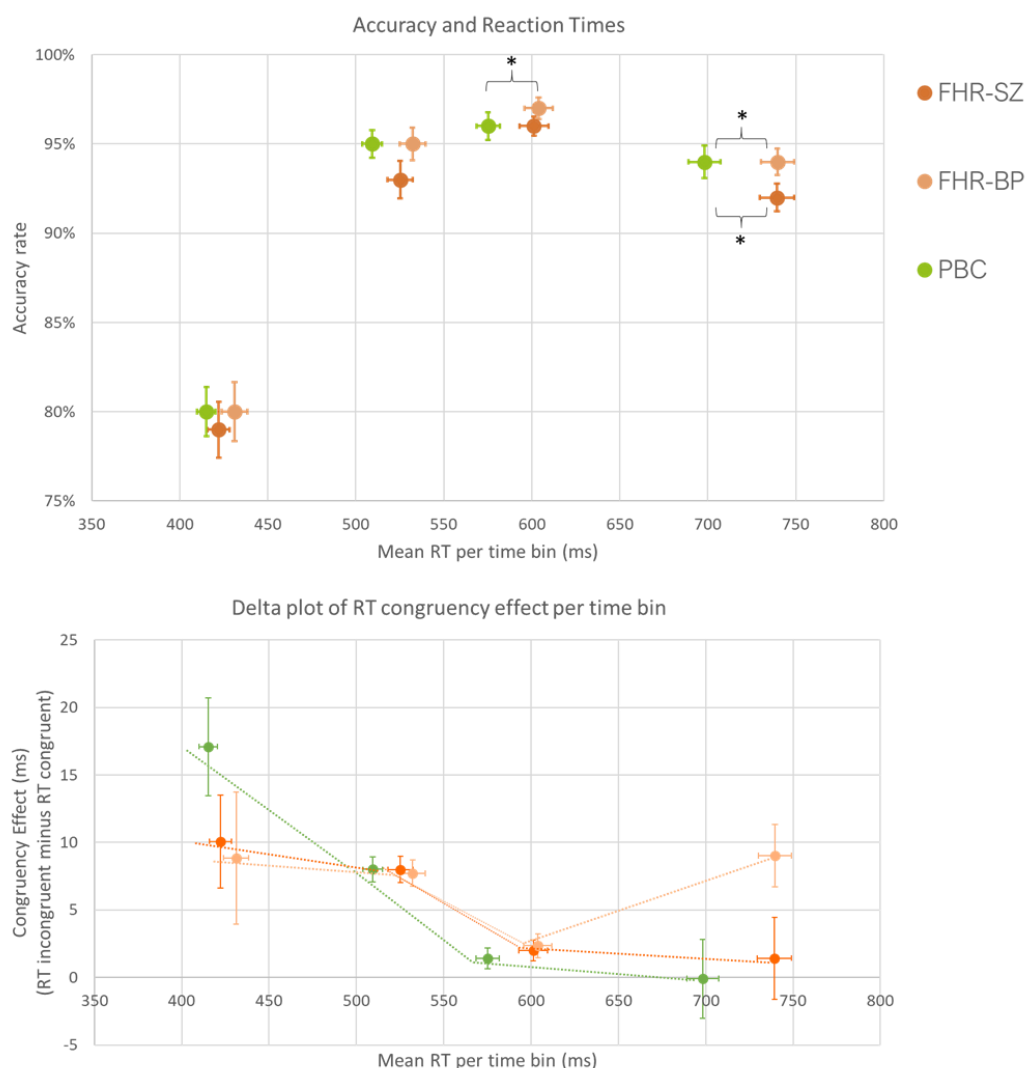


Figure 12 Distributional analyses on the reaction times (RT) of the flanker task in children with familial high-risk for schizophrenia (FHR-SZ), children with familial high-risk for bipolar disorder (FHR-BP), and population-based controls (PBC). Single trials per individual were grouped in four time bins (i.e. quartiles) according to individual distributions of RT, i.e. quartile 1 contains the fastest responses and quartile 4 contains the slowest responses. The upper figure presents the accuracy rates across the groups across the quartiles. The lower figure presents the delta plot of the congruency effect of RT (RT incongruent trials – RT congruent trials) against the mean RT of the quartile of each group. *Indicates significance $p < 0.05$.

9.2.3 EEG results

We found a significant interaction effect (group by condition) for mean P3b amplitude ($F(2,137) = 3.410$, $p = 0.036$), shown by reduced P3b amplitudes in incongruent trials in children with FHR-SZ and with FHR-BP compared to PBC (FHR-SZ versus PBC: $p < 0.001$; FHR-BP versus PBC: $p = 0.011$). Reduced P3b amplitudes were also present in the congruent condition in children with FHR-SZ, compared to PBC. Mean N200 amplitude differed by condition ($F(1,137) = 24.876$, $p < 0.001$), presented by larger mean N200 amplitudes in incongruent than in congruent trials, but this was not significantly different between groups nor by interaction. The peak-to-peak LRP amplitude differed by condition ($F(1,137) = 12.240$, $p = 0.001$) such that LRP amplitudes were greater in incongruent than in congruent trials, but we found no

significant effect of group nor a significant interaction of group by condition (see Figure 13 and 14 for the grand average waveforms and the ERP amplitudes). Post hoc we checked the mean P2 amplitude (on Pz), as a similar amplitude reduction in children with FHR appeared as the one found in P3b. We found that mean P2 amplitudes differed between groups ($F(4,274) = 4.302, p = 0.002$) such that children with FHR-SZ showed smaller P2 amplitudes ($p = 0.001$) than PBC. This was not found for children with FHR-BP.

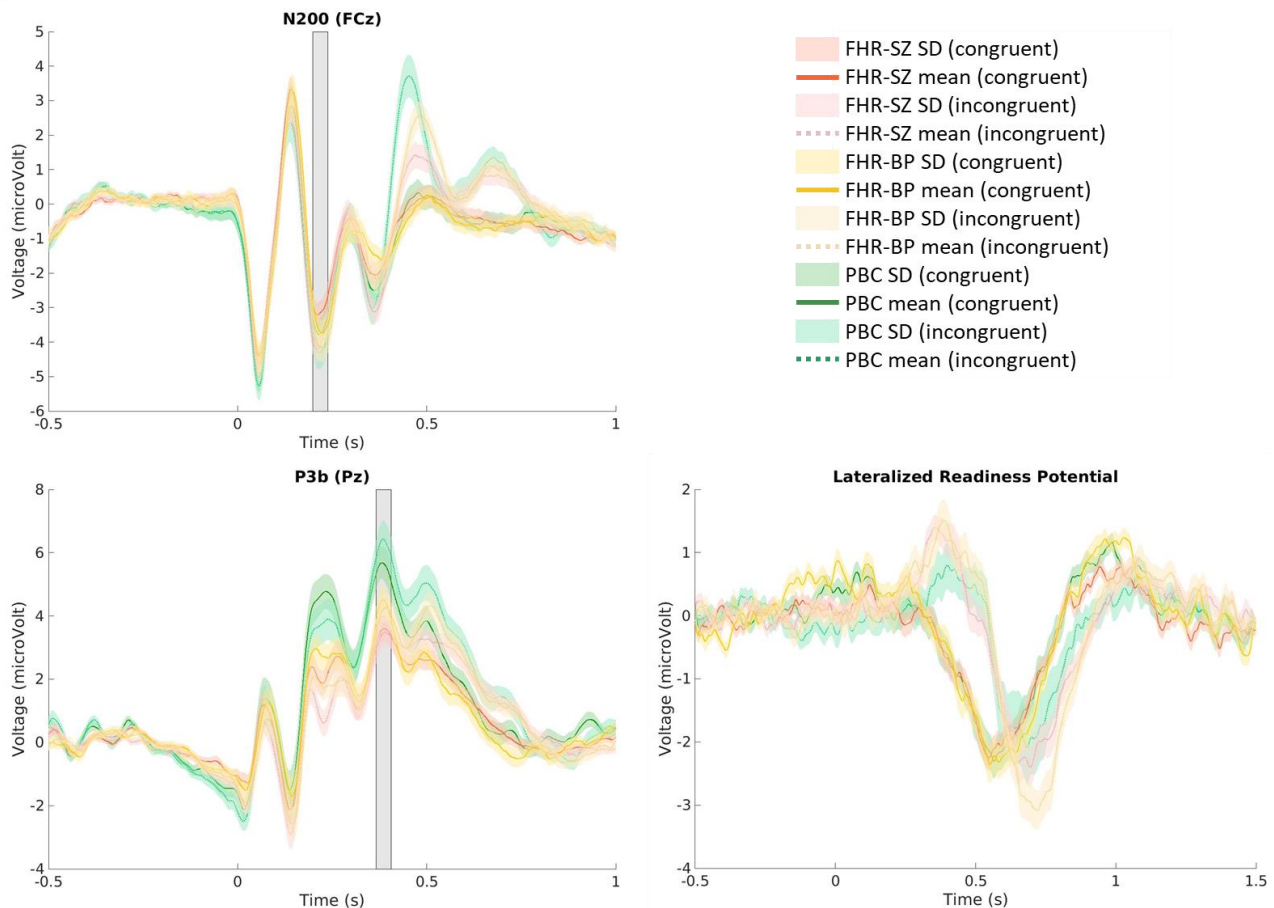


Figure 13 Grand average waveforms of ERPs of interest during the flanker task, i.e. N200, P3b, and the lateralized readiness potential (LRP) in children with familial high-risk for schizophrenia (FHR-SZ), children with familial high-risk for bipolar disorder (FHR-BP), and population-based controls (PBC).

9.2.4 Correlations

We exploratively investigated correlations between ERPs and clinical variables. Mean amplitudes of N200 and P3b were not significantly correlated to emotional and behavioral problems or severity of ADHD symptomatology in the entire group. In PBC, we found one significant negative correlation between the mean P3b amplitude on incongruent trials and the ADHD-RS (total score) ($r_s = -0.352, p = 0.028$). Further, CV_{RT} correlated negatively with the mean amplitude of P3b, in the congruent condition ($r = -0.185, p = 0.029$) as well as in the incongruent condition ($r = -0.284, p = 0.001$). This was found for the entire group (see Figure 15). (See Appendix 2 for all correlations for the entire group and for the groups separately.)

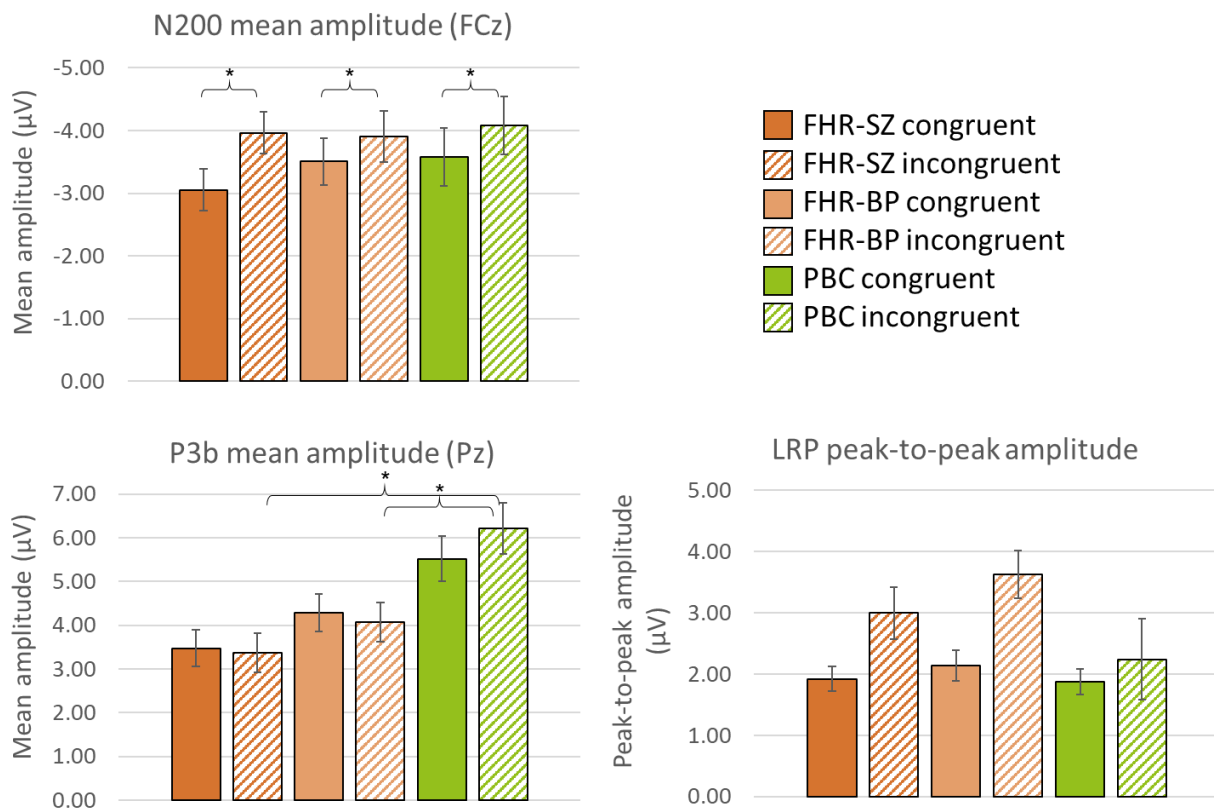


Figure 14 Bar plots of the amplitude values of the ERPs during the flanker task, reflecting conflict monitoring (N200), attended task-relevant stimulus processing (P3b) and motor-response preparation (LRP) in children with familial high-risk for schizophrenia (FHR-SZ), children with familial high-risk for bipolar disorder (FHR-BP), and population-based controls (PBC).

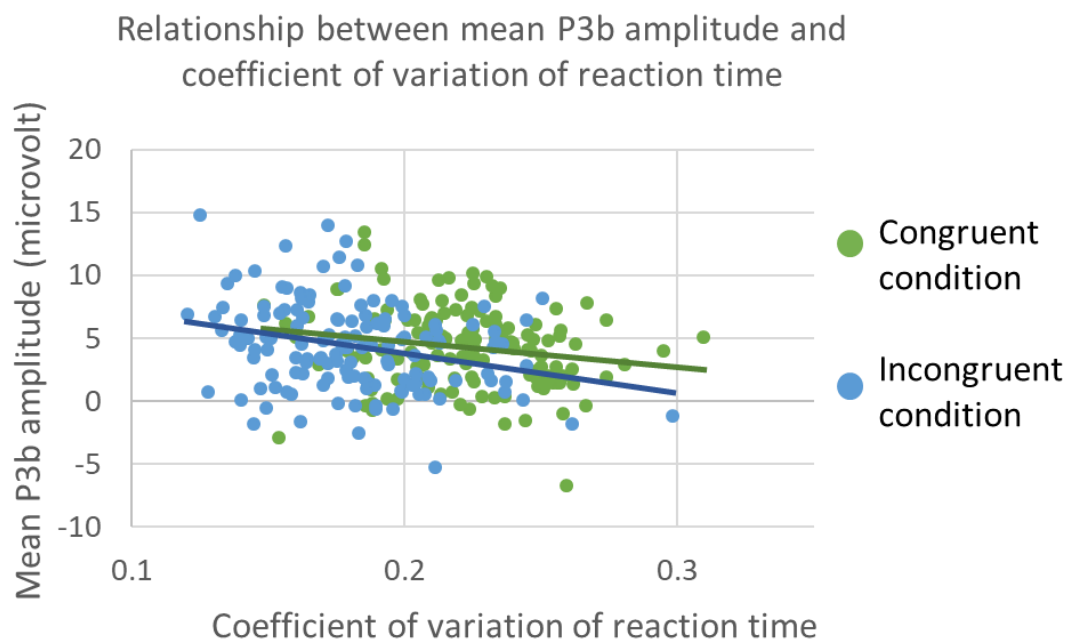


Figure 15 Correlation between mean P3b amplitude and the coefficient of variation of the reaction time (CV_{RT}) in the flanker task among children with familial high-risk for schizophrenia (FHR-SZ), familial high-risk for bipolar disorder (FHR-BP), and population-based controls (PBC), on congruent (green) and incongruent (blue) trials.

9.3 Study 3: Development of visual attention from age 7 to age 12 in children with familial high risk for schizophrenia or bipolar disorder

The aims were to investigate visual attention by using the TVA-based task in children with FHR-SZ, children with FHR-BP and PBC at age 12 as well as to compare their performance between age 7 and age 12. Four theoretical developmental trajectories were potentially examined, developmental lag (slower growth), developmental deficit (stable deficit), developmental deterioration (worsening), and developmental delay (delayed development).

9.3.1 Participants

Data of 133 12-year-old children (50 children with FHR-SZ, 40 children with FHR-BP, and 43 PBC) were included in the cross-sectional analysis. For the follow-up analysis, we included a smaller group of 89 children (32 children with FHR-SZ, 22 children with FHR-BP, and 35 PBC) to compare their performance on visual attention between age 7 and age 12. Several reasons caused that the drop-out rate was 33% (see Figure 16 for an overview of the design and for the exact numbers of drop out per reason). (See Appendix 3 for the demographics and clinical characteristics of the groups.)

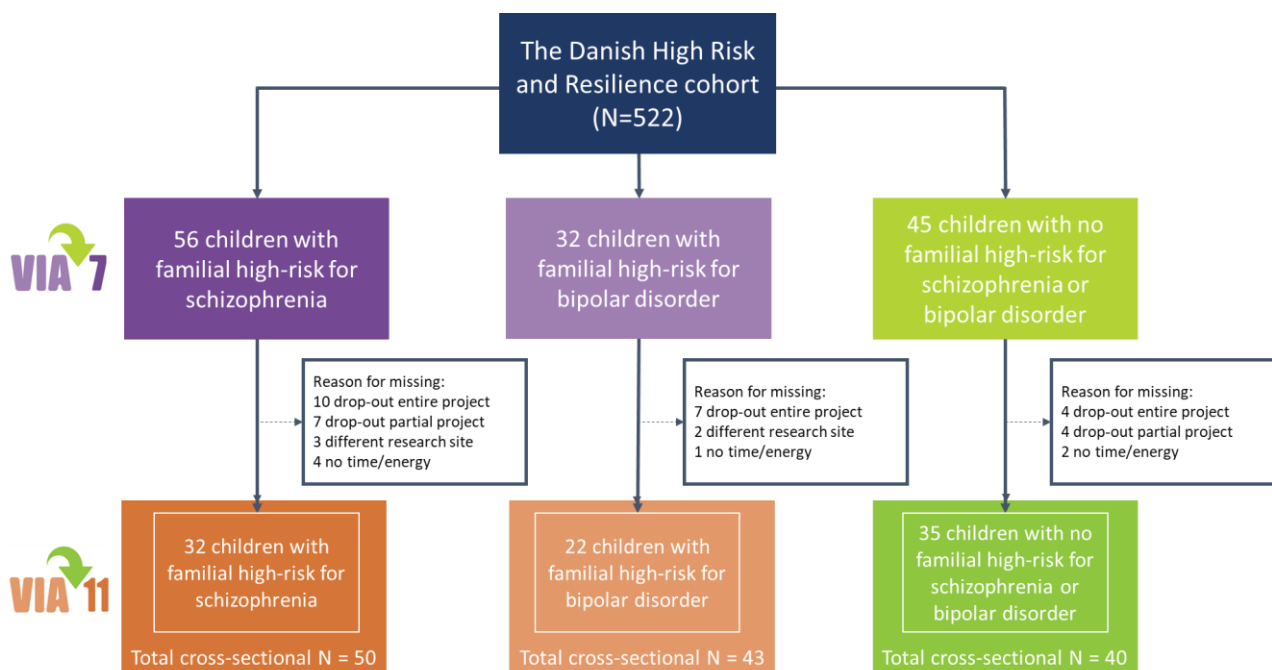


Figure 16 Study design of the TVA-study presenting the number of participants that completed the TVA-based task in the VIA 7 and in the VIA 11 study. The reasons for missing data in the follow-up were: (1) drop-out entire project: no participation in the VIA 11 study; (2) drop-out partial project: no participation on the particular TVA-test day; (3) different research site: the research site in Aarhus had no access to the TVA-based task; and (4) no time/energy: test was omitted out of consideration for the child. The number of total participants for the cross-sectional part is stated for each group.

9.3.2 Cross-sectional results age 12

By comparing the results of the TVA-based task between the groups, we found no significant differences between children with FHR-SZ, FHR-BP, or PBC on visual short-term memory (K), visual processing speed (C), the threshold of visual perception (t_0), or error rate (see Figure 17). A significant correlation with sex and the threshold of visual perception was found, but no interaction effect was found. Sex did not correlate with the other parameters (K or C). (The exact values of the TVA performance and the cross-sectional analyses can be found in Appendix 3.)

9.3.3 Follow-up results compared to age 7

Children at age 12, compared to age 7, improved on the distinct aspects of visual attention, i.e. on visual short-term memory (K) ($F(1,86) = 141.071$, $p < 0.001$), visual processing speed (C) ($F(1,86) = 144.159$, $p < 0.001$), and the threshold of visual perception (t_0) ($F(1,86) = 54.410$, $p < 0.001$). On visual short-term memory (K), we found a significant interaction effect of group by time ($F(2,86) = 3.942$, $p = 0.023$), such that children with FHR-BP improved better than children with FHR-SZ ($p = 0.023$), but not compared to PBC (see Figure 17). (For the exact values of the TVA performance and the follow-up analyses, see Appendix 3.)

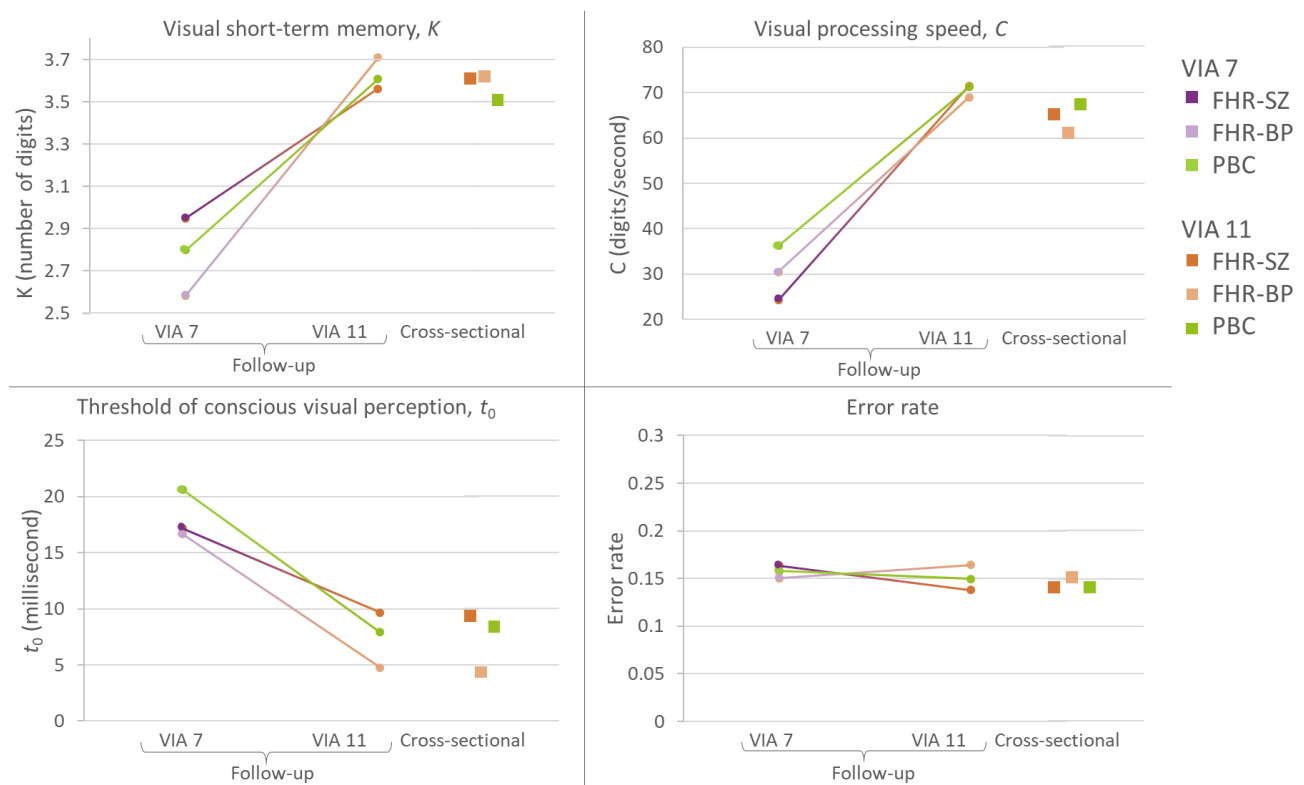


Figure 17 Developmental trajectories on visual attention from age 7 to age 12, using the TVA-based task in children with familial high-risk for schizophrenia (FHR-SZ), children with familial high-risk for bipolar disorder (FHR-BP), and population-based controls (PBC).

9.3.4 Post hoc analyses

We post hoc investigated the effect of the high rate of missing data (33%) through two ways, (1) comparing the baseline TVA performance and characteristics of children that stayed-in (i.e. tested again in the VIA 11 study) the project and the children that dropped-out (i.e. missing data in the VIA 11 study), and (2) by checking whether the findings at baseline remained in the smaller subsample (N=89). First, we found that children with FHR-BP that dropped-out after the VIA 7 study had significantly lower visual processing speed than the children with FHR-BP that were assessed again in the VIA 11 study ($p = 0.041$). This may suggest that the lower functioning children with FHR-BP dropped out. In contrast, there was no difference in the prevalence of psychiatric disorders in children with FHR-BP that stayed-in or dropped-out. Furthermore, a similar difference was not found in children with FHR-SZ or in the other TVA parameters (see Table 3). Second, when checking the baseline TVA performance, we found that deficits on visual processing speed remained in children with FHR-SZ ($p = 0.004$) but not in children with FHR-BP ($p = 0.466$), the latter likely due to the reduced sample size (N=22) and less power (see Table 4).

Table 3 Child characteristics and TVA performance at age 7 of the 44 participants tested in the VIA 7 study but not in the VIA 11 study (drop-out) and of the children that remained in the VIA 11 study (stay-in).

	FHR-SZ			FHR-BP			PBC		
	Drop-out (N=24)	Stay-in (N=32)	Statistics (p-value)	Drop-out (N=10)	Stay-in (N=22)	Statistics (p-value)	Drop-out (N=10)	Stay-in (N=35)	Statistics (p-value)
Child characteristics									
Age, years (s.d.)	7.81 (0.22)	7.77 (0.18)	0.361 ^a	7.79 (0.32)	7.86 (0.17)	0.421 ^a	7.77 (0.14)	7.74 (0.23)	0.638 ^a
Male, N (%)	17 (70.8)	14 (43.8)	0.044 ^b	3 (30.0)	11 (50.0)	0.290 ^b	6 (60.0)	17 (48.6)	0.524 ^b
Psychiatric (axis 1 ^c) disorder at age 7, N (%)	8 (33.3)	7 (21.9)	0.338 ^b	3 (33.3)	4 (18.2)	0.454 ^b	1 (10.0)	3 (8.6)	0.889 ^b
Parameter estimates, mean (s.d.)									
<i>K</i> (maximum span length)	2.60 (0.90)	2.95 (0.91)	0.164 ^a	2.17 (0.68)	2.58 (0.65)	0.109 ^a	2.98 (1.04)	2.80 (0.54)	0.465 ^a
<i>C</i> (digits/second)	25.15 (9.12)	24.24 (11.00)	0.745 ^a	19.98 (9.38)	30.48 (14.15)	0.041 ^{a*}	36.10 (25.07)	36.27 (17.97)	0.981 ^a
<i>t</i> ₀ (milliseconds)	13.86 (15.58)	17.15 (9.95)	0.340 ^a	15.72 (17.07)	16.67 (15.94)	0.880 ^a	15.36 (10.79)	20.62 (16.68)	0.354 ^a
Error rate	0.18 (0.11)	0.16 (0.08)	0.533 ^a	0.21 (0.07)	0.15 (0.07)	0.039 ^{a*}	0.19 (0.05)	0.16 (0.08)	0.143 ^a

^aOne-way ANOVA; ^bPearson Chi-Square test for independence; ^cAny axis 1 psychiatric disorder (without elimination disorder, see also (Ellersgaard et al., 2018)). Abbreviations: *C*, visual processing speed; FHR-BP, familial high-risk for bipolar disorder; FHR-SZ, familial high-risk for schizophrenia; *K*, capacity of visual short-term memory; *N*, number of participants; PBC, population-based children; s.d., standard deviation; TVA, theory of visual attention; *t*₀, threshold for conscious visual perception. *Significant at the 0.05 level.

Table 4 Performance on TVA-based task at age 7 of the follow-up group (N=89)

TVA parameters	FHR-SZ (N=32)	FHR-BP (N=22)	PBC (N=35)	Statistics (p-value)	FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
Visual short-term memory capacity, <i>K</i> (digits), mean (s.d.)	2.95 (0.91)	2.58 (0.65)	2.80 (0.54)	0.191 ^a			
Visual processing speed, <i>C</i> (digits/second), mean (s.d.)	24.24 (11.00)	30.48 (14.15)	36.27 (17.97)	0.006 ^a	0.004 ^b	0.466 ^b	0.399 ^b
Threshold of visual conscious perception, <i>t</i> ₀ (milliseconds), mean (s.d.)	17.15 (9.95)	16.67 (15.94)	20.62 (16.68)	0.503 ^a			

^aOne-way ANOVA; ^bCalculated with Scheffé post hoc test. For the full group-analysis of the TVA performance at age 7, see Hemager et al. (2019). Abbreviations: *C*, visual processing speed; FHR-BP, familial high-risk for bipolar disorder; FHR-SZ, familial high-risk for schizophrenia; *K*, capacity of visual short-term memory; *N*, number of participants; PBC, population-based children; s.d., standard deviation; TVA, theory of visual attention; *t*₀, threshold for conscious visual perception.

9.4 Study 4: Odor identification in 7-year-old children at familial high risk of schizophrenia or bipolar disorder - the Danish high risk and resilience study VIA 7

The aims were to investigate odor identification in 7-year-old children with FHR-SZ, FHR-BP and in PBC. Odor identification was assessed with the BSIT which is a 12-item multiple-choice test. Odor identification was evaluated by comparing the continuous test score (BSIT total score) as well as comparing the proportion of children with abnormal and normal (categorical score) odor identification across the three groups. Additionally, to exploratively investigate how these measures were related to clinical variables, we conducted a hierarchical regression analysis and logistic regression analysis with, respectively, BSIT total score and an abnormal function of odor identification as dependent variable.

9.4.1 Participants

We included 184 children with FHR-SZ, 106 children with FHR-BP, and 186 PBC children from the VIA 7 study. BSIT datasets of 10 children (3 FHR-SZ, 4 FHR-BP, and 3 PBC) were missing and 36 datasets (15 FHR-SZ, 10 FHR-BP, and 11 PBC) were excluded because of sickness that may have influenced olfaction (see Table 5).

Table 5 Demographic, psychopathological, cognitive, and home environmental characteristics of 7-year-old children at familial high-risk for schizophrenia (FHR-SZ), children at familial high-risk for bipolar disorder (FHR-BP), and population-based controls (PBC) presented in raw scores and pairwise comparisons between groups. (Reused from (Ver Loren van Themaat et al., 2020) with permission from the publisher.)

Variables, mean (SD)	Assessed function	N	FHR-SZ	N	FHR-BP	N	PBC	P-value	Pairwise Comparisons (P value)		
									FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
Demographics											
Children		184		106		186					
Female %		46.7		43.4		46.2		0.067 ^a			
Age - years at inclusion		7.8 (0.2)		7.8 (0.2)		7.8 (0.2)		0.850			
Dimensions of psychopathology											
CBCL Internalizing subscale	Internalizing problem behavior	179	6.5 (6.0)	99	6.4 (6.4)	180	4.9 (4.5)	0.007 ^b	0.010	0.104	0.983
CBCL Externalizing subscale	Externalizing problem behavior	178	7.7 (7.3)	100	6.2 (6.8)	180	4.1 (4.8)	<0.001 ^b	<0.001	0.022	0.182
ADHD-RS Inattention subscale	Inattentive symptoms	179	6.8 (5.3)	102	6.6 (5.5)	180	4.8 (4.2)	<0.001 ^b	<0.001	0.016	0.933
ADHD-RS Hyperactive-impulsive subscale	Hyperactive-Impulsive symptoms	179	7.0 (5.7)	102	6.4 (5.2)	180	5.4 (4.5)	0.016 ^b	0.014	0.271	0.669
SRS	Social Responsiveness	157	37.3 (26.1)	93	33.7 (32.3)	159	24.9 (20.6)	<0.001 ^b	<0.001	0.052	0.640
Cognition											
RIST	Intelligence	184	102.5 (11.5)	106	104.1 (9.0)	184	105.1 (10.0)	0.067 ^b	0.053	0.715	0.335
MFS Immediate	Verbal memory (immediate)	183	19.3 (10.1)	106	20.7 (10.0)	185	19.8 (9.4)	0.534	1.00	1.00	0.790
MFS Delayed	Verbal memory (delayed)	183	14.9 (9.1)	106	17.0 (9.3)	185	15.4 (8.4)	0.149	1.00	0.425	0.163
WSR Immediate	Verbal memory (immediate)	177	38.6 (5.7)	105	39.7 (4.7)	185	39.0 (5.0)	0.246	1.00	0.944	0.283
WSR Delayed	Verbal memory (delayed)	176	6.1 (2.0)	104	6.4 (1.5)	182	6.2 (1.6)	0.326	1.00	0.913	0.407
Coding	Processing speed	183	26.6 (7.7)	104	28.9 (7.3)	186	29.4 (7.1)	0.001	0.001	1.00	0.037
Symbol Search	Processing speed	179	15.5 (5.3)	104	17.4 (4.9)	181	17.2 (5.3)	0.001	0.005	1.00	0.008
Letter-Number Sequencing	Verbal working memory	181	12.5 (4.1)	105	13.8 (3.9)	186	13.8 (3.5)	0.001	0.003	1.00	0.014
RVP A'	Attention	173	0.89 (0.06)	104	0.90 (0.06)	180	0.90 (0.05)	0.038	0.032	1.00	0.557
Home environment											
Active Stimulation	Stimulating home environment	179	5.6 (1.5)	105	5.6 (1.4)	185	5.9 (1.5)	0.061	0.078	0.293	1.00
PSP	Parental personal and social functioning	182	73.4 (14.3)	106	74.9 (14.1)	185	84.3 (9.2)	<0.001	<0.001	<0.001	0.989

^a Pearson chi-square.

^b No homogeneity of variance thus Welch's ANOVA and multiple comparisons with Games-Howell. Abbreviations: A', A prime; ADHD-RS, Attention Deficit/Hyperactivity Disorder-Rating Scale; CBCL, Child Behavior Checklist; FHR-BP, Familial high-risk for bipolar disorder; FHR-SZ, Familial high-risk for schizophrenia; MFS, Memory for Stories; PSP, Personal and Social Performance; PBC, Population-Based Controls; RIST, Reynold's Intellectual Screening Test; RVP, Rapid Visual Information Processing; SRS, Social Responsiveness Scale; SD, standard deviation; WSR, Word Selective Reminding. See (Christiani et al., 2019; Ellersgaard et al., 2018; Hemager et al., 2018) for results on the full cohort.

9.4.2 Continuous and categorical outcome

The main findings of this study were that children with FHR-SZ and children with FHR-BP did not significantly differ from PBC on odor identification, using the continuous outcome (BSIT total score) (see Table 6). Comparing the proportion of children with abnormal and normal odor identification, which was based on American normative data, more boys with FHR-SZ had an abnormal odor identification than did boys of the PBC group (see Figure 18 and Table 7). This was not found in girls nor in children with FHR-BP. However, due to the inconsistent findings between the continuous and categorical analyses as well as a lower than expected performance of odor identification in the boys of the PBC group, we calculated a Danish-based threshold to determine normal and abnormal odor identification. This Danish-based threshold defined an abnormal odor identification function as a score <1.5 SD below the mean of the boys of the PBC group. Following this Danish-based threshold, the proportion of boys with FHR-SZ and boys of the PBC group with abnormal odor identification did not significantly differ. Taken together, the findings of the continuous and categorical analyses showed that there was no significant difference in odor identification across the three groups.

Table 6 Two-way ANOVA on a dimensional score of odor identification in 7-year-old children with familial high-risk group and sex as fixed factors. (Reused from (Ver Loren van Themaat et al., 2020) with permission from the publisher.)

	Parameter estimate (B)	Confidence interval (95%)	p-value
Intercept	6.250	5.930–6.570	<0.001
FHR-SZ versus PBC	−0.274	−0.667–0.118	0.170
FHR-BP versus PBC	−0.129	−0.588–0.331	0.583
Female versus male	0.958	0.611–1.306	<0.001

Abbreviations: FHR-BP, Familial high-risk for bipolar disorder; FHR-SZ, Familial high-risk for schizophrenia; PBC, Population-Based Controls.

Table 7 Categories of normal and abnormal olfaction of 7-year-old children at familial high-risk for schizophrenia (FHR-SZ), children at familial high-risk for bipolar disorder (FHR-BP), and population-based controls (PBC). (Reused from (Ver Loren van Themaat et al., 2020) with permission from the publisher.)

Categorical, abnormal odor identification ^a	N	FHR-SZ	N	FHR-BP	N	PBC	P-value	Chi-square tests (P value)		
								FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
All children, %	29	15.8	15	14.2	20	10.8	0.358 ^b			
Boys, %	27	27.6	13	21.7	13	13.0	0.039 ^b	0.013	0.185	0.455
Girls, %	2	2.3	2	4.3	7	8.1	0.213 ^b			

^a Abnormal odor identification boys, BSIT total score < 5; girls, BSIT total score < 4 (Doty, 2001).

^b Pearson chi-square test; Abbreviations: FHR-BP, Familial high-risk for bipolar disorder; FHR-SZ, Familial high-risk for schizophrenia; PBC, Population-Based Controls.

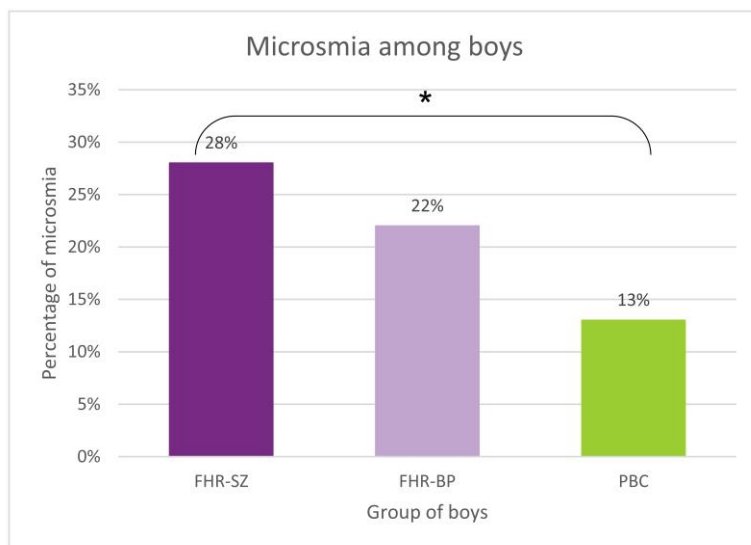


Figure 18 Abnormal odor identification using an American-based threshold (Doty, Marcus, & Lee, 1996) among boys with familial high-risk for schizophrenia (FHR-SZ), children at familial high-risk for bipolar disorder (FHR-BP), and population-based controls (PBC). *Indicates significance $p < 0.05$. (Reused from (Ver Loren van Themaat et al., 2020) with permission from the publisher.)

9.4.3 Regression models

The hierarchical regression model, with the continuous measure (BSIT total score) as dependent variable, showed significant positive associations of odor identification with sex (girls), social responsiveness, and verbal working memory (see Table 8). The logistic regression with the proportion of normal and abnormal odor identification as dependent variable, initially, showed that social responsiveness predicted microsmia in boys with FHR-SZ (see Table 9). However, by using the Danish-based threshold to determine normal and abnormal odor identification, we could not replicate this finding that was based on the American normative data.

Table 8 Hierarchical Regression Analysis of demographical, psychopathological, cognitive, and home environmental predictors on odor identification of 7-year-old children at familial high-risk for schizophrenia (FHR-SZ), children at familial high-risk for bipolar disorder (FHR-BP), and population-based controls (PBC). (Reused from (Ver Loren van Themaat et al., 2020) with permission from the publisher.)

Predictors	Assessed function	Model 1 Estimate	95% CI	Model 2 Estimate	95% CI	Model 3 Estimate	95% CI
Demographics							
High-risk status		0.06	−0.04; 0.18	0.02	−0.09; 0.14	0.01	−0.11; 0.13
Sex (boys)		−0.24*	−0.68; −0.29	−0.19*	−0.57; −0.18	−0.19*	−0.58; −0.18
Age		0.05	−0.24; 0.69	0.05	−0.22; 0.73	0.06	−0.21; 0.74
Dimensions of psychopathology							
CBCL Internalizing Subscale	Internalizing problem behavior			0.00	−0.10; 0.10	−0.01	−0.10; 0.09
CBCL Externalizing Subscale	Externalizing problem behavior			−0.12	−0.20; 0.02	−0.12	−0.20; 0.02
ADHD-RS Inattention Subscale	Inattentive symptoms			0.00	−0.10; 0.12	0.01	−0.10; 0.12
ADHD-RS Hyperactive-impulsive Subscale	Hyperactive- and impulsive symptoms			0.10	−0.03; 0.21	0.10	−0.03; 0.21
SRS	Social Responsiveness			0.18*	0.05; 0.23	0.17*	0.04; 0.22
Cognition							
RIST	Intelligence			0.02	−0.09; 0.13	0.01	−0.10; 0.12
MFS (composite)	Verbal memory			0.11	0.00; 0.20	0.10	−0.00; 0.20
WSR (composite)	Verbal memory			0.06	−0.05; 0.14	0.06	−0.05; 0.15
Processing speed (composite)	Processing speed			−0.01	−0.12; 0.10	−0.02	−0.13; 0.10
Letter-number sequencing	Verbal working memory			0.13*	0.02; 0.22	0.13*	0.02; 0.22
RVP A'	Attention			−0.02	−0.11; 0.08	−0.02	−0.11; 0.08
Home environment							
Active stimulation	Stimulating home environment					0.05	−0.06; 0.15
PSP	Parental personal and social functioning					0.03	−0.05; 0.10
Model squared R		0.064		0.168		0.172	
F change		8.870		4.290		0.781	
P-value		<0.001		<0.001		0.459	

Model 1: High-risk Status, sex, age; Model 2: High-risk Status, sex, CBCL Internalizing subscale, CBCL Externalizing subscale, ADHD-RS Inattention subscale, ADHD-RS Hyperactive-impulsive subscale, SRS, RIST, MFS (composite), WSR (composite), Processing Speed (composite), Letter-Number Sequencing, RVP A'; Model 3: High-risk Status, sex, CBCL Internalizing subscale, CBCL Externalizing subscale, ADHD-RS Inattention subscale, ADHD-RS Hyperactive-impulsive subscale, SRS, RIST, MFS (composite), WSR (composite), Processing Speed (composite), Letter-Number Sequencing, RVP A', Active Stimulation, PSP. Abbreviations: A', A prima; ADHD-RS, Attention Deficit/Hyperactivity Disorder-Rating Scale; CBCL, Child Behavior Checklist; CI, Confidence Interval; FHR-BP, Familial high-risk for bipolar disorder; FHR-SZ, Familial high-risk for schizophrenia; MFS, Memory for Stories; PSP, Personal and Social Performance; PBC, Population-Based Controls; RIST, Reynold's Intellectual Screening Test; RVP, Rapid Visual Information Processing; SRS, Social Responsiveness Scale; WSR, Word Selective Reminding.

* Indicates significance ($p < .05$).

Table 9 Multiple Logistic Regression Analysis of psychopathological and cognitive measures on odor identification of boys at familial high-risk for schizophrenia (FHR-SZ). (Reused from (Ver Loren van Themaat et al., 2020) with permission from the publisher.)

Covariates	Assessed function	Model 1 OR	95% CI	Model 2 OR	95% CI	Model 3 OR	95% CI
SRS	Social responsiveness	1.61*	1.06–2.45	1.62*	1.07–2.46	1.59*	1.07–2.38
MFS (composite)	Verbal memory	1.27	0.84–1.91	1.29	0.87–1.91		
Letter-Number Sequencing	Verbal working memory	1.08	0.65–1.80				

Model 1: SRS, MFS (composite), Letter-Number Sequencing; Model 2: SRS, MFS (composite); Model 3: SRS. Abbreviations: CI, Confidence interval, MFS, Memory for Stories; OR, Odds Ratio; SRS, Social responsiveness Scale.

* Indicates significance ($p < .05$).

10. Discussion

The overarching aim of this dissertation was to investigate early stages of information processing as well as higher-order cognitive functions in children with FHR-SZ and with FHR-BP. This work builds on previous findings of electrophysiological abnormalities in information processing and deficits in cognitive functions found in individuals with CHR for psychosis, first-episode psychosis, and patients with chronic schizophrenia or bipolar disorder as well as their FDR. Together, these findings will enhance the knowledge regarding the development and course of these potential abnormalities which may help future studies in the search for identifiable markers of vulnerability and resilience. First, a short summary of the four studies is presented, followed by an in-depth discussion for each study, followed by general commonalities and differences between the results of the studies.

10.1 Summary of findings

The results of study 1 revealed no alterations in the electrophysiological measure reflecting pre-attentive auditory processing (MMN) in children with FHR-SZ or with FHR-BP, compared to PBC children. During the interference control task in study 2, we found alterations in the brain response reflecting attended, task-relevant stimulus processing during a visual flanker task in children with FHR-SZ and with FHR-BP, in terms of P3b amplitude reductions in the incongruent condition, while the brain responses reflecting conflict monitoring (N200) and motor-response preparation (LRP) were intact. On the behavioral level, both FHR groups showed slower RTs in both conditions and an increased intra-subject RT variability in the incongruent condition. Accuracy rates were similar to that of PBC children. Further, in study 3 we investigated the performance on an unspeeded and accuracy-based visual attention task between the three groups at age 12 and in a smaller sample we compared the performance between age 7 and age 12. We found no differences on distinct aspects of visual attention between the groups at age 12. Follow-up results revealed that all children (FHR-SZ, FHR-BP, and PBC) improved over time on distinct aspects of visual attention, but no differences in improvement compared to PBC children. An interesting finding was that deficits in visual processing speed at age 7 in children with FHR-SZ disappeared at age 12. Lastly, study 4 showed that the risk status and the ability to identify odors appear independent in children at age 7. Finally, we described our questions and the subsequent rationales and approaches in a manuscript (study 5) that clearly defined the methods used and the outcome measures defined beforehand.

10.1.1 MMN

The results on MMN revealed no significant differences between children with FHR-SZ or with FHR-BP and PBC children. Some previous studies have suggested MMN deficits as endophenotypic for schizophrenia (Jessen et al., 2001; Michie et al., 2002; Sevik et al., 2011), which, among other criteria, would mean that deficits should be present in children with FHR-SZ. Our results, however, do not suggest MMN deficits as endophenotype for schizophrenia, or bipolar disorder. To date, this is the first study that investigated MMN in a relatively large group of children with FHR with a narrow age range.

Our study contributes to the literature on MMN in individuals with CHR for psychosis and in FDR of patients with schizophrenia. In individuals with CHR for psychosis, MMN amplitude reductions are often reported (Näätänen et al., 2016), suggesting that MMN deficits predate the onset of the illness (Shaikh et

al., 2012). Accordingly, MMN was proposed as biomarker for schizophrenia by many previous studies (Javitt et al., 2008; Light & Naatanen, 2013; Näätänen et al., 2016). MMN alterations were also reported in young children with antecedents of schizophrenia (Bruggemann, Stockill, Lenroot, & Laurens, 2013). It should be noted that they found enhanced MMN amplitudes, instead of the reduced amplitude that is usually reported in older individuals with CHR (Näätänen et al., 2016). Furthermore, previous literature on MMN in FDR of patients with schizophrenia is rather inconsistent as some found MMN deficits, who suggested MMN deficits as potential endophenotype (Jessen et al., 2001; Michie et al., 2002; Sevik et al., 2011), while others did not (Bramon, 2004; Hall et al., 2009; Magno et al., 2008). These studies included adult FDR, with a mean age of 43 years, who were beyond the most vulnerable period for developing psychosis. In contrast, our cohort consisted of individuals in a young and early pubertal stage who are still relatively vulnerable to developing psychosis. As our results did not show MMN deficits in children with FHR-SZ or with FHR-BP, we cannot support the notion of MMN as endophenotype for schizophrenia nor psychosis. Our findings were in accordance with an earlier, smaller study including children with FHR-SZ that also reported no MMN deficits as compared to control children (Schreiber, Stolz-Born, Kornhuber, & Born, 1992) and we expand this finding to children with FHR-BP. Taken together, our findings do not support MMN deficits as endophenotype, but possibly as biomarker for schizophrenia as it is possible that the children with the smallest MMN amplitudes eventually develop schizophrenia, however, this is currently not noticeable at the group level.

Further, it has been suggested that frequency MMN (FreqMMN) may be indexing illness progression, while duration MMN (DurMMN) may be a more likely biomarker of schizophrenia (Lavoie et al., 2019). This view is supported by studies showing an intact FreqMMN until the post-acute phase of first-episode psychosis (Devrim-Ucok, Keskin-Ergen, & Ucok, 2008), its normal presence in FDR (Magno et al., 2008), and its correlation with the duration of illness (Umbricht & Krljes, 2005). In contrast, deficits in DurMMN have been found in individuals with CHR for psychosis (Atkinson, Michie, & Schall, 2012; Jahshan et al., 2012; Perez et al., 2014; Shaikh et al., 2012), in first-episode patients with schizophrenia (Oranje, Aggernaes, Rasmussen, Ebdrup, & Glenthøj, 2017; Rydkjaer et al., 2017), as well as in, some (Jessen et al., 2001; Michie et al., 2002; Sevik et al., 2011) but not all FDR (Bramon, 2004; Magno et al., 2008). Moreover, several studies have suggested that DurMMN reductions can forecast the transition to psychosis in individuals with CHR for psychosis (Bodatsch et al., 2015; Näätänen et al., 2016; Perez et al., 2014; Shaikh et al., 2012) due to the smaller DurMMN amplitudes found in individuals with CHR that subsequently converted to psychosis as compared to those that did not convert to psychosis. Our study showed, on a group level, no deficits in DurMMN or FreqMMN. However, it may be that those of our included children with small DurMMN amplitudes eventually develop schizophrenia, which would support DurMMN as biomarker for the illness. Further, deficits in FreqMMN would only arise in those children that develop psychosis. Only longitudinal studies, such as a follow-up of our current study will be able to shed light on these hypotheses.

Studying clinical variables assessing potential problem behavior, the severity of autistic traits, and global functioning allowed us to gain insights into the cohort's functioning as well as potential links with MMN measures. As some retrospective studies showed that behavioral problems emerged during the childhood of patients with schizophrenia and bipolar disorder (Cannon et al., 2000; Haim, Rabinowitz, & Bromet, 2006), children with higher rates of problem behavior may represent a group at higher risk for

developing such disorders. Accordingly, our results showed a significant correlation between worse global functioning and prolonged MMN latencies in all children. Patients with schizophrenia (Light & Braff, 2005) as well as individuals with CHR (Koshiyama et al., 2018) showed a similar significant relation between global functioning and MMN deficits, although these deficits comprised amplitude reductions. Therefore, it could be suggested that worse global functioning and MMN alterations are linked and could be used for risk estimations in the future. However, our other results showed no relationships between clinical variables (i.e. the severity of autistic traits and problem behavior) and MMN measures. The lack of a variable measuring subclinical psychotic symptoms (which is part of our overall project but was not yet available at the time of the current analyses) is an important limitation of this study, resulting in that we were unable to precisely evaluate the clinical risk or status of our included children.

To summarize, our finding does not support MMN deficits as endophenotype for schizophrenia, or psychosis-related disorders in general. Although only speculative, MMN deficits might be currently present in children that will transition to schizophrenia at a later developmental stage, which would support MMN deficits as biomarker. However, on a group level, this effect may be too small to be significant as the transition rate of children with FHR-SZ is relatively small (roughly 10% (Rasic et al., 2014)). Therefore, it is important that longitudinal studies of children with FHR-SZ are conducted, which may be able to further elaborate on MMN as biomarker as well as on the predictive value of potential MMN deficits. Including children with FHR-BP would clarify whether it is specific to schizophrenia or to psychosis-related disorder in general.

10.1.2 EEG during an interference control task

The results revealed alterations in the electrophysiological measure reflecting attended, task-relevant stimulus processing (P3b) in children with FHR-SZ and with FHR-BP in the incongruent condition of the flanker task, while children with FHR-SZ also showed P3b alterations in the congruent condition. No electrophysiological alterations were found in responses reflecting conflict monitoring (N200) and motor-response preparation (LRP) in children with FHR-SZ or with FHR-BP.

10.1.2.1 N200

Typically, in a flanker task, an enhanced N200 amplitude is elicited in response to incongruent compared to congruent trials, indicating that N200 indexes conflict monitoring (Bartholow et al., 2005; Botvinick et al., 2001). Our results confirmed enhanced N200 amplitudes in incongruent trials compared to congruent trials, however, we found no group differences on N200 amplitude. As accuracy rates in both conditions were similar between the three groups, these results suggest that children with FHR-SZ and with FHR-BP do not have behavioral deficits in interference control and neither in proposed neural mechanisms supporting conflict control. Although children with FHR-BP and girl with FHR-SZ of our cohort showed lower accuracy rates in the incongruent condition compared to PBC children at age 7 (Burton et al., 2018), most studies studying cognitive control found deficits in processing speed or in RTs in young individuals with FHR (Bora et al., 2014; Doyle et al., 2009; Patino et al., 2013).

10.1.2.2 P3b

With respect to P3b, previous studies have proven its high heritability and stability which make, together with its amplitude reductions found in individuals with CHR, first-episode psychosis (Graber et al., 2019; Lepock et al., 2018) and chronic schizophrenia (Jeon & Polich, 2003) as well as in FDR (Bramon et al.,

2005), P3b deficits a potential endophenotype for psychosis (Turetsky et al., 2007). Our finding of P3b amplitude reductions in children with FHR-SZ and with FHR-BP supports this view. Importantly, we showed that P3b deficits are present in both FHR groups, expanding previous research that P3b deficits are not specific to schizophrenia (Sur & Sinha, 2009; Wada et al., 2019).

It has been proposed that reduced P3b amplitudes reflect impairments in attention-related stimulus processing and evaluation (Johnstone & Galletta, 2013; Polich, 2007). P3b alterations may be the result of inefficiency or dysfunction of underlying brain networks that are responsible for the generation of P3b, likely temporo-parietal brain areas (Bledowski et al., 2004; Polich, 2007). It should be noted that our children with FHR-SZ demonstrated general P3b amplitude reductions, regardless of the condition of the flanker task, while children with FHR-BP only showed P3b amplitude reductions in the incongruent condition of the task. The latter finding suggests a closer link between attention and P3b amplitude in children with FHR-BP, considering that incongruent trials require greater attentional resources. Furthermore, our post hoc analyses revealed that the amplitude of the earlier ERP P2 was also reduced in our paradigm in children with FHR-SZ, but not in those with FHR-BP. This may have implications for the origin of these underlying deficits, which is seemingly broader in children with FHR-SZ than in children with FHR-BP.

10.1.2.2.1 Link between P3b and intra-subject RT variability

Here, a short summary of our behavioral findings is presented, which will then be linked to the P3b finding. Not only were our children of both FHR groups generally slower, i.e. higher RTs in congruent and incongruent trials, they were also less consistent during incongruent trials, shown by increased intra-subject RT variability, as compared to PBC children. Although the precise physiological and psychological meaning of increased intra-subject RT variability is still under debate, it is typically interpreted as the reflection of attention lapses, i.e. a failure of sustained attention that does not result in an omission error (Tamm et al., 2012).

Interestingly, the correlation of our study showed that children with smaller P3b amplitudes were more variable, i.e. showed a higher intra-subject RT variability, suggesting a link between the two. An important note here is that this association persisted while we controlled for the severity of ADHD-symptomatology, as increased intra-subject RT variability is often reported in children and adults with ADHD (Tamm et al., 2012). Our findings corroborate previous findings on increased intra-subject RT variability in children with FHR-SZ (Burton et al., 2018) and FHR-BP (Adleman et al., 2014; Brotman et al., 2009; Pagliaccio et al., 2017) and may point to the contributing factor of P3b to intra-subject RT variability. To summarize, we found P3b alterations in children with FHR-SZ and with FHR-BP potentially reflecting impairments in attention-related stimulus processing, which is also confirmed by the increased intra-subject RT variability found in these children. Further research is warranted on mechanisms mediating increased intra-subject RT variability and the role of P3b.

10.1.2.3 LRP

Whereas the analysis on P3b allowed us to investigate mechanisms related to attention-related stimulus processing, the analysis of LRP enabled to study neural mechanisms of motor-response preparation. This disentanglement was important because of the possibility that general slowing or increased intra-subject RT variability might be caused by longer or inefficient preparation of the motor-response. Results

demonstrated that LRP amplitudes were higher in incongruent than in congruent trials, which reflects the initial activation of the incorrect motor cortex in the incongruent condition, followed by an increase of activation according to the correct response (Coles, 1989). We observed no differences in the preparation of the motor-response between the groups, reflecting no pre-movement alterations over the primary motor cortex in children with FHR-SZ and with FHR-BP.

Comparison and interpretation of our LRP findings are challenging since previous literature regarding this topic is scarce in similar populations. Previous research described motor deficits in children with FHR-SZ, in terms of delays in gross and fine motor development, coordination, involuntary movements, and walking milestones (Burton et al., 2016; Burton et al., 2017). As our finding suggested that the activity reflecting motor-response preparation was normal in children with FHR-SZ and with FHR-BP, it may be that the motor impairments present in children with FHR-SZ (Burton et al., 2017) are rather caused by impaired processes related to executing and controlling the ultimate actions.

10.1.3 Visual attention

Results on the TVA-based task in 12-year-old children did not demonstrate deficits on distinct aspects of visual attention in children with FHR-SZ or with FHR-BP at age 12, i.e. visual short-term memory (K), visual processing speed (C), or the threshold of visual perception (t_0). Furthermore, the follow-up design allowed the comparison of the TVA performance between age 7 to age 12 and our results showed that all children improved on these three parameters through development. We found that children with FHR-BP showed a greater improvement in visual short-term memory (K) than children with FHR-SZ, although not significantly different from PBC children. No developmental group differences on visual processing speed (C) and on the threshold of visual perception (t_0) were found. Hence, we could not provide any evidence of developmental deterioration (worsening), developmental deficits (stable deficits), developmental lags (slower growth), or developmental delay (delayed development) on distinct aspects of visual attention in children with FHR-SZ or with FHR-BP.

Our follow-up findings contribute to the current literature of developmental trajectories of cognition in individuals at-risk for developing psychosis. Retrospective studies observed deficits in processing speed in young individuals that would later develop schizophrenia (Reichenberg et al., 2010) or a psychotic disorder (Mollon, David, Zammit, Lewis, & Reichenberg, 2018). Further, these studies showed that in the long term, these young individuals demonstrated a lower rate of growth in processing speed. It could be suggested that the retrospective nature of these previously mentioned studies explains the discrepancy with our findings. While the majority of the children in our FHR groups will not develop schizophrenia or a psychotic disorder (Rasic et al., 2014), the abovementioned studies only included individuals that would eventually develop schizophrenia or a psychotic disorder. Our findings showed that deficits in visual attention are not present in all children with FHR, however, it may be possible that the children with the lowest scores on visual attention may be especially vulnerable. Further studies are warranted to answer this hypothesis.

Surprisingly, when visual attention was assessed in our cohort at age 7 by Hemager et al. (2019), both FHR groups showed deficits in visual processing speed compared to PBC children, whereas our current results report normal visual processing speed at age 12. One possible explanation is an attrition bias in the follow-up study (Ahern & Le Brocq, 2016). The relatively high drop-out rate (33%) might affect the

results at age 12 through the possibility that children with the lowest performance in the VIA 7 study did not participate again in the VIA 11 study. Accordingly, our post hoc analysis comparing the TVA performance at age 7 of children participating in the VIA 11 study and children that did not participate in the VIA 11 study (stay-in versus drop-out), revealed a significant difference on visual processing speed (C) in the group of children with FHR-BP. Specifically, children with FHR-BP that did not participate in the VIA 11 study had a lower visual processing speed at age 7 than those that did participate in the VIA 11 study. However, this difference was only observed in the FHR-BP group (i.e. not in the FHR-SZ group) and only on one of the aspects of visual attention. Thus, this drop-out analysis suggested that the attrition bias might have had a small effect on the analyses including the children with FHR-BP but no effect on the analyses of the children with FHR-SZ. To deal with this attrition bias, we have considered the possibility of data imputation. However, the reasons against imputation included the high rate of missing data (33%) and data was not missing at random (Jelicic, Phelps, & Lerner, 2009; Nicholson, Deboeck, & Howard, 2016). Unfortunately, at the time of the current analyses, the data of the extensive neurocognitive test battery was not available yet, thus we were unable to examine the potential effect of attrition on other cognitive measures. This is planned for the following studies in this project.

Another additional post hoc analysis proved that the children with FHR-SZ that were included in our follow-up sample showed deficits at age 7, which was not found for children with FHR-BP. This indicated that normalization of visual processing speed in children with FHR-SZ was present, however, not in children with FHR-BP. Lastly, it needs to be mentioned that the drop-out rate in the overall project was approximately 10% and not 33%. Of the 44 children (33%) that were not included in the TVA study, 47% did not participate in the project as a whole, 25% did not participate on the test day of the TVA-based task, 15% could not continue on the test day due to a lack of time or energy, and 13% participated at the other research site in Aarhus where the TVA-based task was not available. Taken together, our findings suggest that deficits in visual processing speed in 7-year-old children with FHR-SZ disappear at age 12, which would support that deficits found at a young age may reflect a marker of vulnerability. Future cognitive studies of the VIA 11 study will demonstrate whether the same is found in other cognitive functions.

10.1.4 Odor identification

Our results showed that children with FHR-SZ and with FHR-BP compared to PBC children did not differ on odor identification. When comparing the proportions of children with an abnormal and normal odor identification ability, based on gender- and age-specific normative data (Doty, 2001), we initially found that more boys with FHR-SZ (28%) had abnormal odor identification abilities compared to boys in the PBC group (13%). This was not observed in the FHR-BP group and neither for girls. However, boys of the PBC group performed worse compared to what was expected from normative data (based on American data), which made the threshold for abnormal or normal odor identification questionable to utilize for Danish children. By using a threshold of 1.5 SD below the mean of the boys of the PBC group, we found no such difference in the proportion of abnormal and normal odor identification between the groups of boys. To summarize, both the dimensional and categorical analyses showed that the FHR status is independent of the ability of odor identification at the age of 12.

These findings extend the literature on odor identification in schizophrenia and bipolar disorder as well as its potential of being an endophenotype. Deficits in odor identification were reported in adult

unaffected FDR of patients with schizophrenia (Kamath et al., 2014; Kopala et al., 2001; Moberg et al., 2014). One reason that the young FDR in our cohort did not show deficits in odor identification may be their age. The majority of previous studies included adult FDR, with a mean age varying from 35 to 43 years (Kamath et al., 2014; Kopala et al., 2001; Turetsky et al., 2008). Normal maturation of olfaction is slow during childhood years and rapid during adolescence (Doty et al., 1984). Therefore, it may be that olfactory maturation will evolve in the following years, as well as its eventual deficits. Hence, olfactory maturational impairments may develop in a later developmental phase.

Another important finding is that deficits in odor identification have been found in youth with CHR for psychosis (Brewer et al., 2003; Kamath et al., 2014; Keshavan et al., 2009; Woodberry et al., 2010), but not, as shown by our results, in children with FHR-SZ or with FHR-BP. This suggests that deficits in odor identification may arise in the prodromal phase which may contribute to understanding the underlying origin of these deficits.

Our study also indicated that a better odor identification was associated with being female, better social reciprocity (fewer traits of autism), and better verbal working memory skills in all 7-year-old children. This model explained 17% of the variance of odor identification. Considering the association that was found in all 7-year-old children, it is interesting to note that common brain structures (such as the OFC and amygdala) are (partially) responsible for social cognition and olfaction (Malaspina and Coleman, 2003) and that impaired olfactory and social functioning may glean from deficits in these brain areas (Brewer et al., 1996; Goudsmit et al., 2003). Furthermore, other cognitive, psychopathological, and home environmental factors did not associate with odor identification. The finding of the current study that odor identification is independent of intelligence, verbal memory, processing speed, sustained attention, and the severity of ADHD-symptomatology is in line with other studies including children and adults with autism or Tourette's (Kronenbuerger et al., 2018; Muratori et al., 2017).

10.2 From early information processing to higher-order cognitive functioning

To address the aim of this dissertation, our findings suggested that children with FHR-SZ and with FHR-BP do not show abnormalities in pre-attentive auditory processing (MMN) and neither in brain responses reflecting conflict monitoring during an attended visual task (N200). The preattentive measure MMN is free of attentional or motivational artifacts (Braff & Light, 2004; Näätänen, 2003) and the enhanced brain response N200, which reflects conflict monitoring, is independent of motor components (Kopp et al., 1996). Furthermore, both FHR groups did not show abnormalities on an unspeeded, accuracy-based visual attention task that was unconfounded by motor responses; therefore controlling for motivational factors (Vangkilde, Bundesen, & Coull, 2011). Also, despite that a motor response was required in the flanker task, the distributional analyses of the RT showed comparable accuracy rates and mean RT between the three groups in the fastest trials, i.e. trials that depend mostly on automatic and reflexive motor responses. Taken together, a commonality of these unaffected processes is that they do not or minimally depend on attentional or motivational factors, and that these processes are rather pre-attentive or automatic responses to perceptual input.

On the other hand, attention-dependent cognitive functions reflected by P3b can be influenced by the level of task engagement, motivational factors, emotional factors, and performance incentives (Binder, Kelly, Villanueva, & Winslow, 2003; Carrillo-de-la-Peña & Cadaveira, 2000; Pailing & Segalowitz, 2004).

Similarly, increased intra-subject RT variability relates to a deficit in the control of attention, subsequently leading to attentional lapses (Tamm et al., 2012). Thus, the alterations in P3b amplitude and the increased intra-subject RT variability found in children with FHR-SZ and with FHR-BP may propose that the rather attentional-dependent processes are part of the vulnerability for schizophrenia and bipolar disorder, whereas the pre-attentive and more automatic processes appear unaffected and are therefore not part of the vulnerability. Alternatively, as deficits in pre-attentive processes are often suggested as biomarker for schizophrenia, it is possible that some of the children with FHR in our cohort currently show deficits in pre-attentive processes, but that these are not visible on the group level.

10.3 Endophenotype or biomarker?

To gain further insight into the significance of the findings of this dissertation, it is important to clarify the definitions of an endophenotype and a biomarker. The endophenotype must be related to the illness in the population; heritable; present in active illness-states as well as in remission states (i.e. state-independent); present at a higher rate in family members of affected individuals relative to the general population; and reliably measurable (Gottesman & Gould, 2003). Biomarkers are defined as biological markers that can objectively measure, index or evaluate pathological processes or treatment responses (Biomarkers Definitions Working, 2001). Thus, in relation to our findings, the most important difference between an endophenotype and a biomarker is that all children with FHR would be observed with the endophenotype, representing the vulnerability for the disorder, but not all children with FHR would be observed with the biomarker; only in children that will eventually develop the disorder. The latter can cause a problem that the effect is not visible at group level. Longitudinal studies will allow drawing conclusions on potential biomarkers. With these definitions in mind, some theoretically possible scenarios can be outlined considering the results of this dissertation.

Previous studies have suggested deficits in MMN (Michie et al., 2002; Price et al., 2006) and in odor identification (Kamath et al., 2014; Kopala et al., 2001) as potential endophenotypes for schizophrenia. As one of the criteria of an endophenotype is that deficits must be present in FDR, the absence of deficits in MMN and in odor identification in children with FHR-SZ or with FHR-BP does not support the notion of an endophenotype. It could be argued that deficits in MMN and in odor identification may be part of the pathological process that are affected by the neurobiological start of the illness, which is supported by studies including individuals with CHR for psychosis with deficits in MMN (Lepock et al., 2018; Näätänen, Shiga, Asano, & Yabe, 2015) as well as in odor identification (Brewer et al., 2003; Lin et al., 2015). That would mean such deficits arise as part of the illness, but rather early in the course. Further neuroimaging studies may elaborate on the potential early abnormal brain development.

As suggested by previous research, P3b amplitude reductions (Bramon et al., 2005; Hall et al., 2009; Thaker, 2008) and increased intra-subject RT variability (Adleman et al., 2014; Brotman et al., 2009; Burton et al., 2018; Pagliaccio et al., 2017) meet several of the criteria of an endophenotype for schizophrenia and bipolar disorder. It may also show that neurodevelopmental abnormalities play a role in cognitive dysfunction in bipolar disorder, and not only in schizophrenia. That being said, it does not meet the criterium of being specific to an illness. Nevertheless, both measures may represent an endophenotype for developing psychosis-related disorders, which is relevant for future clinical, genetic, and brain imaging studies and for understanding vulnerability.

10.4 Strengths

The strengths of the studies in this project include the recruitment strategy of the Danish High Risk and Resilience Study, by means of using the Danish nationwide registers to recruit a relatively large cohort. Moreover, no study to date has investigated electrophysiological measures in such a cohort, including both children with FHR-SZ and with FHR-BP. Also, the narrow age range of the children in the VIA 7 and VIA 11 study is a strength, especially in this critical period concerning brain development. In addition, including both children with FHR-SZ and with FHR-BP allows comparing the variables between these two groups, which is important regarding the shared or distinct nature of the deficits in the groups. The inclusion of both groups may help to clarify the etiological and pathological processes of the disorders. Further, research assessors were blinded to the child's risk status. The blind status ensured equal investigation of the children in each group and thus minimized confirmation bias. Lastly, the longitudinal perspective of the project allows us to, in the future, study the development of electrophysiological measures in a cohort like this, which would be the first in the field. Such follow-up studies of this project can potentially unravel whether the electrophysiological measures are predictive for the clinical status of the child and whether cognitive measures remain stable, worsen, or improve over time.

10.5 Limitations

The studies include several limitations. First, some families declined participation in the VIA 11 study which might have created a selection bias. Children and families that participated in the VIA 7 study knew that participation was time-consuming and demanding. Families were allowed to withdraw at any stage during the project which has led to some families not finishing all test days. It could be hypothesized that dropouts are higher in lower-functioning families, although it may also happen in the well-functioning and busy families. Study 3, the TVA study, suffered from a high proportion of missing data as the study included follow-up data, and potentially study 1 and 2 did as well. To understand the effect of this potential problem in study 3, we performed analyses on the baseline data of the children to compare the performance of those that remained in the study and those that dropped out, as well as we compared the performance on the TVA-based task on the smaller group at age 7. Results showed that one aspect (out of three) of visual attention was worse in children with FHR-BP at age 7 that did not participate in the VIA 11 study than in children with FHR-BP that did participate again. In addition, the deficit found in visual processing speed was absent in the restricted sample of children with FHR-BP at baseline, however, the deficit was still present in children with FHR-SZ. Potentially this attrition bias also affected the results of the other studies including the 12-year-old children, however, the prevalence of psychiatric disorders (at age 7) in children with FHR-BP that did not participate again was not significantly different from those that did participate again. This may indicate that the missing data were not from lowest-functioning children, i.e. that were at the highest risk. The necessary data to perform the attrition bias extensively was not available at the time of these analyses but are planned at later stages for the entire project.

Second, the cross-sectional electrophysiological data limited studying the maturation or development of electrophysiological measures. EEG was not recorded in the VIA 7 study as it was of great importance to providing a comfortable, first experience for the families without challenging examinations, such as MRI and EEG. This limitation also applies to the odor identification task, which was only performed in the VIA 7 study. Unfortunately, the BSIT had not survived the strict selection of included tasks in the VIA 11 study.

It is, however, important to do follow-up studies because the absence of deficits at age 7 does not mean its absence on the longer run. It is possible that deficits appear later, or that current deficits that may be present in some of the children normalize later throughout development (Gogtay et al., 2007).

Third, the studies of this dissertation could not include a measure to assess psychotic-like experiences. Although an interview about psychotic-like experiences is part of the entire project, due to time limitations, it was not ready to be included in this dissertation. Further parts of the study will investigate correlations between psychotic-like experiences and the electrophysiological measures as well as odor identification. This might have explained some of the variances.

Fourth, even though traditional diagnostic categories are currently the gold standard in psychiatry, it may have obscured potential findings. Instead of using these categorical entities, using levels of symptoms (e.g. high negative/positive symptoms), specific subgroups (e.g. delusional subgroup), or more comprehensive information about the disorder (e.g. age of onset of the disorder, number of psychoses, and history of psychotic symptoms) enables investigating more specific aspects. From the genetic perspective, different subtypes may have a different genetic load to the children. From the environmental perspective, it might be that parents experienced their psychotic episode(s) before the child's birth, i.e. the child was never exposed to the psychotic state (Gandal et al., 2018). One solution to handle this limitation would be to use clinical classifications that cut across the current diagnostic groups. In practice, that would mean that patients would be grouped based on particular symptoms or other features (e.g. outcome, course). Such classifications would more closely map onto risk factors than do the current diagnostic entities (O'Donovan & Owen, 2016).

11. Conclusion

The studies included in this dissertation provided novel perspectives on electrophysiological characteristics and higher-order cognitive functions in children with FHR-SZ and with FHR-BP. We provide evidence that children with FHR-SZ and with FHR-BP have intact automatic sensory processing as a group (auditory MMN) but show deficits in the electrophysiological measure reflecting attention-related and cognitive processes (visual P3b). The absence of deficits in N200 and LRP indicates that processes underlying visual conflict monitoring (N200) and motor-response preparation (LRP) are intact in children with FHR-SZ and with FHR-BP at the age of 12, at least at the group level. These outcomes showed shared electrophysiological characteristics between children FHR-SZ and with FHR-BP at age 12. Further, visual attention improved over time in children with FHR-SZ, FHR-BP and PBC children. Moreover, deficits in visual processing speed in children with FHR-SZ improved to a level that they were not significantly different anymore compared to the PCB children at age 12. Lastly, odor identification and the FHR status seem independent at age 7 (at group level). The following sections will explain the clinical implications of these findings as well as recommendations for future research.

11.1 Clinical implications

Although we found no significant differences at group level in most of the studies of this dissertation, it still might mean that those individuals with the highest deficits might be the ones most at risk for developing schizophrenia, bipolar disorder or psychosis in general. Therefore (some of) these measures may still serve as biomarker. Such biomarkers can be used as quantifying parameters, but normal and pathological ranges need to be identified to be clinically useful. Electrophysiological abnormalities have the potential to predict psychosis and therefore may assist as an early diagnostic tool. One study provided a prediction model to forecast a first episode of psychosis among individuals with CHR, which included P300 amplitude and social-personal adjustment. Reduced P300 amplitude and poor social-personal adjustment predicted the first psychotic episode among individuals with CHR (Nieman et al., 2014). Combining neurophysiological measures with social functioning and neurocognitive abilities may help the clinician to make a rather individualized risk estimation of transition to psychosis. This may not only be applicable in individuals with CHR for psychosis but perhaps also for young individuals with FHR (Mesman & Hillegers, 2017).

Furthermore, understanding the etiology of neurobiological abnormalities that are related to the onset of psychosis may be useful in designing new interventions. Current interventions include improving stress resilience and social skills and minimizing adverse environmental circumstances. With regard to brain development, the idea of optimizing brain maturation has been proposed as a potential intervention (Sommer et al., 2016). A potentially useful technique is neurofeedback training, which is a technique that learns an individual to produce specific patterns of brain wave activity by giving sensory rewarding feedback (Surmeli, Ertem, Eralp, & Kos, 2012). The premise of neurofeedback training is to help the individual in the self-regulation of their own brain responses. Until further supporting research, the use of neurofeedback training as optimization of brain maturation will remain controversial.

Lastly, the developmental trajectories of cognitive functions (such as visual attention, interference control, and odor identification) in children with FHR-SZ and with FHR-BP may be meaningful to clinical staging.

If deficits appear at a later developmental stage, this may help the clinician to provide appropriate interventions, such as cognitive remediation.

11.2 Perspectives for future research

Future follow-up studies and other longitudinal FHR-studies are important to investigate the developmental maturation and trajectories of electrophysiological measures and cognitive functions in children with FHR-SZ and with FHR-BP. Longitudinal studies can inform us about the timing and origin of certain electrophysiological or cognitive deficits, which would gain insight into the premorbid stage as well as of factors of resilience in those children that do not develop psychosis. Also, replication of our findings in other samples of children with FHR is warranted. Together, those findings would be useful in predictive models including neurophysiological, neurocognitive, and clinical measures which could contribute to creating an individual risk calculator for children with FHR-SZ and with FHR-BP (Mesman & Hillegers, 2017). Such risk calculators would enable better recognition of children at-risk which, in turn, emphasizes the urge to improve the current preventative interventions. Therefore, future studies should be focusing on early preventative interventions for children with FHR-SZ and with FHR-BP.

From a broader perspective, and already introduced by some research groups (e.g. (Bodatsch et al., 2015; Clementz et al., 2016)), future studies should focus on neurobiological heterogeneity among individuals with psychosis, rather than relying on the current clinical diagnosis. Given the substantial overlap in vulnerability genes, etiological theories, clinical symptoms, and phenotypes across schizophrenia and bipolar disorder, a similarity in underlying neurobiological mechanisms could also be expected. By not focusing on one characteristic in future studies, e.g. one electrophysiological measure or one neurocognitive measure, but rather on large panels of different characteristics (e.g. neurocognitive, electrophysiological, and brain activity), it may be possible to create distinct biotypes (biologically distinctive phenotypes) of psychosis (Clementz et al., 2016). Although the phenotypical manifestation may be the same, patients of different psychosis-biotypes would benefit from different treatment strategies, which highlights the need to understand the neurobiology of these disorders or symptoms.

Future studies including EEG should consider investigating combinations of electrophysiological measures instead of only focusing on one ERP. Given the complex nature of psychiatric disorders, the substantial overlap in clinical symptoms and in prodromal or early stages of disorders as well as etiological theories, it may be more likely that combinations of electrophysiological markers can be used to identify clinical stages or even vulnerability stages (Lavoie et al., 2019; Lepock et al., 2018).

Lastly, another aspect of the research on the etiology of mental illnesses is the focus on resilience. The aim of resilience research is to comprehend the great variation in individuals' responses to the same experiences which, in turn, can influence the outcome. This variation can be utilized in novel interventions to encourage positive development. Children with FHR who mature without the development of a mental illness possess protective skills that have evolved over time, and that are likely the combination of neurobiological systems of stress-regulation, families, health care systems, socio-cultural and ecological systems (Masten, 2019). More future studies should also focus on resilient young individuals which would gain knowledge on a healthy development even though the genetic and environmental predisposition for an SMI.

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13. Appendices

Appendix 1: Normal mismatch negativity in children with familial high risk of schizophrenia or bipolar disorder

Normal Mismatch Negativity in 12-year-old Children with Familial High Risk of Schizophrenia or Bipolar Disorder

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Conflict of interest statement

HRS has received honoraria as speaker from Sanofi Genzyme, Denmark and Novartis, Denmark, as consultant from Sanofi Genzyme, Denmark and as senior editor (NeuroImage) and editor-in-chief

(Neuroimage Clinical) from Elsevier Publishers, Amsterdam, The Netherlands. HRS has also received royalties as book editor from Springer Publishers, Stuttgart, Germany and Gyldendahl Publishers, Copenhagen, Denmark.

Number of total words: 3483 words

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1 **Abstract**

2 Background. Amplitude reductions in mismatch negativity (MMN) have been consistently observed in
3 patients with schizophrenia (SZ), and, to a lesser degree, with bipolar disorder (BP), as well as in individuals
4 with a clinical high-risk for psychosis. Yet, it is unclear when MMN deficits emerge and whether it is related
5 to the (first) clinical symptoms of SZ or BP. Studying MMN in children with familial high-risk for SZ (FHR-
6 SZ) or BP (FHR-BP) allow elucidating whether MMN alterations arise in this early developmental phase.

7 Methods. Using electroencephalography, we recorded MMN in 54 children with FHR-SZ, 41 children with
8 FHR-BP and 41 population-based children (PBC), all of age 12. The MMN paradigm consisted of a
9 frequency, a duration, and a combined frequency and duration deviant. We further investigated potential
10 associations between MMN and ratings of emotional/behavioral problems, severity of autistic traits, and
11 global functioning.

12 Results. We found no significant group differences in MMN amplitude or latency on three different MMN
13 deviants. Children with worse levels of global functioning showed prolonged MMN latency (frequency
14 deviant only). Emotional/behavioral problems and the severity of autistic traits did not correlate with MMN.

15 Conclusion. Twelve-year old children with FHR-SZ or FHR-BP show normal MMN as compared to control
16 children. Follow-up studies are required to investigate the development of MMN in the following, crucial,
17 years of these children, which may enable specifying the time point that MMN alterations occur. This may
18 clarify whether MMN alterations can contribute to predict the illness onset.

19

20 Keywords: Neurodevelopment, mismatch negativity, electroencephalography, offspring

1 Introduction

Schizophrenia (SZ) and bipolar disorder (BP) are major mental disorders with a high impact on the life of patients and their relatives (Millier et al., 2014). SZ is predominantly characterized by psychotic experiences and delusional thoughts (Freedman, 2003), while BP is characterized by recurrent cycling mood fluctuations (Duffy et al., 2017). However, these typical symptoms do often not emerge before late adolescence or young adulthood, which makes identification of these disorders at an early stage difficult. Nevertheless, significant cognitive, social, and emotional dysfunctions are already present in children who will develop SZ or BP later in life (de la Serna et al., 2017; Duffy et al., 2017; Rasic et al., 2014). These early signs are rather non-specific which makes it a major challenge to accurately and reliably identify individuals at-risk for these disorders. Early detection is important because treatment at an early stage has proven to result in better long-term outcomes (Lieberman et al., 2001). Taken together, there is a great need for early and precise vulnerability markers for SZ and BP to improve diagnostic accuracy and to develop preventive interventions.

Underlying neural mechanisms of clinical, behavioral, and cognitive impairments in SZ and BP remain poorly understood. Electroencephalography (EEG) provides the tools to investigate neuronal responses to e.g. auditory or visual stimuli which can uncover underlying processes related to auditory or visual information processing (Näätänen, 1990). Mismatch negativity (MMN) is elicited in a so-called oddball paradigm, in which a discriminable and relatively infrequent auditory “deviant” tone is interspersed within a stream of similar repetitive auditory “standard” tones. By subtracting the neural response to the standard tone from that to the deviant tone, one gets the difference wave MMN. MMN is reflected as negative peak at around 100-250 ms after the deviant stimulus onset (Garrido et al., 2009). MMN represents an automatic, memory-based comparison mechanism aimed to detect any discrepancy between regular stimuli and suddenly appearing (deviant) stimuli; it is elicited regardless of an individual paying attention to the stimuli (Näätänen et al., 2014).

Reductions in MMN amplitude have been consistently found in patients with chronic SZ, with an effect size of 0.99 (Umbricht and Krljes, 2005), as well as in individuals with their first psychotic episode (Oranje et al., 2017; Rydkjaer et al., 2017) and in those with clinical high-risk for psychosis (CHR) (Atkinson et al., 2012). Moreover, MMN amplitude reductions have been proven useful to predict the transition from an at-risk state to psychosis (Bodatsch et al., 2015; Perez et al., 2014). Also, MMN amplitude is positively associated to levels of global functioning in patients with SZ (Light and Braff, 2005) and in the earlier clinical stages (Koshiyama et al., 2018). Some studies showed MMN reductions in adult unaffected first-degree relatives of patients with SZ (Jessen et al., 2001; Michie et al., 2002; Sevik et al., 2011), although negative findings are reported too (Bramon, 2004; Magno et al., 2008). Importantly, these unaffected first-degree relatives had a mean age of 43 years and were thus beyond the most vulnerable period for developing psychosis. One study to date included young offspring of parents with SZ and found that MMN amplitude did not significantly

differ from control children (Schreiber et al., 1992). Taken together, MMN alterations are found along the clinical continuum of psychosis but the presence in young first-degree relatives remains unclear.

Specifically, deficits in duration-based MMN, in which duration is the deviating feature, have been found along all clinical stages of psychosis, indicative of a trait-marker of psychosis (Hirt et al., 2019; Näätänen et al., 2016). In contrast, MMN amplitude reductions resulting from frequency deviants are suggested as state-marker of the pathological process of the disorder as these deficits gradually develop according to illness progression (Lavoie et al., 2019; Todd et al., 2008).

In contrast to the robust evidence of MMN deficits in SZ, less is known about MMN in patients with BP. Whereas earlier studies of MMN claimed its specificity to patients with SZ (Hall et al., 2009; Salisbury et al., 2007; Umbricht et al., 2003), recent research have found MMN amplitudes reductions and/or increased latencies in patients with BP (Jahshan et al., 2012; Kaur et al., 2011). Explanations for the absence of group differences may be methodological matters, such as small sample sizes and lower symptom severities (Hermens et al., 2018). One study comparing patients with early schizophrenia-spectrum or early bipolar-spectrum disorders observed MMN deficits in all patient groups. Also, they found associations between reduced MMN peak amplitudes and higher levels of psychiatric symptoms, as well as with lower levels of quality of life (Kaur et al., 2012). MMN alterations are also documented in children with autism spectrum disorders (Kujala et al., 2013). Therefore, MMN may not be specific to SZ and potentially reflect broader transdiagnostic psychopathology rather than traditional diagnostic clusters.

Owing to its consistent finding in patients with chronic SZ, its stability across time despite of fluctuations in clinical symptoms, its heritability and the presence in clinical high-risk and first-degree relatives of patients with SZ (Jessen et al., 2001; Michie et al., 2002; Näätänen et al., 2016; Owens et al., 2016; Sevik et al., 2011), deficits in MMN may serve as vulnerability marker for psychosis. Yet, the few studies make it difficult to conclude on the time point that MMN deficits emerge in individuals that later develop SZ and, if at all, emerge in patients with BP. Therefore, this study investigated MMN in a large group of children with familial high-risk for SZ (FHR-SZ) and children with familial high-risk for BP (FHR-BP) who have an increased risk for developing psychiatric disorders. We hypothesized a reduced MMN amplitude in children with FHR-SZ relative to population-based controls (PBC) children. Due to the finding that relatives of BP show normal MMN (Hall et al., 2009) we hypothesized that children with FHR-BP would show comparable MMN as PBC. Additionally, we aimed to investigate whether MMN correlates to ratings of emotional/behavioral problem, severity of autistic traits, and global functioning. Given that the evidence that MMN deficits, based on duration deviants, are related to the trait of the disorder while frequency-based deficits are more indicative for illness progression, we expect greatest differences on duration-based deviants.

2 Methods

2.1 Participants

54 children of parents with a diagnosis of schizophrenia spectrum disorder (FHR-SZ), 41 children of parents with a diagnosis of bipolar disorder (FHR-BP), and 41 children of parents with none of these disorders (PBC) were included in this study. These children were recruited through the Danish registers at age 7 as being part of the Danish High Risk and Resilience Study – VIA 7, which is a longitudinal prospective cohort study with planned follow-ups every four years (Thorup et al., 2015). The current study is part of the first follow-up, the Danish High Risk and Resilience Study – VIA 11, in which the children have the age of 11-12 (Thorup et al., 2018). Electrophysiological recordings were not conducted at baseline (VIA 7) but were introduced at the first follow-up (VIA 11). Children participating in the VIA 11 study were assigned to one of the two research sites, in Aarhus or Copenhagen (Denmark), and EEG was only recorded at the research site in Copenhagen, at the Danish Research Centre for Magnetic Resonance (DRCMR) at the Copenhagen University Hospital Hvidovre. This Danish High Risk and Resilience Study – VIA 11 was approved by the Ethical Committee of the Capital Region of Denmark. Informed consent was obtained from legal holders.

2.2 Experimental design

Children went through an electrophysiological assessment battery (Ver Loren Van Themaat et al., 2019). This paper will only present MMN data; data of the other paradigms will be described elsewhere. Children were seated in a comfortable adjustable chair in a quiet room. Standard procedure was to let parents wait in a room close by, however, in a few occasions the parent stayed in the EEG laboratory to make the child feel more comfortable. Children were instructed to relax and to sit as still as possible and to ignore the auditory stimuli they were presented with. During MMN assessment, children watched a (muted) video to withdraw attention from the task because MMN is best elicited during non-attending task demands. Testers were blinded to the FHR status of the children.

2.3 MMN paradigm

This paradigm has been described before (Düring et al., 2016), in short: The MMN paradigm contained 1800 stimuli that were binaurally presented through tubal insert ear phones (EARtone, Etymotic Research) using PsychToolbox running Matlab. Four stimuli were presented, one standard tone and three types of deviant tones. The standard tone (76%) had a frequency of 1000 Hz, intensity of 75 dB, and a duration of 50 ms (see Figure 1). All three deviant tones (each 8%) had an intensity of 75 dB, while the frequency deviant differed from the standard by having a frequency of 1200 Hz; the duration deviant differed by having a duration of 100 ms; and the frequency-duration deviant differed by having a frequency of 1200 Hz and a duration of 100 ms. The deviant tones were randomly presented between the standard tones with a randomized interstimulus interval between 400 and 600 ms. The MMN paradigm had a duration of approximately 16 min.

2.4 Signal recording and processing

The BioSemi system (Amsterdam, Netherlands) recorded the EEG signal using 128 active electrodes at a sampling frequency of 4096 Hz. In addition to these 128 electrodes, we placed two electrodes on the mastoids, two on the earlobes, two above and under the right eye, one on the nose, and one on the pulse. We used BESA version 5.2.4 (MEGIS Software GmbH, Grafelfing, Germany) to analyze and process the EEG signal. We checked the electrodes that were expected to reach maximum amplitudes, which are the frontal/midline electrodes Fz, FCz, and Cz (Wienberg et al., 2010), and only analyzed data on the electrode with maximum amplitude (Fz). First the data was resampled from 4096 Hz to 250 Hz. Second, an adaptive method of BESA removed eye-artifacts from the data. Third, we defined our epochs from 100 ms pre-stimulus to 900 ms post-stimulus and removed movement artifacts i.e. epochs containing amplitude differences of 60 microvolt between 0 and 400 ms post-stimulus (the time window where MMN was expected). Fourth, the data were filtered between 1 – 40 Hz. Subsequently, we constructed the three MMN per subject by subtracting the average ERP to the standard stimulus from the average ERP to each of the deviant stimuli. Grand mean averages for each group and deviant type (frequency deviant: FreqMMN, duration deviant: DurMMN, frequency*duration deviant: FDMMN) were obtained for purposes of visual display and MMN topographic distribution. The grand mean averages were also used to determine the latency windows for MMN scoring. Peak amplitude and peak latency were extracted from the EEG data. The scoring window for the frequency deviant was 130 – 250 ms, for the duration deviant 150 – 265 ms, and for the frequency*duration deviant 140 – 230 ms.

2.5 Functional and behavioral variables

To estimate the children's IQ, we used the Reynold's Intellectual Screening Test (RIST) (Reynolds et al., 2003) and the Child Behavior Checklist (CBCL) (Bilenberg, 1999) to assess problem behavior. Severity of traits of autism were assessed with the Social Responsiveness Scale (SRS) (Constantino and Gruber, 2005). The Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983) scales the child's global functioning.

2.6 Statistical analyses

Statistical analyses were performed using SPSS version 25.0 (Corp, 2013). We used the Kolmogorov-Smirnov to check for normal distribution of the data. When assumptions for an analysis of variance (ANOVA) were met, we carried out a repeated-measures with the three sorts of deviants of MMN as within-subject (3 levels; FreqMMN, DurMMN, FDMMN) and group as between-subject factor (3 levels; FHR-SZ, FHR-BP, PBC), for peak amplitude and peak latency separate. In case of non-distributed data, we used the non-parametric Kruskal-Wallis test with three groups. We used age and sex as covariate yet only when they reached significance. We used JASP (JASP Team 2018) to compute the Bayes factor (BF) to capture the likelihood of the alternative hypothesis H_1 (i.e. the MMN amplitude/latency in the three groups is not the same) over the null hypothesis H_0 (i.e. the MMN amplitude/latency in the three groups is the same) (Dienes,

2016). For correlations with functional and behavioral variables, we either used Pearson's correlation and Spearman's correlation depending on the distribution of the data.

158

159 **3 Results**

160 *3.1 Participants*

161 Groups did not differ on age, gender, or handedness (see Table 1 for demographic and clinical characteristics
162 of the children). Children with FHR-SZ and FHR-BP had higher ratings on the CBCL total score and the
163 SRS, indicating more emotional and behavioral problems and higher levels of autistic traits compared to
164 control children. The lifetime prevalence of ADHD or ASD diagnoses was not significantly different
165 between the groups. Furthermore, children with FHR-SZ and FHR-BP had lower ratings on the CGAS,
166 meaning lower levels of global functioning than control children. The FHR groups did not differ from each
167 other.

168 Three MMN datasets (one FHR-SZ and two PBC) were not analyzed due to bad EEG data quality. Thus,
169 data of 133 children were included in the statistical analyses.

170 *3.2 MMN peak amplitude*

171 We did not find different MMN peak amplitudes between the three groups for the three deviants (see Figure
172 2). Kruskal-Wallis tests revealed no significant group differences for FreqMMN ($p = 0.510$), DurMMN ($p =$
173 0.938), and FdMMN ($p = 0.472$). Removing three outliers (identified as more than 3 standard deviants from
174 the mean) in FreqMMN resulted in a normal distribution, however, this did not change the significance level
175 of the results (see Figure 3). Subsequently, the BF was calculated to determine the strength of evidence for
176 the hypothesis that the MMN peak amplitude was similar between the groups (H_0). In a Bayesian repeated-
177 measure ANOVA design, we found $BF_{10} = 0.231$, indicating strong evidence for H_0 .

178 *3.3 MMN peak latency*

179 MMN peak latency was not different between the three groups for the three deviants. The ANOVA with
180 DurMMN as dependent variable showed a non-significant difference between groups ($F(2,130) = 2.528$, $p =$
181 0.084). The Kruskal-Wallis test on latency of FreqMMN revealed a trend towards significance ($p = 0.053$).
182 Subsequent Mann-Whitney U tests showed a prolonged latency for FHR-SZ compared to PBC ($p = 0.012$);
183 this was not found comparing FHR-BP either with PBC ($p = 0.435$) or FHR-SZ ($p = 0.197$). The Kruskal-
184 Wallis test on latency of FdMMN was non-significant ($p = 0.704$). The BF was calculated to determine the
185 strength of evidence for the hypothesis that the MMN peak latency was similar between the groups (H_0). In a
186 Bayesian repeated-measure ANOVA design, we found $BF_{10} = 0.083$, indicating decisive evidence for H_0 .

187

188 *3.4 Correlations with clinical variables*

189 Children with worse levels of global functioning, indicated by lower scores on the CGAS, showed prolonged
190 latencies of FreqMMN ($r_s = -0.177$, $p = 0.046$) (see Figure 4). We found no significant correlations within
191 the separate groups. No other significant correlations were found between MMN and global level of
192 functioning, nor with scales of emotional and/or behavioral problems or severity of autistic traits.

194 **4 Discussion**

195 This study investigated MMN in 12-year-old children born to parents diagnosed with either SZ or BP or
196 none of these disorders. The results showed strong evidence for the absence of differences in MMN
197 amplitude or latency between the three groups, indicating normal MMN in 12-year-old children with FHR-
198 SZ and FHR-BP. Children with lower levels of global functioning showed a prolonged MMN latency (in one
199 of the deviant types), but other variables were unrelated to MMN.

200 This study expands on the literature of MMN in samples including at-risk individuals. Previous studies
201 observed MMN amplitude reductions in adults with CHR for psychosis (Erickson et al., 2016; Näätänen et
202 al., 2007) suggesting that MMN alterations predate the onset of psychosis (Shaikh et al., 2012). The latter
203 was also supported by one study including 9 to 12-year-old children with antecedents of SZ who showed
204 MMN alterations, although in the opposite direction as older individuals with CHR for psychosis
205 (Bruggemann et al., 2013). Interestingly, our results show normal MMN in young children with FHR-SZ and
206 FHR-BP, replicating earlier findings on children with FHR-SZ (Schreiber et al., 1992), indicating that MMN
207 alterations may only arise in the prodromal phase of psychosis-related disorders. This would have important
208 implications for the underlying origin of MMN alterations and would support the notion of MMN as a
209 biomarker for psychosis. Second, studies including unaffected first-degree relatives of patients with SZ or
210 BP reported MMN alterations in some cases (Jessen et al., 2001; Michie et al., 2002; Sevik et al., 2011) but
211 not all (Bramon, 2004; Hall et al., 2009; Magno et al., 2008). Our study is not in line with those studies that
212 found MMN reductions in unaffected first-degree relatives (Jessen et al., 2001; Michie et al., 2002; Sevik et
213 al., 2011). This discrepancy may be attributed to the older mean age (43 years) of included individuals in
214 those studies, since important developmental maturational processes will take place during adolescence
215 (Handy, 2005). Specifically, the cortical network responsible for generating MMN undergoes substantial
216 changes in the period pre- to post-puberty (Gomes et al., 2000; Mahajan and McArthur, 2015). Additionally,
217 the adult brain shows more stable brain responses than the young brain (Cheour et al., 2000). Taken together,
218 if maturational processes are influenced, i.e. by the effects of being on FHR for SZ or BP (Bois et al., 2015;
219 de Zwarte et al., 2019), MMN alterations may not be visible in the earlier stages of adolescence but may
220 arise in the later stages of adolescence when the brain underwent these maturational processes. Importantly,

221 longitudinal research of children with FHR would enable to examine whether and when MMN alterations
222 may arise.

223 Our finding that levels of global functioning relates to MMN latency is to some extent in line with previous
224 research including patients with SZ (Light and Braff, 2005), which found that MMN deficits were associated
225 with worse levels of global functioning. Similar associations have been found in individuals with recent-
226 onset SZ and with ultra-high risk for psychosis (Koshiyama et al., 2018) and first-episode psychosis
227 (Hermens et al., 2010). The relationship between MMN and psychosocial and high-order cognitive measures
228 follow the logic that efficiency at basic levels of information processing are required to successfully function
229 on a social and cognitive level (Light et al., 2007). Although other studies found the association between
230 global functioning and MMN amplitude, and not latency, our result may also indicate the relationship
231 between global functioning and MMN.

232 Although prospective FHR-studies include several major advantages, the conversion rate to SZ or BP in this
233 type of cohort is still quite low, estimated roughly on 10% (Seidman and Nordentoft, 2015), meaning that the
234 majority of these children will go on to typical development. Therefore, the robustness of the altered effect of
235 interest must be relatively large to show statistical significance for the overall group. In line with this, it may
236 be that children with FHR-SZ, and perhaps children with FHR-BP, with the lowest MMN amplitude, will,
237 eventually, develop SZ or psychosis. However, on a group level, this phenomenon may be obscured by
238 children with FHR who will not eventually develop these disorders.

239 This study has several strengths, including the well-sized sample groups; the narrow age range of the
240 children which is especially important in this developmental period; the use of an MMN paradigm with three
241 kinds of deviant tones that has been used in other studies before (Düring et al., 2016); and the blinded status
242 of the research assessors. Several limitations of this study also need to be addressed. First, the cross-sectional
243 nature of the current study limits the possibility to investigate maturational processes of MMN and to
244 whether reduced MMN in some of the children of our cohort predicts later illness onset. Another limitation is
245 the lack of a puberty measure since important developmental changes occur during puberty and the age of 12
246 is variable regarding the status of puberty. Third, the current study lacked a measure of psychotic-like
247 experiences that could be used to distinguish children with a higher risk from those with a lower risk.
248 Follow-up research is essential to establish developmental trajectories of MMN in children with FHR-SZ and
249 FHR-BP as well as it would provide evidence of the eventual development of psychosis.

250

251 **5 Conclusion**

252 In conclusion, our results provide evidence for normal MMN in 12-year-old children with FHR-SZ and
253 FHR-BP, highlighting the need to follow-up on these children in order to understand the potential differential

254 developmental trajectories of MMN in the following critical neurodevelopmental period. There is still a
255 possibility, which may have been obscured in the current study by the majority of children with FHR that
256 will not develop SZ, that MMN has a predictive value for the transition to SZ (Frangou, 2019). To be able to
257 validate this latter proposal, it is important to follow-up on these children in order to determine who will
258 make the transition to SZ and who will not.

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Table 10 Demographics and characteristics of the included children with familial high-risk for schizophrenia (FHR-SZ), bipolar disorder (FHR-BP), and population-based children (PBC).

	FHR-SZ		FHR-BP		PBC		Statistics (p-value)	FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
Number of children, N	53		41		39		0.162 ^a			
Age, years (s.d.)	12.09 (0.24)		12.13 (0.24)		12.16 (0.29)		0.459 ^b			
Male, N (%)	25 (47.2)		22 (53.7)		18 (46.2)		0.759 ^a			
Handedness, N right-handed (%)	46 (86.8)		36 (87.8)		36 (92.3)		0.693 ^a			
	N		N		N					
ADHD ¹ , N (%)	52	8 (15.4)	41	2 (4.9)	39	4 (10.3)	0.262 ^a			
ASD ¹ , N (%)	52	2 (3.9)	41	3 (7.3)	39	1 (2.6)	0.566 ^a			
RIST total IQ ² , mean (s.d.)	53	97.30 (9.72)	41	99.37 (8.26)	39	99.03 (8.82)	0.489 ^b			
CBCL total score ² , mean (s.d.)	51	19.78 (17.41)	40	17.03 (15.30)	39	10.95 (11.47)	0.025 ^c	0.012 ^d	0.034 ^d	0.554 ^d
SRS ² , mean (s.d.)	52	30.46 (25.83)	40	27.30 (21.70)	39	16.64 (11.96)	0.005 ^c	0.004 ^d	0.005 ^d	0.762 ^d
CGAS ² , mean (s.d.)	50	66.80 (15.06)	39	69.80 (14.55)	37	76.50 (14.07)	0.005 ^c	0.002 ^d	0.018 ^d	0.407 ^d

¹ Lifetime prevalence of ADHD or ASD diagnoses derived from the VIA 7 study; see Ellersgaard et al. (2018) for the psychopathology on the total cohort at age 7; ² IQ and dimensional scales are derived from the VIA 11 study. ^a Pearson chi-square test of independence; ^b One-way ANOVA; ^c Kruskal-Wallis test; ^d Mann-Whitney test. Abbreviations: ADHD, Attention-Deficit Hyperactivity Disorder; ASD, Autism Spectrum Disorders; CBCL, Child Behavior Check-List; CGAS, Children's Global Assessment Scale; FHR-BP, familial high-risk for bipolar disorder; FHR-SZ, familial high-risk for schizophrenia; N, number; PBC, population-based control; RIST, Reynold's Intellectual Screening Test; s.d., standard deviation; SRS, Social Responsiveness Scale.



s	Standard tone	Stand	76%	1000 Hz, 50 ms, 75 dB
d1	Frequency deviant	FreqMMN	8%	1200 Hz, 50 ms, 75 dB
d2	Duration deviant	DurMMN	8%	1000 Hz, 100 ms, 75 dB
d3	Frequency*duration deviant	FDMMN	8%	1200 Hz, 100 ms, 75 dB

Figure 1 Auditory stimuli in the MMN specifying the characteristics and occurrence of the standard tone (s) and three types of deviant (d1, d2, d3) tones.

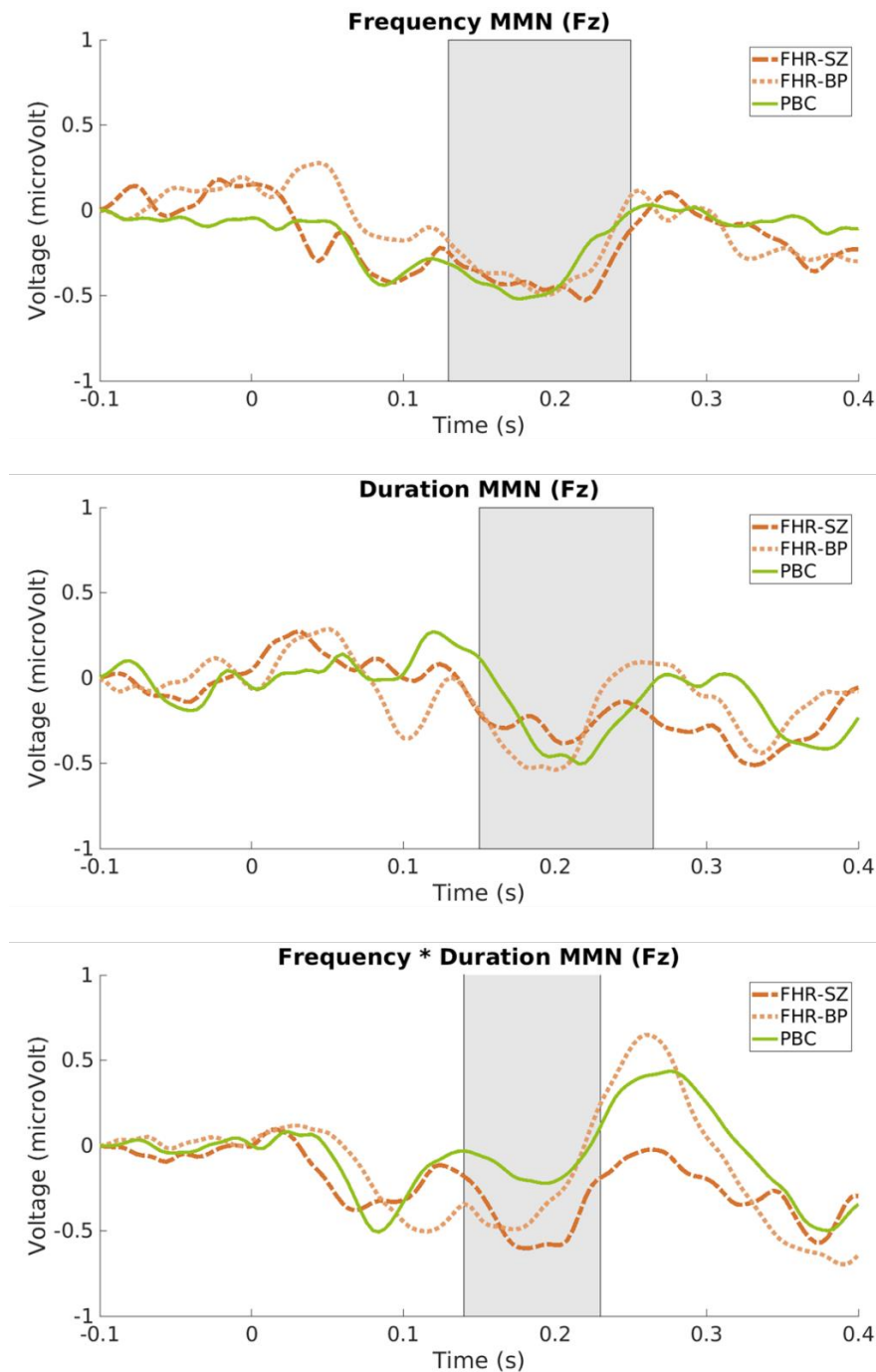


Figure 2 Grand-averages of frequency MMN (FreqMMN), duration MMN (DurMMN), and frequency*duration MMN (FDMMN) for electrode Fz, in children with familial high-risk for schizophrenia (FHR-SZ), for bipolar disorder (FHR-BP), and population-based children (PBC). Grey rectangles are the time windows in which MMN was scored. The scoring window for the frequency deviant was 130 – 250 ms, for the duration deviant 150 – 265 ms, and for the frequency*duration deviant 140 – 230 ms.

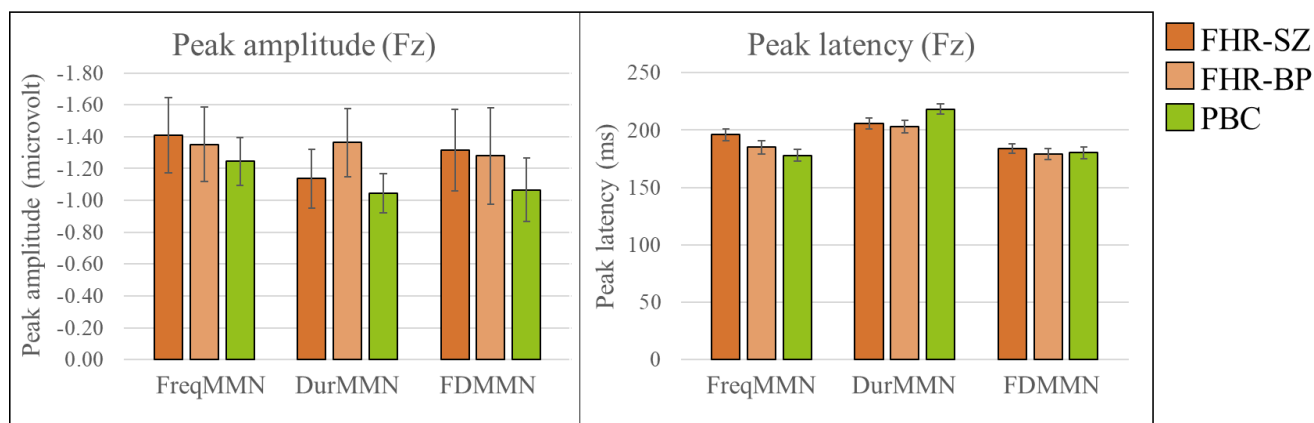


Figure 3 Peak amplitude and peak latency of frequency MMN (FreqMMN), duration MMN (DurMMN), and frequency*duration MMN (FDMMN) for electrode Fz in children with familial high-risk for schizophrenia (FHR-SZ), for bipolar disorder (FHR-BP), and population-based children (PBC).

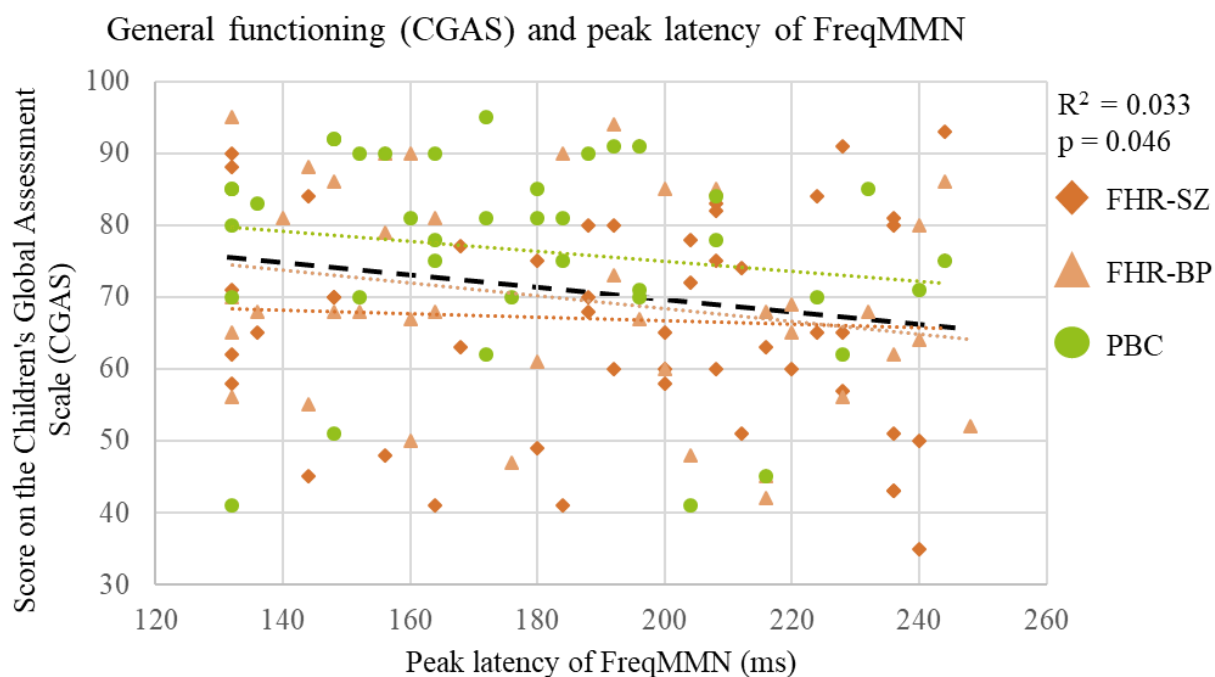


Figure 4 The relationship between the scale of global functioning (CGAS) and peak latency of frequency MMN (FreqMMN) for children with familial high-risk for schizophrenia (FHR-SZ), for bipolar disorder (FHR-BP), and population-based children (PBC). The black dotted line represents the significant negative association for all children, indicating lower global functioning in children with longer MMN latency.

Appendix 2: Behavioral performance and neural responses during a visuomotor conflict task in children with familial high risk for schizophrenia and bipolar disorder

Behavioral performance and neural responses during a visuomotor conflict task in children with familial high risk for schizophrenia and bipolar disorder

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1 Key points

2 Question: Do children with familial high risk for schizophrenia or bipolar disorder show
3 electrophysiological impairments during a visuomotor conflict task?

4 Findings: This population-based Danish cohort study including 145 children demonstrated
5 significant increased intra-subject variability of reaction time and reduced P3b amplitudes reflecting
6 attentional resources in those children at familial high risk for schizophrenia or bipolar disorder.

7 Meaning: P3b amplitude reductions may serve as vulnerability marker for schizophrenia and
8 bipolar disorder and may be linked to increased reaction time variability.

9 Abstract

10 Importance: Electrophysiological abnormalities during visuomotor conflict tasks are present in
11 patients with schizophrenia and bipolar disorder. Assessment of such potential abnormalities in
12 children with familial high risk for schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) may clarify
13 underlying mechanisms of vulnerability and contribute to better clinical predictions.

14 Objective: To determine whether electrophysiological measures are impaired in children with FHR-
15 SZ or FHR-BP.

16 Design: Data were collected from April 15, 2017, to June 28, 2019, as part of the second wave of
17 the cohort study the Danish High Risk and Resilience Study – VIA 11. Assessors were blinded to
18 the risk status.

19 Setting: Participants were recruited through Danish registers and were invited to the university
20 hospital research site in Copenhagen.

21 Participants: 59 children with FHR-SZ, 44 children with FHR-BP, and 42 population-based children
22 (PBC) were included with a narrow age range around 12 years and comparable sex ratio.

23 Exposure: Parents diagnosed with schizophrenia, bipolar disorder, or neither diagnosis.

24 Main Outcomes and Measures: Electroencephalography was recorded during a flanker task to
25 elicit visual N200, P3b, and lateralized readiness potential. Accuracy rate, reaction time, and intra-
26 subject variability of reaction time on the congruent and incongruent condition were calculated.

27 Results: This study included 145 children in the analyses. Children with FHR-SZ (n=59) included
28 33 girls (46%) (mean [SD] age, 12.10 [0.23] years), children with FHR-BP (n=44) included 20 girls
29 (45%) (mean [SD] age, 12.12 [0.22] years), and PBC (n=42) included 20 girls (48%) (mean [SD]
30 age, 12.19 [0.30] years). P3b amplitudes were reduced in the incongruent condition for children
31 with FHR-SZ (Cohen $d=0.82$) and with FHR-BP (Cohen $d=0.65$) compared to PBC. Children with
32 FHR-SZ also showed P3b reductions in the congruent condition (Cohen $d=0.65$) relative to PBC.
33 Increased intra-subject variability of reaction time was observed in the incongruent condition for
34 children with FHR-SZ (Cohen $d=0.67$) and FHR-BP (Cohen $d=0.33$) compared to PBC. Children

35 with higher intra-subject variability of reaction time showed smaller P3b amplitudes across
36 conditions.

37 Conclusions and Relevance: Deficits in P3b amplitude and increased variability in reaction time
38 during a visuomotor conflict task is evident already in FHR-SZ and FHR-BP children at age 12.
39 This suggests that P3b amplitude deficits have a potential sensitivity to clinical outcomes.

Introduction

Schizophrenia (SZ) and bipolar disorder (BP) show partially overlapping symptoms and shared genetic liability.^{1,2} SZ is considered as neurodevelopmental disorder with cognitive impairments emerging long before the clinical illness manifestation³ while equivocal evidence exists for BP.⁴ Different structural patterns of brain abnormalities have been found in first-degree relatives (FDR) of patients with SZ and BP suggesting distinct neurodevelopmental trajectories contribute to these disorders.⁵ Cognitive deficits seem to take distinct paths as studies found larger effect sizes in patients with SZ, prior to and post illness onset, than in patients with BP.⁶ Changes in neurobiological processes, that contribute to cognitive functioning, may be part of the characterization of the vulnerability state prior to the manifestation of clinical symptomatology of SZ and BP. Children born to parents with SZ (i.e. familial high-risk for SZ (FHR-SZ)) or BP (FHR-BP) have a higher risk of developing similar or other mental disorders as their parents⁷ and can provide better insights into the (non-)specific underlying vulnerability of the impairments preceding illness onset, as well as the mechanisms contributing to the development of these disorders.

The Eriksen flanker task⁸ assesses aspects of attention and cognitive control that are often observed impaired in young individuals with FHR-SZ^{9,10} and FHR-BP.^{11,12} In a flanker task, participants are required to respond to the target stimulus that is flanked by distracting stimuli either pointing in the congruent or incongruent direction of the target stimulus. Typically, incongruent (i.e. conflict-loaded) trials result in lower accuracy rates and higher reaction times (RT) relative to congruent (i.e. conflict-free) trials.⁸ Individuals with SZ usually show longer RTs in incongruent conditions than controls.^{13,14} Additionally, the coefficient of variation of RT (CV_{RT}) provides a measure of the intra-subject variability of RT. An increased CV_{RT} is thought to reflect intermittent attentional lapses.^{15,16} Interestingly, studies have shown that unaffected FDR of individuals with BP show increased CV_{RT} in attention-related tasks,^{11,12,17} which is also reported in individuals with chronic BP^{11,17} and in those with chronic SZ.¹⁸ In contrast, our baseline results on

interference control showed that 7-year-old children with FHR-BP did not show increased CV_{RT} relative to control children, however, those with FHR-SZ did.⁹

To address questions about underlying neural mechanisms contributing to such cognitive functions, event-related potentials (ERPs) have proven useful.¹⁹ Two ERPs have been of particular interest in flanker tasks, N200 and P3b reflecting neural mechanisms responsible for perceptual conflict or interference control (N200)²⁰⁻²² and to the evaluation and processing of a stimulus (P3b) respectively.²³ The conflict present in the incongruent condition and the increased attentional resources required to process this conflict elicit increased N200 and P3b amplitudes, as compared to the congruent condition.^{21,24-28} Few studies included individuals with SZ^{29,30} or BP³¹ in a flanker task, but reduced visual P3b amplitudes in other attentional tasks are a consistent finding in patients with SZ.³² Similarly, studies including individuals with clinical high-risk for psychosis (CHR) revealed that P3b amplitude reductions are already present prior to clinical manifestation of the illness.³³⁻³⁵ Few studies investigating ERPs in children with FHR-SZ showed deficits in auditory N200 and P300,^{36,37} but no study to date has examined ERPs during a flanker task in children with FHR-SZ or FHR-BP. In addition to N200 and P3b, the lateralized readiness potential (LRP) serves as a real-time index for central motor processes related to motor-response preparation. For example, preparing a left-hand motor response leads to activation in the right motor cortex reflected by a negative-going potential.³⁸ Since children with FHR-SZ show motor deficits,³⁹ possibly indicating functional abnormalities of the motor cortex, deficits in motor-response preparation may have an effect on the behavioral performance in a flanker task, causing longer RTs or greater CV_{RT} .

This study investigated the neural correlates when resolving a visuomotor conflict task in children with familial high-risk for SZ (FHR-SZ) or BP (FHR-BP) and control children. We assessed accuracy rates, RT, and CV_{RT} during a modified flanker task simultaneously recorded with EEG to investigate neural correlates of conflict monitoring (N200), task-relevant attentional resources and stimulus evaluations (P3b), and motor-response preparation (LRP). Finally, we explored the

associations between the EEG measures and emotional and problem behavior as well as with severity of ADHD-symptomatology. We expected that children with FHR-SZ relative to PBC would show deficits on the flanker task represented by lower accuracy rates, higher RT, and higher CV_{RT} in the incongruent condition. We hypothesized reduced amplitudes of N200, P3b, and LRP in children with FHR-SZ compared to PBC as reflecting their impairments in interference control. As children with FHR-BP typically perform intermediate between FHR-SZ and controls, we expected that their behavioral performance and EEG measures would lie between those of FHR-SZ and PBC.

Methods

Participants

We examined 60 children with FHR-SZ (40%), 44 children with FHR-BP (30%), and 45 PBC (30%). Children were recruited through the Danish High Risk and Resilience Study – VIA 7; a prospective cohort study starting in 2013 by investigating 522 7-year-old children (202 children with FHR-SZ (39%), 120 children with FHR-BP (23%), and 200 PBC (38%)). Details about recruitment, inclusion, exclusion criteria can be found in the study protocol.^{40,41} In the first follow-up (the VIA 11 study)⁴¹ children were invited to one of the two research sites (Aarhus or Copenhagen) in Denmark. EEG was only assessed in Copenhagen, and as a result, only a subgroup of the VIA 11 study was invited for an EEG assessment. To strive for evenly distributed groups between research sites, the place of residence, gender, and the FHR status of the children was considered in this selection. The VIA 11 study was approved by The Danish Data Protection Agency (ID number RHP-2017-003, I-suite no. 05333) and by the local Ethical Committee (H 16043682). Children and their primary caregivers were informed about participation in the project and guardians gave their written informed consent for their child to approve participation.

Procedure

As part of the VIA 11 study, children were invited to the Danish Research Centre for Magnetic Resonance (DRCMR) at the Copenhagen University Hospital Hvidovre, where the EEG recordings

118 took place. Assessors were blinded to the child's risk status. On the day of their participation,
119 children also participated in an MRI-study of which the results will be published elsewhere. To
120 assure that children understood exactly what was expected from them, and due to the intense
121 nature of the day, we explained all elements of the day thoroughly with images. During EEG
122 recordings, children participated in three independent paradigms.⁴² The current study presents
123 data from the EEG-flanker task.

124

125 Eriksen flanker test

126 Children were seated in a comfortable chair approximately one meter in front of the computer
127 screen in a quiet room. A modified flanker task⁸ was implemented in the E-prime-2 experiment
128 programming platform (Psychology Software Tools). We used left or right pointing arrows as
129 flankers and targets. Each trial started with a central fixation dot presented for 700 ms followed by
130 the flankers. Flankers were shown for 100 ms followed by the target that was shown for 1000 ms.
131 Two conditions occurred, (1) when flankers and the target pointed into the same direction, i.e. the
132 congruent condition (e.g. <<< < <<<), and (2) when flankers and the target pointed in the opposite
133 direction, i.e. the incongruent condition (e.g. <<< > <<<) (Figure 1). Children were instructed to
134 keep their thumbs on the left and right response buttons and to respond with the button that
135 corresponded to the direction of the target, as fast and as accurate as possible. The response
136 window was 1000 ms.

137 First, children completed a practice round of 20 trials to assure their understanding as well as to
138 calculate the individual mean RT and standard deviation (SD) (based on correctly answered
139 incongruent trials with a minimum of seven; otherwise a second practice round was performed).
140 Then, in the actual task, an individual threshold was based on 1.5 times the SD of the mean RT
141 derived from the practice round. In order to keep the task challenging, the child saw an
142 exclamation mark (200 ms) when the response time exceeded the child's individual threshold.

143 The task was presented in two blocks of 200 trials, randomized, and with a fixed-order between
144 subjects. The task was set up in such a way that 50% of the trials were congruent and balanced
145 between right and left responses.

146 Behavioral performance was evaluated by accuracy rates, RT, and CV_{RT} separately for the
147 congruent and incongruent condition, after excluding trials when (1) the RT was within 200 ms after
148 the presentation of the target (considered as anticipatory responses),^{9,11} or when (2) there was no
149 response (omission error).^{9,11} This resulted in an average elimination of 4% of trials per subject.
150 Children with more than 30% errors (commission errors) were excluded assuming that they were
151 inadequately engaged with the task.⁴³ This was the case for four children (one FHR-SZ and four
152 PBC). For each condition, the accuracy rate was determined by the number of correct trials divided
153 by the number of total trials (excluding anticipatory trials and omission trials); RT was the time
154 between target presentation and the first response by button press; and CV_{RT} was calculated by
155 dividing the SD by the mean RT of each individual.

156

157 EEG recordings and preprocessing

158 EEG data were recorded using a 128 channel ActiveTwo BioSemi System (BioSemi, Amsterdam,
159 Netherlands) at a sampling frequency of 4096 Hz. Preprocessing was carried out using FieldTrip.⁴⁴
160 Continuous EEG data were referenced to the averaged of the two mastoids. Data were filtered
161 between 0.5 and 45 Hz using a finite impulse response filter. For artifact removal/reduction, EEG
162 data were segmented into stimulus-locked epochs (-0.5 ms and +1.5 ms). To detect artifacts, i.e.
163 eye movements, muscle tension, and jumps/peaks, we used an in-house script. Artifacts were
164 removed if amplitudes exceeded 100 microvolts. We used the triangulation method for channel
165 interpolation, i.e. for each trial, every bad channel was corrected by building a triangle of nearby
166 electrodes. Data were baseline-corrected according to a 500 - 10 ms window prior to the stimulus.
167 Data of five subjects (two FHR-SZ and three PBC) were removed due to poor EEG data quality.

168

169 Averaging and data extraction

170 To identify time intervals around each ERP interval, epochs were averaged separately on the
171 congruent and incongruent condition. Analyses were done on correct trials only.

172 Mean amplitudes for N200 and P3b were calculated since mean amplitudes are robust against
173 noise⁴⁵ compared to peak amplitudes, especially recommended for children.⁴⁶ To identify time
174 windows for the mean amplitude, we used the peak value of the grand average of all children
175 (pooled across groups, N=140) and took 20 ms around it, resulting in a time window of 40 ms in
176 total.⁴⁶ This resulted in a time window of 190-230 ms after stimulus for the mean N200 amplitude
177 and 360-400 ms for the mean P3b amplitude.

178 We obtained the LRP by calculating the difference in EEG activity between electrodes C3 and C4,
179 i.e. contralateral minus ipsilateral to the responding hand. Thus, for the right responses, we
180 subtracted the EEG activity of the ipsilateral side (right motor cortex; electrode C4') from the
181 contralateral side (left motor cortex; electrode C3') and vice versa.³⁸ These two differences were
182 then averaged for congruent and incongruent separately. To identify time windows for the peak-to-
183 peak analyses of the LRP, we used the positive and negative peak values of the grand average
184 and took 100 ms around it to capture the entire peak. Time windows were specific for each group
185 to correct for potential differences in reaction time (eTable 1 in Supplement).

186

187 Clinical variables

188 To estimate the children's IQ, we used Reynold's Intellectual Screening Test (RIST).⁴⁷ The Child
189 Behavior Checklist (CBCL)^{48,49} and the Attention-Deficit/Hyperactivity Disorder – Rating Scale
190 (ADHD-RS)^{50,51} assessed the severity of dimensions of psychopathology and were administered by
191 the primary caregiver.

192

193

194

195 Statistical analyses

196 We compared continuous demographic and clinical variables across the FHR groups using
197 univariate analysis of variance (ANOVA) or Kruskal-Wallis tests in case data were non-normally
198 distributed, and the chi-square tests for independence for categorical data.

199 Analysis of missing data was conducted on the behavioral and EEG data. Data was checked on
200 normality through the K-S test and visual inspection of Q-Q plots.

201 For comparing behavioral performance across the three groups, we used repeated measures
202 ANOVA (RM-ANOVA). We performed post hoc multiple comparisons by means of Bonferroni
203 corrections and set at $p < 0.05$. Sex was entered as a covariate, post hoc, in case of any
204 statistically significant effects. We used Greenhouse-Geisser correction for repeated measures.

205 Congruency effects of accuracy and RT were calculated by subtracting the accuracy rate or RT of
206 the congruent condition from the incongruent condition, which was then tested for group
207 differences by an ANOVA. Additionally, we performed distributional analyses of RT distributions.
208 Slow responses can be considered as deliberate responses that are more likely to be correct. In
209 contrast, fast responses can occur automatically, which, in the incongruent condition, can lead to a
210 higher probability of an incorrect response. Comparing the accuracy rates of fastest and slowest
211 responses provides a measure of global inhibition, whereas the congruency effect of RT for the
212 fastest and slowest responses gives a measure of selective inhibition of incorrect responses.⁵²

213 Therefore, for each subject, RT of correct responses (of both conditions but without omission
214 errors and anticipatory responses) were rank-ordered and divided into four equal-sized speed bins
215 (quartiles), so that 25% of the total number of correct trials fell in one quartile. Only correct
216 responses were used that were preceded by a correct response, because of post-error slowing
217 that occurs in the trial after an erroneous response. Hereafter, incorrect responses and the non-
218 stable correct responses were added to the quartiles in order to calculate accuracy rate and mean
219 RT for each quartile separately. Accuracy rates and delta plots for RT were constructed by plotting

220 accuracy rate or the congruency effect of RT as a function of mean RT per quartile. We performed
221 RM-ANOVA with the quartiles as within-group factor across the three groups.
222 For EEG data, we conducted RM-ANOVA to compare mean N200 and P3b amplitude as well as
223 LRP peak-to-peak amplitude between the three groups. We performed post hoc multiple
224 comparisons by means of Bonferroni corrections. Cohen d was calculated to estimate effect sizes.
225 Correlations between mean N200 and P3b amplitudes and clinical scales CBCL total score and
226 ADHD-RS total score were performed using Pearson's or Spearman's correlations when
227 appropriate. Data were analyzed using SPSS Statistics software (version 25; IBM Corp).⁵³

228

229 Results

230 Group characteristics

231 The three groups did not significantly differ in terms of age, sex, handedness, and IQ. Children with
232 FHR-SZ and FHR-BP showed higher dimensional levels of problem behavior compared to control
233 children but not compared to each other. Only children with FHR-SZ showed higher dimensional
234 levels of ADHD-symptomatology compared to control children (Table 1).

235

236 Behavioral performance

237 RT differed by group ($F(2,142)=4.121, p=0.018$) such that children with FHR-SZ and FHR-BP were
238 slower in both conditions (FHR-SZ vs PBC: Cohen $d=0.49, p=0.045$; FHR-BP vs PBC: Cohen
239 $d=0.61, p=0.032$) than controls. CV_{RT} differed by group and condition ($F(2,142)=3.456, p=0.034$)
240 such that children with FHR-SZ and FHR-BP showed a higher CV_{RT} on the incongruent condition
241 compared to controls (FHR-SZ vs PBC: Cohen $d=0.67, p=0.019$; FHR-BP vs PBC: Cohen $d=0.33,$
242 $p=0.044$), but not in the congruent condition. Lastly, accuracy rates differed by condition
243 ($F(1,142)=317.746, p<0.001$) such that the congruent condition showed higher accuracy rates than
244 the incongruent condition, but there was no significant group ($F(2,142)=1.198, p=0.305$) nor
245 interaction effect ($F(2,142)=0.716, p=0.491$). No significant group difference was found on the
246 congruency effect on accuracy ($F(2,142)=0.7136, p=0.491$) nor on RT ($F(2,142)=0.327, p=0.721$).

(See Figure 2 and eTable 2 in the Supplement for the exact values.) Correcting for possible sex effects did not significantly change observed results.

Distributional analyses

MeanRT per time bin differed by group ($F(6,282)=2.642$, $p=0.017$) such that children with FHR-SZ had significantly higher RTs in the fourth (slowest) time bin (Cohen $d=0.61$, $p=0.008$) and children with FHR-BP had higher RTs in the third (Cohen $d=0.60$, $p=0.049$,) and fourth time bin (Cohen $d=0.69$, $p=0.014$) than controls. Accuracy rates differed by time bin ($F(3,140)=227.102$, $p<0.001$), with lower accuracy rates in fast trials and higher accuracy rates in slower trials whereas there was no interaction effect with group ($F(6,282)=0.569$, $p=0.755$). Groups did not significantly differ on the congruency effect of RT within each time bin ($F(6,282)=1.269$, $p=0.272$). (See Figure 3 and eTable 3 in the Supplement for the exact values.)

EEG data

P3b amplitudes differed by the interaction effect of group and condition ($F(2,137)=3.410$, $p=0.036$) such that children with FHR-SZ and FHR-BP had reduced amplitudes in incongruent trials (FHR-SZ vs PBC: Cohen $d=0.82$, $p<0.001$; FHR-BP vs PBC: Cohen $d=0.65$, $p=0.011$) compared to controls, which children with FHR-SZ also showed in the congruent condition (FHR-SZ vs PBC: Cohen $d=0.65$, $p=0.005$). N200 amplitude differed by condition ($F(1,137)=24.876$, $p<0.001$) shown by larger amplitudes in incongruent than in congruent trials, but no significant effect by group ($F(2,137)=2.508$, $p=0.824$) nor interaction ($F(2,137)=1.896$, $p=0.154$). LRP amplitude differed by condition ($F(1,137)=12.240$, $p=0.001$) such that amplitudes were greater in incongruent than in congruent trials, but no significant effect of group ($F(2,137)=1.863$, $p=0.159$) nor interaction ($F(2,137)=1.478$, $p=0.232$). (See Figure 4 and 5 for the ERP result and eTable 4 in the Supplement for the exact values.)

272 In order to investigate whether deficits were specific to P3b or to the earlier ERP too, we performed
273 a post hoc analysis on the mean P2 amplitude (time window: 197-267 ms). Post hoc analyses of
274 P2 amplitude revealed group differences ($F(2,137)=7,523$, $p=0.001$) such that children with FHR-
275 SZ showed smaller P2 amplitudes than controls (Cohen $d=0.68$, $p=0.001$). (See eTable 4 in the
276 Supplement for the exact values.)

277

278 Correlations

279 Negative correlations were found between P3b amplitude and CV_{RT} in both the congruent condition
280 ($r=-0.185$, $p=0.029$) and in the incongruent condition ($r=-0.284$, $p=0.001$) (see eFigure 1 in the
281 Supplement).

282 Post hoc analysis of the P3b including CV_{RT} as a covariate revealed that the group difference
283 persisted after correcting for CV_{RT} , but the interaction effect disappeared. Also, a post hoc analysis
284 on the relationship between N200 and the accuracy rate did not show significant results.

285 We found no significant correlations between the ERPs (mean N200 and mean P3b amplitudes)
286 and emotional and behavioral problem behavior nor with the severity of ADHD-symptoms in the
287 whole group. The only significant correlation we found was in control children between the mean
288 P3b amplitude on incongruent trials and the ADHD-RS total score ($r_s=-0.352$, $p=0.028$), indicating
289 a greater mean P3b amplitude relating to less prominent attentional deficits. (See eTable 6 for the
290 correlations in the whole group and eTable 7 for the separate groups.)

291

292 Discussion

293 This study compared the behavioral performance and ERPs between 12-year-old children with
294 FHR-SZ, children with FHR-BP, and controls when resolving a visuomotor conflict task (i.e. flanker
295 task). Children from both FHR groups were slower in the congruent and incongruent condition than
296 control children. Distributional analysis revealed that children with FHR-SZ and FHR-BP were
297 significantly slower in the slowest, deliberate, responses, with no effect on their accuracy rate.

298 Furthermore, in the incongruent condition, children from both FHR groups showed greater RT
299 variability as well as reduced P3b amplitudes, relative to control children. In addition, children with
300 FHR-SZ showed reduced P3b amplitudes in the congruent condition, as well as reduced P2
301 amplitudes in both conditions, indicating broader neural alterations in children with FHR-SZ. We
302 found no group differences on accuracy rate nor on N200 or LRP amplitude. In all children, the P3b
303 amplitude was negatively associated with the RT variability, mapping potential neural mechanisms
304 of attentional lapses.

305 First, our findings in 12-year-old children with FHR-SZ or FHR-BP expand on the literature of P3b
306 amplitude reductions in the prodromal phase of psychosis-related disorders and in individuals with
307 SZ and BP. Previous studies observed reduced P3b amplitudes in individuals with CHR for
308 psychosis.³³ Our findings revealed that these neurophysiological abnormalities are already present
309 at a younger developmental phase. As most children with FHR will develop typically, P3b deficits
310 seem state-independent and may serve as a neurobiological vulnerability marker. Second, several
311 studies including unaffected FDR of individuals with SZ⁵⁴ and BP⁵⁵ observed P3b reductions.
312 Those studies included adult FDR with a mean age varying from 41 up to 51, which is beyond the
313 vulnerability phase of developing psychosis. Our finding that also younger FDR, who are still in an
314 early developmental phase, show these neurophysiological abnormalities may have important
315 considerations for the origin of these deficits.

316 Furthermore, this ERP study is carried out to provide insights into the cognitive dysfunctions which
317 accompany children with FHR-SZ or FHR-BP. An increased P3b amplitude reflects greater
318 attentional resources,⁵⁶ specifically, P3b amplitude indexes the attentional resources utilized for
319 evaluation and processing of the target stimulus.⁵⁷ Therefore, we speculate that the reduced P3b
320 amplitude may reflect inefficient attentional resources and impairments during stimulus processing.
321 Moreover, we found intra-subject RT variability in both FHR groups in the incongruent condition,
322 considered to reflect attentional lapses, which replicated previous studies using different behavioral
323 tasks.^{9,11,12,17} The association found between high RT variability and reduced P3b amplitudes may

324 suggest the neural contributions to attentional lapses.^{15,16} Notably, as children with FHR-SZ
325 showed P2 amplitude reductions in both conditions, the inefficiency in neural underpinnings may
326 be broader in those with FHR-SZ compared to FHR-BP, whose P2 amplitude did not significantly
327 differ from controls. Together with the P3b findings, this provides evidence of broader impairments
328 in the neural circuit generating P3b and P2 in children with FHR-SZ, in a conflict-loaded and
329 conflict-free context, while those with FHR-BP show a rather specific impaired neural mechanism
330 only in a conflict-loaded context.

331 Our observation of greater N200 amplitudes in incongruent compared to congruent trials is in line
332 with previous studies.^{21,24} However, in contrast to our expectation, the comparable N200
333 amplitudes across groups in each condition suggested intact underlying neural mechanisms of
334 conflict monitoring in children of both FHR groups, which was also supported by the non-significant
335 group differences on accuracy rates. Further, LRP enabled to study neural processes related to
336 motor-response preparation and disentangled those linked to stimulus evaluation (P3b). The
337 absence of significant group differences on LRP amplitude indicates normal motor-response
338 preparation in children of both FHR groups, reflecting an intact neural circuit (motor cortex) for
339 selecting and directing the correct response. As LRP reductions were found in individuals with
340 SZ,^{58,59} such deficits may arise in later developmental or clinical stages.

341 Strengths of this study were the inclusion of children with FHR-SZ and with FHR-BP which allowed
342 studying shared or distinct neurodevelopmental deficits; the inclusion of a relatively large group of
343 children within a narrow age range, which is especially important in this critical developmental
344 period; the simultaneous recordings of EEG during the modified flanker task; and the blinding of
345 clinical assessors in this study. However, several limitations also need to be addressed. We could
346 only provide cross-sectional data at this time point. A modified flanker task has been assessed in
347 the first wave of the project⁹, however, the task had to be adapted to our protocol. This restricted
348 us from comparing the behavioral performance on the two test sessions (EEG was not part of the
349 first wave). To overcome this in the future, follow-up assessments of this set-up are planned in four

350 years. Second, we could not study the error-related negativity due to the low rate of errors made in
351 the task, although this is suggested by others.²⁶ Future studies should study the maturational
352 processes of N200, P3b, and LRP, to investigate whether deficits in these measures will only
353 develop in those children that will develop SZ later in life. Accordingly, it would be interesting to
354 investigate whether reductions in P3b amplitude may predict psychosis onset at a later stage.

355 In conclusion, the findings of this study provide further evidence that children with FHR-SZ and
356 FHR-BP are generally slower when resolving a visuomotor conflict task as well as less consistent
357 in the conflict-loaded condition. Reduced P3b amplitudes in children with FHR-SZ and FHR-BP
358 may point to impaired neural mechanisms of attention-dependent stimulus processing and may
359 indicate vulnerability for developing psychosis. The relationship between reduced P3b and
360 increased variability in RT may explain how difficulties in stimulus processing result in attentional
361 lapses, however, further research is needed to investigate this association. Perhaps in combination
362 with several neurophysiological or other characteristics of children with FHR-SZ or FHR-BP, these
363 findings could contribute to a prediction model for the illness onset as well as provide insights into
364 the resilience factors of the children with FHR that will not develop on to psychosis. The findings of
365 this study contribute to the understanding of the underlying pathophysiological processes and may
366 be useful in drug development as well as early identification markers.

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374

375 Conflict of interest

376 HRS has received honoraria as speaker from Sanofi Genzyme, Denmark and Novartis, Denmark,
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381

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Table 1 Demographics and clinical characteristics of familial high-risk groups.

		FHR-SZ (N=59)		FHR-BD (N=44)		PBC (N=42)	Statistics (p-value)	FHR-SZ vs. PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
Age in years, mean (SD)		12.10 (0.23)		12.12 (0.22)		12.19 (0.30)	0.162 ^a			
Gender, N boys (%)		26 (44)		24 (55)		22 (52)	0.527 ^b			
Handedness, N right-handed (%)		51 (86)		39 (89)		40 (95)	0.347 ^b			
	N		N		N					
RIST (IQ), mean (SD)	59	96.54 (10.52)	44	99.73 (8.19)	42	98.55 (8.44)	0.215 ^a			
CBCL total, mean (SD)	57	20.28 (17.83)	43	17.00 (15.41)	41	10.49 (9.74)	0.020 ^c	0.008 ^d	0.040 ^d	0.458 ^d
ADHD-RS total (without conduct), mean (SD)	58	10.81 (9.43)	43	8.37 (6.64)	42	6.12 (4.75)	0.045 ^c	0.017 ^d	0.109 ^d	0.323 ^d

^a One-way ANOVA; ^b Pearson chi-square test of independence; ^c Kruskal-Wallis test; ^d Mann-Whitney U test. Abbreviations: ADHD-RS, Attention Deficit Hyperactivity Disorder – Rating Scale, CBCL, Child Behavior Checklist; FHR-BP, familial high-risk of bipolar disorder; FHR-SZ, familial high-risk of schizophrenia; n, number; PBC, population-based control; RIST, Reynold's Intellectual Scaling Test; SD, standard deviation.

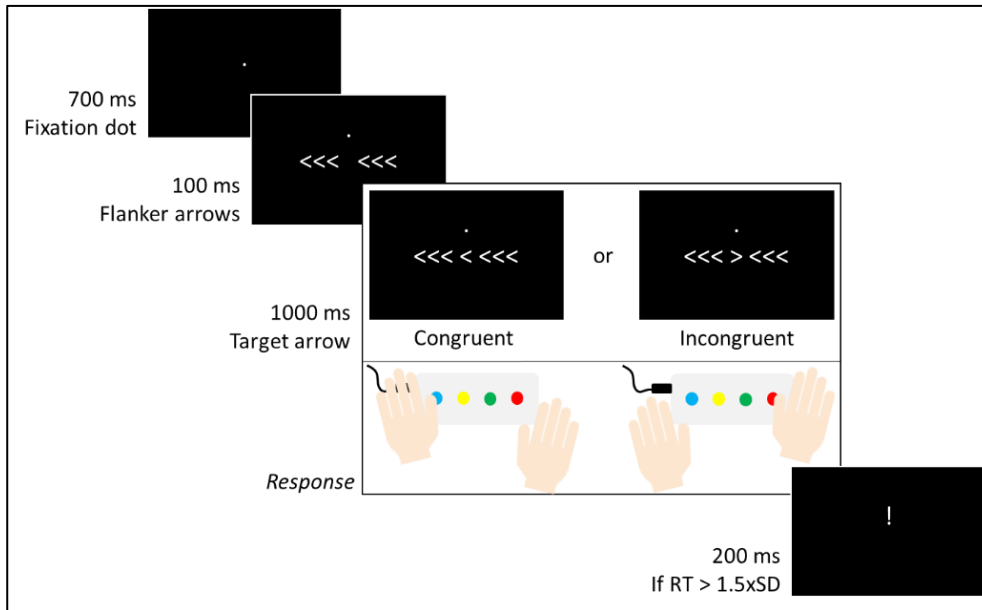


Figure 1 Outline flanker task. After seeing the fixation dot and the flanking arrows, the child has to press a button according to the direction of the middle (target) arrow. In the congruent condition, all arrows point in the same direction whilst in the incongruent condition, the flanking arrows point in the opposite direction of the target arrow. Children are instructed to respond as fast and as accurately as possible. When they are too slow, based on an individual threshold, an exclamation mark appears.

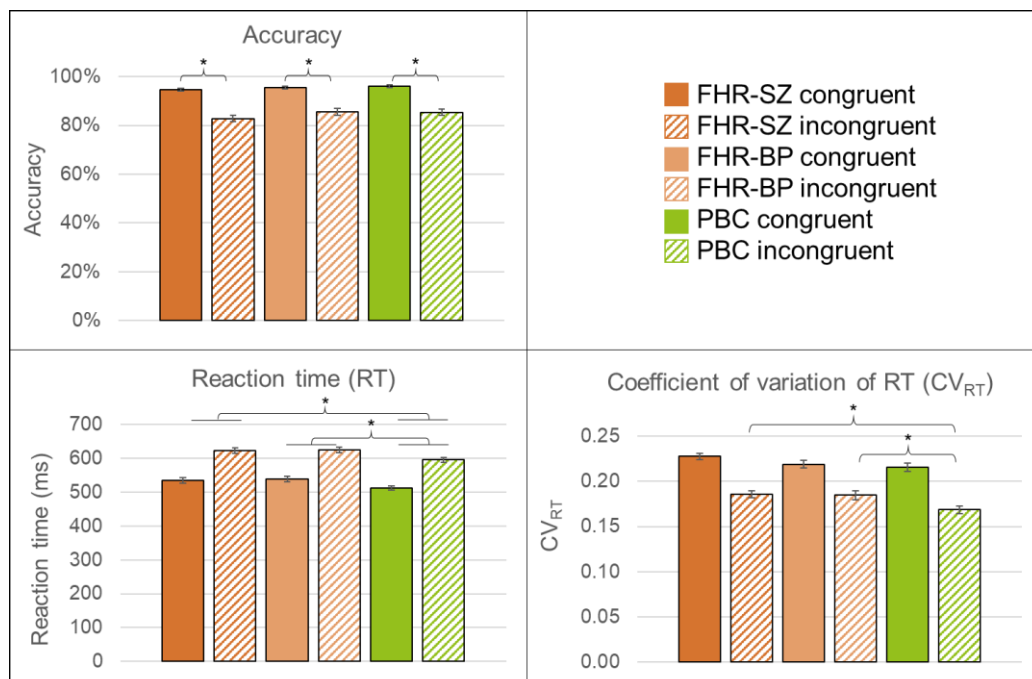


Figure 2 Behavioral performance on the flanker task by familial high-risk groups. Behavioral performance is based on the accuracy rate, reaction time (RT), and the coefficient of variation of RT (CV_{RT}). Abbreviations: CV_{RT}, Coefficient of variation of reaction time; FHR-BP, familial high-risk of bipolar disorder; FHR-SZ, familial high-risk of schizophrenia; ms, milliseconds; PBC, population-based controls; RT, reaction time. * Indicates significance $p < 0.05$.

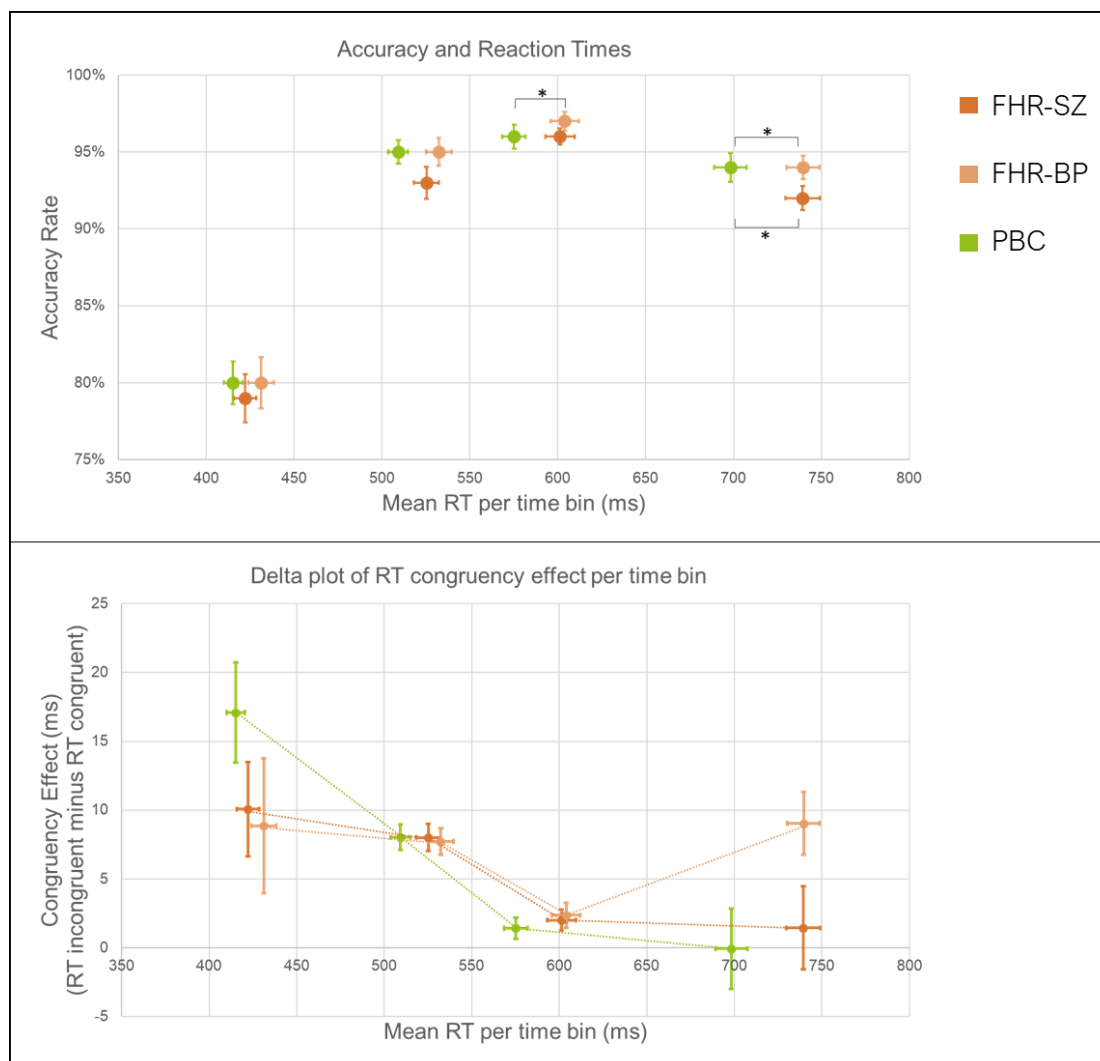


Figure 3 Distributional analysis of behavioral performance on flanker task by familial high-risk groups. In the distributional analyses, trials were grouped in four time bins (quartiles) according to the individual distribution of reaction time, e.g. the first quartile contains the fastest responses and the fourth quartile contains the slowest responses. Accuracy rates and mean reaction times (RT) were calculated per quartile per group and compared across groups. The upper figure presents the accuracy rates across the groups across the quartiles. The lower figure presents the delta plot of the congruency effect of RT against the mean RT of the quartile of a group. Abbreviations: FHR-BP, familial high-risk of bipolar disorder; FHR-SZ, familial high-risk of schizophrenia; ms, milliseconds; PBC, population-based controls; RT, reaction time. * Indicates significance $p < 0.05$.

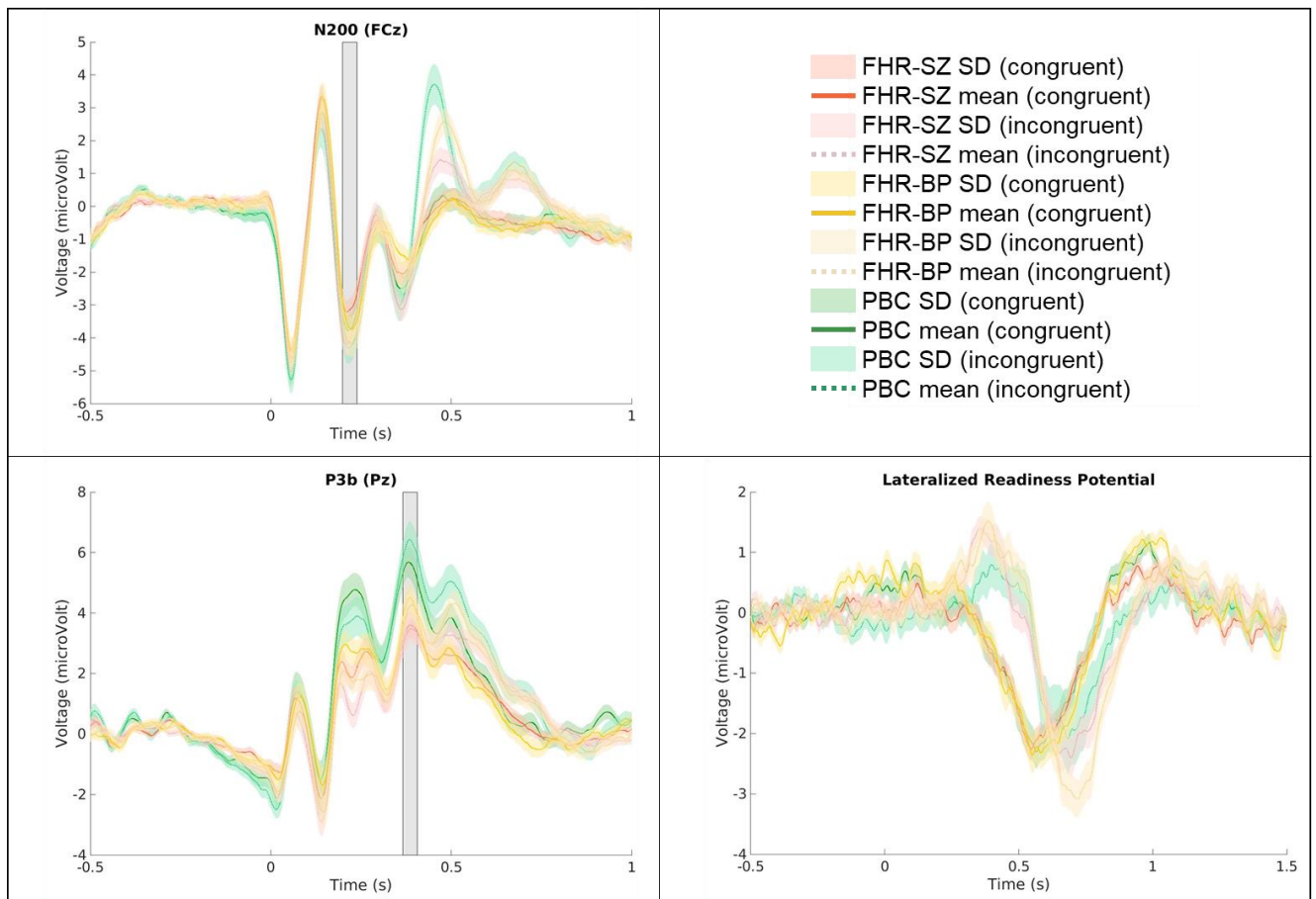


Figure 4 Grand average waveforms of ERPs during a flanker task by familial high-risk groups. Grey rectangles represent the time windows, i.e. for N200 190-230 ms and for P3b 360-400 ms. FCz indicates the frontocentral electrode; Pz the parietal electrode. Abbreviations: ERPs, event-related potentials; FHR-BP, familial high-risk of bipolar disorder; FHR-SZ, familial high-risk of schizophrenia; PBC, population-based controls; s, seconds; SD, standard deviation.

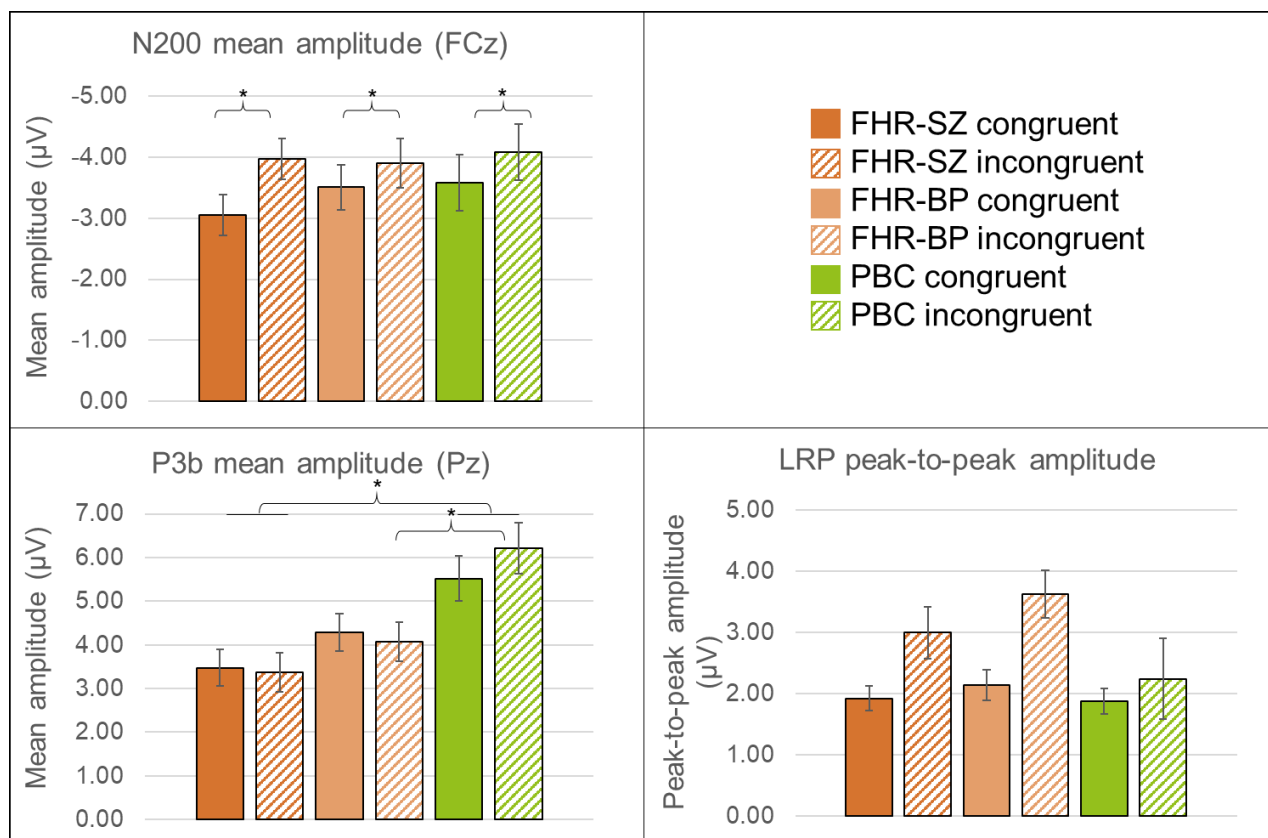


Figure 5 N200, P3b and lateralized readiness potential (LRP) by familial high-risk groups. FCz indicates the frontocentral electrode; Pz the parietal electrode. Abbreviations: FHR-BP, familial high-risk of bipolar disorder; FHR-SZ, familial high-risk of schizophrenia; μV, microvolts; LRP, lateralized readiness potential; PBC, population-based controls. * Indicates significance $p < 0.05$.

Supplement

Online-Only Tables

eTable 1. Group-specific time windows of the lateralized readiness potential (LRP)

	FHR-SZ		FHR-BP		PBC	
	Positive peak	Negative peak	Positive peak	Negative peak	Positive peak	Negative peak
Congruent	111 – 311 ms	447 – 647 ms	178 – 378 ms	450 – 650 ms	273 – 483 ms	465 – 665 ms
Incongruent	259 – 459 ms	595 – 795 ms	286 – 486 ms	621 – 842 ms	298 – 498 ms	582 – 882 ms

Group-specific time windows to determine the positive and negative peaks for the individual groups to correct for group differences on reaction time, used to calculate peak-to-peak amplitude of the lateralized readiness potential (LRP). Abbreviations: FHR-BP, familial high-risk for bipolar disorder; FHR-SZ, familial high-risk for schizophrenia; LRP, lateralized readiness potential; ms, milliseconds; PBC, population-based control.

eTable 2. Behavioral performance on a flanker task by familial high-risk groups

	FHR-SZ (N=59)		FHR-BP (N=44)		PBC (N=42)		Main effect Condition	Main effect Group	Interaction Condition *Group
	Con.	Incon.	Con.	Incon.	Con.	Incon.			
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F1, p, η^2	F1, p, η^2	F1, p, η^2
Accuracy (%)	0.95 (0.05)	0.83 (0.10)	0.95 (0.04)	0.86 (0.09)	0.96 (0.04)	0.86 (0.09)	317.746, <0.001, 0.691	1.198, 0.305, 0.017	0.716, 0.491, 0.010
RT (mean, SD)	534.75 (59.72)	622.06 (57.67)	538.43 (49.84)	624.52 (52.05)	511.54 (40.46)	595.02 (43.08)	1867.778, <0.001, 0.929	4.121, 0.018, 0.055	0.327, 0.721, 0.005
CV_{RT} (mean, SD)	0.23 (0.03)	0.19 (0.03)	0.22 (0.03)	0.18 (0.03)	0.22 (0.03)	0.17 (0.03)	441.778, <0.001, 0.757	3.540, 0.032, 0.047	3.456, 0.034, 0.046

Abbreviations: Con., congruent trials; CV_{RT}, coefficient of variation of reaction time; FHR-BP, familial high-risk for bipolar disorder; FHR-SZ, familial high-risk for schizophrenia; Incon., incongruent trials; LRP, lateralized readiness potential; ms, milliseconds; N, number of participants; PBC, population-based control; SD, standard deviation.

eTable 3. Results from the distributional analyses by familial high-risk groups

	FHR-SZ (N=59)				FHR-BP (N=44)				PBC (N=42)			
timebin	1	2	3	4	1	2	3	4	1	2	3	4
Accuracy, mean (SD)	0.79 (0.12)	0.93 (0.08)	0.96 (0.04)	0.92 (0.06)	0.80 (0.11)	0.95 (0.06)	0.97 (0.04)	0.94 (0.05)	0.80 (0.09)	0.95 (0.05)	0.96 (0.05)	0.94 (0.06)
Mean RT, mean (SD)	422.17 (48.70)	525.23 (54.28)	601.22 (63.20)	739.36 (75.08)	431.18 (48.24)	532.26 (48.17)	603.91 (52.78)	739.61 (61.87)	415.17 (33.94)	509.28 (36.40)	575.12 (42.97)	698.19 (59.11)

Abbreviations: FHR-BP, familial high-risk for bipolar disorder; FHR-SZ, familial high-risk for schizophrenia; N, number of participants; PBC, population-based control; RT, reaction time; SD, standard deviation.

eTable 4. Amplitudes of N200, P3b, and LRP by familial high-risk groups

	FHR-SZ (N=57)	FHR-BD (N=44)	PBC (N=39)
	Mean (SD)	Mean (SD)	Mean (SD)
N200 mean amplitude (μV)			
Congruent	-3.05 (2.52)	-3.51 (2.46)	-3.58 (2.87)
Incongruent	-3.97 (2.53)	-3.90 (2.70)	-4.08 (2.87)
P3b mean amplitude (μV)			
Congruent	3.47 (3.16)	4.28 (2.87)	5.52 (3.18)
Incongruent	3.37 (3.33)	4.08 (2.96)	6.22 (3.61)
LRP peak-to-peak amplitude (μV)			
Congruent	2.04 (1.51)	2.34 (1.87)	2.14 (1.56)
Incongruent	3.47 (3.10)	4.12 (3.37)	2.54 (4.87)

Abbreviations: FHR-BP, familial high-risk for bipolar disorder; FHR-SZ, familial high-risk for schizophrenia; LRP, lateralized readiness potential; N, number of participants; PBC, population-based control; SD, standard deviation; μV, microvolt.

eTable 5. Amplitudes of P2 by familial high-risk groups (post hoc analysis)

	FHR-SZ (N=57)	FHR-BD (N=44)	PBC (N=39)
	Mean (SD)	Mean (SD)	Mean (SD)
P2 mean amplitude (μV)			
Congruent	2.10 (3.04)	3.09 (2.53)	3.99 (3.23)
Incongruent	1.17 (3.11)	1.87 (2.43)	3.74 (3.64)

Abbreviations: FHR-BP, familial high-risk for bipolar disorder; FHR-SZ, familial high-risk for schizophrenia; N, number of participants; PBC, population-based control; SD, standard deviation; μV, microvolt.

eTable 6. Correlations between ERP and clinical variables by familial high-risk groups

	Children (N=143)			
	Mean amplitude N200		Mean amplitude P3b	
	Con.	Incon.	Con.	Incon.
CBCL - total score, r_s (p)	0.011 (0.903)	-0.028 (0.750)	-0.061 (0.480)	-0.071 (0.412)
ADHD-RS (only ADHD; not conduct disorder), r_s (p)	0.057 (0.504)	0.50 (0.557)	-0.098 (0.254)	-0.118 (0.167)

Abbreviations: ADHD-RS, Attention Deficit/Hyperactive Disorder-Rating Scale; CBCL, Child Behavior Checklist; Con., congruent trials; FHR-BP, familial high-risk for bipolar disorder; FHR-SZ, familial high-risk for schizophrenia; Incon., incongruent trials; N, number of participants; PBC, population-based control; r_s , Spearman's correlation.

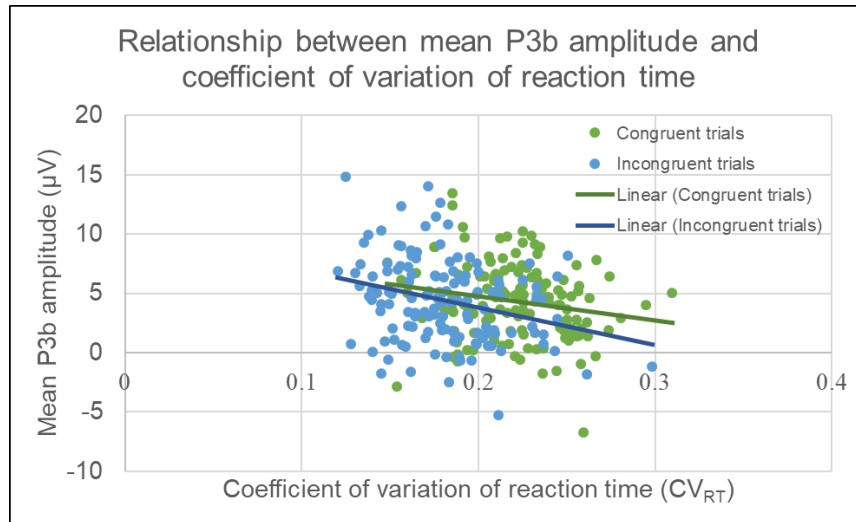
eTable 7. Correlations between ERP and clinical variables by familial high-risk groups

	FHR-SZ (N=57)				FHR-BP (N=44)				PBC (N=39)			
	Mean amplitude N200		Mean amplitude P3b		Mean amplitude N200		Mean amplitude P3b		Mean amplitude N200		Mean amplitude P3b	
	Con.	Incon.	Con.	Incon.	Con.	Incon.	Con.	Incon.	Con.	Incon.	Con.	Incon.
CBCL - total score, r_s (p)	-0.163 (0.235)	-0.189 (0.166)	0.067 (0.626)	0.084 (0.540)	0.135 (0.389)	-0.017 (0.912)	0.023 (0.882)	0.056 (0.720)	0.122 (0.464)	0.137 (0.411)	-0.118 (0.479)	-0.138 (0.408)
ADHD-RS (only ADHD; not conduct disorder), r_s (p)	-0.167 (0.220)	-0.135 (0.322)	0.018 (0.894)	0.047 (0.728)	0.272 (0.077)	0.171 (0.273)	0.084 (0.593)	0.102 (0.513)	0.194 (0.237)	0.186 (0.256)	-0.272 (0.094)	-0.352* (0.028)

Abbreviations: ADHD-RS, Attention Deficit/Hyperactive Disorder-Rating Scale; CBCL, Child Behavior Checklist; Con., congruent trials; FHR-BP, familial high-risk for bipolar disorder; FHR-SZ, familial high-risk for schizophrenia; Incon., incongruent trials; N, number of participants; PBC, population-based control; r_s , Spearman's correlation.

Online-Only Figures

eFigure 1. Relationship between mean P3b amplitude and CV_{RT} (whole group N=140).



Negative correlations between mean P3b amplitude and coefficient of variation of reaction time (CV_{RT}) for congruent trials ($r=-0.185$, $p=0.029$) and incongruent trials ($r=-0.284$, $p=0.001$) for the whole group. Abbreviations: CV_{RT} , Coefficient of variation of reaction time; μV , microvolt.

Appendix 3: Development of visual attention from age 7 to age 12 in children with familial high risk for schizophrenia or bipolar disorder

Development of visual attention from age 7 to age 12 in children with familial high risk for schizophrenia or bipolar disorder

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1 Abstract

2 Background. Children with familial high risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP) are
3 at increased risk of developing similar disorders and show cognitive deficits during childhood. The aim of
4 this paper is to investigate visual attention and its developmental trajectories in children with FHR-SZ and
5 with FHR-BP to increase our knowledge about potential cognitive endophenotypes of these two disorders.

6 Methods. We included 133 12-year-old children with FHR-SZ and with FHR-BP and population-based
7 control children to investigate visual attention as well as we compared the performance of a smaller
8 subsample (N=89) between age 7 and age 12, as part of the Danish High Risk and Resilience Study. We used
9 the TVA-based whole report paradigm, based on the Bundesen's Theory of Visual Attention (TVA) to
10 investigate visual attention.

11 Results. We found no attentional deficits at age 12 between the groups. Children with FHR-SZ that showed
12 deficits in visual processing speed at age 7 improved to a level that was not significantly different from
13 controls at age 12. Lastly, all children improved over time.

14 Conclusions. Children with FHR-SZ did not show developmental deficits or lags and, together with children
15 with FHR-BP, they develop similarly to control children between age 7 to age 12 on visual attention. This
16 emphasizes the potential of beneficial neuroplastic changes in cognitive deficits found at younger ages in
17 children with FHR-SZ. It also highlights the importance of identifying and characterizing cognitive
18 developmental trajectories of high-risk children and provides hope that visual attention may develop
19 appropriately in these groups.

20

21 Introduction

22 Cognitive dysfunction is common in individuals with schizophrenia (SZ) and bipolar disorder (BP) (Bora,
23 2016) and is often present in both first-episode (Bora and Pantelis, 2015) and chronic (Krabbendam *et al.*,
24 2005) phases of the disorders, as well as prior to the illness onset supporting the neurodevelopmental
25 hypothesis (Insel, 2010, Rapoport *et al.*, 2012). More pronounced cognitive deficits are reported in
26 individuals prior to and after the onset of SZ compared to BP (Bora, 2016). Cognitive deficits may represent
27 endophenotypes for SZ and BP and may be clinically relevant for identifying individuals at risk for the
28 disorders (Agnew-Blais and Seidman, 2013, Hemager *et al.*, 2018, Miskowiak *et al.*, 2017). Children with
29 familial high-risk for schizophrenia (FHR-SZ) and children with familial high-risk for BP (FHR-BP) are at
30 risk for developing both disorders (Rasic *et al.*, 2014). FHR studies are thus useful for studying potential
31 vulnerability markers for later transition to illness as well as investigating resilience factors in those
32 individuals that do not develop the disorder.

33 Children with FHR-SZ consistently show, compared with community-based control children, lower verbal
34 memory (de la Serna *et al.*, 2017, Sanchez-Gutierrez *et al.*, 2019), working memory (Davalos *et al.*, 2004, de
35 la Serna *et al.*, 2017, Hemager *et al.*, 2018, Sanchez-Gutierrez *et al.*, 2019), speed of information processing
36 (Hemager *et al.*, 2018, Sanchez-Gutierrez *et al.*, 2019), visual memory (de la Serna *et al.*, 2017, Sanchez-
37 Gutierrez *et al.*, 2019), and visuospatial abilities (Hemager *et al.*, 2018, Seidman *et al.*, 2006). However, the
38 evidence of cognitive deficits in children with FHR-BP is less consistent; some studies reported deficits in
39 processing speed (Bora *et al.*, 2019, de la Serna *et al.*, 2017, Hemager *et al.*, 2019), verbal fluency (Bora *et al.*,
40 2019), visual memory (Bora *et al.*, 2019, de la Serna *et al.*, 2017), and working memory (Bora *et al.*,
41 2019, Klimes-Dougan *et al.*, 2006), whilst some did not find deficits (Diwadkar *et al.*, 2011, Hemager *et al.*,
42 2018). Although the evidence is stronger for SZ, it seems that individuals with a predisposition to developing
43 SZ, as well as BP, show cognitive deficits (Bora *et al.*, 2014, Bora and Ozerdem, 2017, Hemager *et al.*,
44 2018).

45 However, the majority of the above-mentioned studies often used broad, extensive cognitive test batteries
46 assessing a variety of neuropsychological functions across domains simultaneously, without the possibility of
47 disentangling specific processes within a cognitive domain. The TVA-based whole report (Vangkilde *et al.*,
48 2011) on the other hand, based on the theoretical framework provided by the theory of visual attention
49 (TVA) (Bundesen, 1990), focuses specifically on aspects of visual attention. In fact, the TVA-based whole
50 report does not rely on speeded reaction times, making it a suitable test for children with FHR (Burton *et al.*,
51 2016, Burton *et al.*, 2017). The test's capacity to distinguish between distinct aspects of visual attention at
52 the individual level could potentially establish specific attentional profiles in children with FHR-SZ and
53 FHR-BP (Diwadkar *et al.*, 2011, Hemager *et al.*, 2018).

54 The TVA-based whole report has been used to characterize attentional profiles in several disorders such as
 55 dyslexia (Bogon *et al.*, 2014), ADHD (Low *et al.*, 2018, McAvinue *et al.*, 2015), and neurodegenerative
 56 disorders. Using computer-based testing, three parameters of visual attention are estimated that describe the
 57 attentional capabilities of each participant. First, the parameter visual processing speed (C) is defined as the
 58 speed with which visual information is processed and is measured in items (e.g., letters or numbers)
 59 processed per second. Second, items are encoded into the visual short-term memory (VSTM), which has a
 60 maximum storage capacity of K items (K). Third, the threshold of conscious visual perception (t_0) is the
 61 shortest time at which items are still consciously perceived. Lastly, in addition to the estimated parameters,
 62 the error rate is defined as the probability that a reported letter was incorrect. The TVA-based whole report
 63 showed good internal and test-retest reliability (Habekost, 2015, Habekost and Starrfelt, 2009) and
 64 interestingly, intelligence does not seem to affect the parameters K and C in a non-clinical adult population
 65 (Finke *et al.*, 2005), in normally developing young children (Caspersen, 2016) nor in children with FHR-SZ
 66 or FHR-BP (Hemager *et al.*, 2019).

67 The development of cognitive trajectories over time in children at FHR-SZ and FHR-BP lacks valid
 68 observations, even though imperative for distinguishing between developmental deterioration (worsening),
 69 developmental deficit (stable), developmental lag (slower growth) (Reichenberg *et al.*, 2010), and
 70 developmental delay (catching up) (Dickson *et al.*, 2018) (see Figure 1). A longitudinal study with three
 71 timepoints and including children with antecedents of SZ, a family history of SZ and typically developing
 72 children reported stable deficits for verbal working memory in youth with FHR-SZ relative to typically
 73 developing youth, between the ages of 9 and 16 (Dickson *et al.*, 2018). Interestingly, deficits in executive
 74 functioning (only on inhibition/switching and not on accuracy/switching or fluency), general intelligence
 75 (matrix reasoning) and word reading at age 9 were caught up at age 13 in children with FHR-SZ, i.e. an
 76 example of developmental delay. Importantly, participants did not show a developmental deterioration on
 77 any of the cognitive subtests and emphasizing the importance of differentiating between specific cognitive
 78 impairments (Dickson *et al.*, 2018). Another study retrospectively investigated cognitive development
 79 between age 7 and 13 in individuals that later developed SZ or recurrent depression or none of these
 80 disorders (Reichenberg *et al.*, 2010). Youth who later developed SZ showed, relative to healthy controls,
 81 developmental deficits on tests indexing verbal and visual knowledge acquisition, reasoning, and
 82 conceptualization as well as developmental lags (slower growth) in processing speed, attention, visuospatial
 83 memory, and working memory, which was not found for those who later developed recurrent depression
 84 (Reichenberg *et al.*, 2010). Partially in line with these findings, the Avon Longitudinal Study of Parents and
 85 Children (ALSPAC) found developmental lags between 8 and 20 years in processing speed, working
 86 memory, and attention in those individuals that later developed a psychotic disorder, and static deficits in
 87 language and visuospatial abilities. This finding was unique to psychotic disorders, as these cognitive deficits
 88 were not present in individuals that later developed depression or psychotic experiences (subclinical

psychotic symptoms) (Mollon *et al.*, 2018). Taken together, these findings contribute to the potential value of identifying separable developmental trajectories of cognitive domains in SZ and typically developing children. In comparison, knowledge is missing for the developmental trajectories in children with FHR-BP.

The overall purpose of this study was to assess the developmental trajectories of visual attention in children with a familial risk of severe mental disorders during a developmental period. We included 12-year-old children with FHR-SZ, FHR-BP, and children not at FHR (control group) and compared their visual attention to their performance at age 7 (Hemager *et al.*, 2019). At age 12, we expected that children with FHR-SZ and with FHR-BP exhibit deficits, relative to control children, on visual processing speed (C), with more pronounced deficits in children with FHR-SZ than in children with FHR-BP. Second, following the results of age 7 (Hemager *et al.*, 2019), we hypothesized that children with FHR-SZ would exhibit developmental lags (meaning a slower growth relative to control children) or developmental deficits (meaning stable deficits) for visual processing speed. Based on the little evidence that exists for BP, we expected developmental deficits on visual processing speed for FHR-BP. We expected that the FHR groups would not develop differently from each other. To our knowledge, this is the first study including a group of FHR-SZ and FHR-BP measuring visual attention at multiple time-points within individuals, using the same, unspeeded visual attention test. By investigating the individual trajectories, as well as the group trajectories, we aimed to contribute to the existing literature of premorbid cognitive functioning and development with the identification of potentially clinically relevant vulnerability markers that could help to identify individuals at risk.

Methods

Participants

The current study is part of the Danish High Risk and Resilience Study - VIA 11 (described elsewhere (Thorup *et al.*, 2018)). The VIA 11 study is the first follow-up after the VIA 7 study, a prospective cohort study initiated in 2013 of children with FHR-SZ or FHR-BP and population-based control children (PBC). Children were recruited through the Danish Civil Registration System (Pedersen *et al.*, 2006) and the Danish Psychiatric Central Register (Mors *et al.*, 2011) based on having a parent diagnosed with either schizophrenia spectrum psychosis, defined as schizophrenia, delusional disorder or schizoaffective disorder (ICD 10-codes: F20, F22, F25 or ICD 8-codes: 295, 297, 298.29, 298.39, 298.89, 298.99), or bipolar disorder (ICD 10 codes F30 or F31 or ICD 8-codes 296.19 or 296.39), or none of these two disorders. Children of parents with neither a diagnosis of SZ nor BP are referred to as PBC children, who were matched on age, sex, and municipality to children of parents with SZ. Children of parents with BP were not matched but did not differ in age or sex at baseline (Christiani *et al.*, 2019, Ellersgaard *et al.*, 2018). The Danish Data Protection Agency approved the project and the Danish for Health Research Ethics received the project

guidelines, but their approval was not required as the study did not include any intervention. Legal guardians of the children gave written informed consent for the children's participation in the study. Children were required to be born and living in Denmark and have Danish as their first language.

Design of the study

The TVA-based whole report is part of a large clinical and neurocognitive assessment battery included in the VIA 7 study and the VIA 11 study (Thorup *et al.*, 2018, Thorup *et al.*, 2015). First, this study provides cross-sectional data analyses of 133 12-year-old children that were part of the VIA 11 study. Second, of these 133 children, 89 children had performed the TVA-based whole report in the VIA 7 study (Hemager *et al.*, 2019), hence, we compared their performance between age 7 and age 12. Assessors were trained and blinded to the risk status of the child. Due to the ongoing status of the VIA 11 study, not all data of clinical and neurocognitive assessments is available yet.

Assessment procedure

The TVA-based whole report utilized E-Prime 2 software. Participants were placed in front of a computer (viewing distance approx. 65 cm) in a comfortable and stationary chair in a dark room with indirect lighting. The assessor explained the task verbally, supported by two blocks of eight practice trials, followed by three examination blocks of 30 trials each. Participants were instructed to fixate on a central red cross. Then, six red digits, chosen from a predefined set of numbers [0, 1, 2, 3, 4, 5, 6, 7, 8, 9] (size 2 cm x 3.5 cm), were presented on a black background for one of the six (or seven) exposure durations ((10 ms,) 20 ms, 30 ms, 50 ms, 80 ms, 140 ms, and 200 ms) and were then masked by pattern masks for 500 ms. Digits were only presented once per trial and all trials were presented in a fixed-order between participants (see Figure 2a). Participants were instructed to, in an unspeeded manner, name as many digits as possible but refrain from pure guessing. Digits were entered via the keyboard by the assessor. Performance reports followed each block, informing participants of their accuracy rate as they were encouraged to keep their accuracy rate between a range of 80 – 90% correct. The TVA-based test took approximately 18 minutes.

Notably, the reason for either six or seven exposure durations is that we evaluated the test performance after the first 20 children included in the VIA 11 study. We found that the lowest exposure duration was not low enough for precise parameter estimation. Therefore, to capture the entire performance range from floor to ceiling and to ensure optimal data for parameter estimation, we added the 10 ms exposure duration to the task. No significant differences were present for any attention outcomes between the first 20 children and the ensuing participants.

156 Computational modelling

157 The TVA-based whole report is a mathematical model that is based on the biased competition model
158 (Bundesen *et al.*, 2005). This model describes the competition among objects in the visual field in which
159 attention determines which visual stimuli will win a race to become encoded into a limited capacity short-
160 term memory. The mathematical equations that the TVA-based whole report is based on, allows us to
161 estimate independent parameters of visual attention which can be tested between patient groups or under
162 certain conditions (Kyllingsbæk, 2006).

163 The computational framework of the TVA-based whole report provides three estimates of parameters of
164 visual attention. The ability of participants to report as many digits as they possible can, is assessed as a
165 function of the array exposure durations. The likelihood of reporting digits at each exposure duration is
166 modelled by an exponential growth function. The growth parameter reflects the rate at which digits can be
167 processed, also explained as the visual processing speed, C . The asymptote shows the maximum number of
168 digits that can be stored; the capacity of visual short-term memory, K . Finally, the lowest exposure duration
169 at which stimuli are consciously perceived is the threshold for conscious visual perception, t_0 . Each
170 participant's observed performance goes through the TVA model fitting, which then provides the estimates
171 for C , K , and t_0 (see Figure 2b for an example). Specifically, for each child, the observed performance was
172 characterized by a computational model with 7 degrees of freedom (df) comprising: K (5 df), C (1 df), and t_0
173 (1 df). The reported K values is the expected K given a particular probability distribution (i.e., the
174 probabilities that $K = 1, 2, \dots, 5$), where $K = 6$ accounts for the remaining probability up to a value of 1. For
175 any model fits where $t_0 < 0$, we refitted the model with $t_0 = 0$.

176

177 Statistical analyses

178 Demographic, clinical, and neurocognitive characteristics were compared between the three groups using
179 parametric (ANOVA) and non-parametric (chi-square) analyses when appropriate.

180 For the cross-sectional analyses, we checked skewness and outliers of all variables visually through
181 histograms, Q-Q plots, and using Shapiro-Wilk tests. To assure that we did not have a test-retest effect in
182 part of the children at age 12 (as some children had done the task in the VIA 7 study and others did not), we
183 compared the performance on the TVA-based whole report between children that did the test for the first
184 time and the second time in the VIA 11 study. To compare the children's performances on the TVA-based
185 whole report, we did a multivariate analysis of variance (MANOVA) on the four primary outcome measures
186 K , C , t_0 , and error rate. We adjusted for multiple comparisons using Scheffé post hoc tests. The level of
187 statistical significance was set at 0.05.

188 To analyze the follow-up data of the performance on the TVA-based whole report, we used a repeated
189 measure (RM-)ANOVA with each of the four TVA measures (K , C , t_0 , error rate) as dependent variable,
190 group (FHR-SZ, FHR-BP, PBC) as between-subject factor, and test session (VIA 7, VIA 11) as the within-
191 subject factor. We conducted post hoc analyses of within-group differences of performance on the two test
192 sessions with paired sampled t -tests. Furthermore, we compared the characteristics and VIA 7-test
193 performance of children that dropped out of the study to those that remained in the study to investigate
194 potential effects of attrition bias (Ahern and Le Brocque, 2016). Finally, we checked whether the parameter
195 estimates of the TVA-based whole report were associated between the two test sessions with a Pearson's
196 correlations test.

197 Age, sex, and, for the follow-up analyses, time between the two test sessions, were accepted as covariates if
198 they reached the accepted level of significance ($p < 0.05$). All statistical analyses were conducted in SPSS
199 (version 25.0).

200

201 Results

202 Cross-sectional analyses

203 Demographic characteristics

204 Data of 133 participants were included; 50 children with FHR-SZ, 40 children with FHR-BP, and 43 PBC
205 children. No participants were excluded due to an insufficient amount of trials or a too high error rate ($>$
206 35%). Participants across FHR groups did not differ regarding age or sex. The groups differed on daily level
207 of functioning and the hyperactivity-impulsivity subscale (Table 1).

208

209 Performance on the TVA-based whole report

210 The MANOVA showed no significant effect ($F(8,256)=0.945$, $p=0.480$) of FHR group on the four primary
211 TVA outcomes (K , C , t_0 , and error rate) (see Figure 4). Due to a significant correlation of sex with t_0
212 (Pearson's r : $p < 0.001$), we conducted an ANCOVA with sex as covariate, but we found no interaction effect
213 between sex and FHR group on t_0 ($F(2,127)=0.835$, $p=0.436$). The exact values of the cross-sectional
214 analysis can be found in supplementary material 1.

215

216 Follow-up analyses

217 Demographic characteristics

218 Eighty-nine children were included in the follow-up analyses; 32 children with FHR-SZ, 22 children with
219 FHR-BP, and 35 PBC children. No statistical differences between the groups were found in age, sex, and

inter-session interval (Table 2). Forty-four children of the original subgroup that were assessed in the VIA 7 study did not complete the TVA-based whole report in the VIA 11 study (24 FHR-SZ, 10 FHR-BP, and 10 PBC). Reasons for drop out are stated in Figure 3. Characteristics and test performance of the drop-out children compared to the non-drop-out children of the VIA 7 study can be found in supplementary material 2.

Performance on the TVA-based whole report

Our observed-cases RM-ANOVA with K as dependent variable revealed a main effect of ‘Session’ in the predicted direction ($F(1,86)=141.071$, $p<0.001$) and an interaction effect of ‘Session x group’ ($F(2,86)=3.942$, $p=0.023$), but no main effect of ‘group’ ($F(2,86)=0.283$, $p=0.754$). Post-hoc multiple comparisons showed that children with FHR-BP improved more than children with FHR-SZ ($p=0.023$); no differences were found relative to PBC children. The RM-ANOVA with C as dependent variable revealed a main effect of ‘Session’ in the predicted direction ($F(1,86)=144.159$, $p<0.001$) but no main effect of ‘group’ ($F(2,86)=0.673$, $p=0.513$) nor an interaction effect ($F(2,86)=1.353$, $p=0.264$). The RM-ANOVA with t_0 as dependent variable revealed a main effect of ‘Session’ in the predicted direction ($F(1,86)=54.410$, $p<0.001$) but no main effect of ‘group’ ($F(2,86)=1.052$, $p=0.354$) nor an interaction effect ($F(2,86)=1.400$, $p=0.252$). Finally, the RM-ANOVA with Error rate as dependent variable revealed, as predicted, no main effect of ‘Session’ ($F(1,86)=0.561$, $p=0.456$), ‘group’ ($F(2,86)=0.117$, $p=0.888$), nor an interaction effect ($F(2,86)=1.447$, $p=0.241$) (Figure 4).

Paired t-tests showed that K and C improved over time for all groups, t_0 decreased over time for all groups, and the error rate did not change over time (see supplementary material 3 for the exact values).

As reported by Hemager et al. (2019), the sample of the VIA 7 study ($N=133$) showed deficits in C in both FHR groups. To check whether these deficits remained in our smaller follow-up sample of 89 children, we tested post hoc the performance at age 7 of these 89 children. In line with the prior publication, the MANOVA confirmed the group difference ($F(8,256)=3.052$, $p=0.007$), such that children with FHR-SZ had a significantly lower visual processing speed (C) than PBC children ($p=0.004$). However, in contrast to the prior report, no difference was found between children with FHR-BP and PBC children, probably due to the reduced sample size ($N=22$) and less power (see supplementary material 4).

To investigate the stability of the parameters across the two sessions, we investigated intra-parameter correlations for between the two test sessions. All three parameters showed significant, moderate correlations (K : $r(87)=0.43$, $p<0.001$; C : $r(87)=0.39$, $p<0.001$; and t_0 : $r(87)=0.37$, $p<0.001$), suggesting the stability of the functions in the children. The correlation of error rate was not significant.

Discussion

This study investigated distinct aspects of visual attention in children with FHR-SZ, children with FHR-BP, and control children at age 12 as well as the developmental trajectories of visual attention in a subsample between age 7 and age 12. First, performance on visual attention at age 12 was comparable between the three groups, which was based on the capacity of visual short-term memory (K), visual processing speed (C), and their threshold of conscious visual perception (t_0). Second, follow-up results revealed that all three groups improved significantly from age 7 up to 12 on these aspects of visual attention. The magnitude of improvement differed between the two FHR groups on visual short-term memory, indicating that children with FHR-BP improved more than children with FHR-SZ, but not compared to controls. No significant difference was found in the magnitude of growth on visual processing speed or the threshold of conscious visual perception. As described by Hemager et al. (2019), 7-year-old children with FHR-SZ or with FHR-BP exhibited deficits in visual processing speed relative to control children. This deficit was greater for the FHR-SZ group compared to the FHR-BP group ($d = 0.75$ versus $d = 0.54$). As our follow-up subsample was smaller than the original group of Hemager et al. (2019), we checked whether their results remained in our subsample. Results showed that the deficits in visual processing speed at age 7 in children with FHR-SZ remained in the subsample, and follow-up results showed that these deficits disappeared at age 12. The small sample size of children with FHR-BP ($N=22$), however, may have caused that deficits in visual processing speed were not different from controls at baseline. Therefore, children with FHR-SZ showed an improvement on visual processing speed to a level that it was not significantly different from controls at age 12, emphasizing the absence of a developmental deficit.

This study advances knowledge in multiple ways. First, a surprising finding was that deficits in visual processing speed at age 7 (Hemager *et al.*, 2019) were unnoticeable at age 12. The cohort may have an attrition bias in the VIA 11 study as compared to the VIA 7 study (Ahern and Le Brocque, 2016). Children and their parents knew what participation entailed, which may have led to a negative decision, although only approximately 10% of the families declined to participate in the VIA 11 study. This is more likely to happen for families that are more affected by the disorders, which is supported by the finding that the group of children with FHR-BP that dropped out had a significantly lower visual processing speed compared to those children with FHR-BP that remained in the study. However, it should be stressed that this was only the case for the FHR-BP group (not within the FHR-SZ group) and only on one of the three parameters, which, assumingly, only has a small effect. Due to this finding, we checked post hoc whether deficits in visual processing speed were present at baseline in the children that participated later in the VIA 11 study. Deficits were still present in the children with FHR-SZ at baseline, however, not in children with FHR-BP. The effect size of this deficit at baseline ($d = 0.54$) was smaller in children with FHR-BP, hence, the deficit was more sensitive to the selection of the sample. Taken together, deficits on visual attention in children with FHR-SZ

287 are not static and stable during development, which is useful for the development of novel interventions such
288 as cognitive remediation.

289 Second, two previous studies found deficits in processing speed in young individuals that would later
290 develop a psychotic disorder (Mollon *et al.*, 2018) or SZ (Reichenberg *et al.*, 2010) and showed a lower rate
291 of growth over time for processing speed in these individuals. These retrospective studies included only
292 individuals, who later developed a psychotic disorder or SZ, whereas our study included children of which
293 the majority will not develop these disorders (Rasic *et al.*, 2014). Those children in our study, who will later
294 manifest with a serious disorder, thus only account for a small part of the respective groups potentially
295 obscuring the effects of later psychopathology. Another contributing factor could be that we addressed visual
296 processing speed, compared to processing speed in the digit symbol coding test, used by Reichenberg *et al.*
297 (2010) and Mollon *et al.* (2018). The digit symbol coding test measures the speed and efficiency with which
298 different cognitive functions can be executed and retained in short-term/working memory, i.e. perceptual
299 scanning, matching, switching, and writing operations. In the case of the TVA-based whole report, visual
300 processing speed is measured without taking into account writing or motor abilities, which have been found
301 to be impaired in children with FHR-SZ (Burton *et al.*, 2017). These two forms of processing speed may thus
302 rely on different underlying neural mechanisms.

303 Third, our findings demonstrate an intact ability of visual short-term memory in children with FHR-SZ and
304 FHR-BP. Other studies reported deficits in visual memory in children with FHR-SZ and FHR-BP (de la
305 Serna *et al.*, 2016, Hemager *et al.*, 2018). Visual memory tests used in those studies may also rely on active
306 manipulation of working memory content whereas the visual short-term memory parameter derived from the
307 TVA-based whole report rather relies on the passive maintenance of visual information in short-term
308 memory.

309 Strengths of this study are the follow-up design including a group, with a narrow age range, of children with
310 FHR-SZ or FHR-BP, the blinding status of the clinical assessors, the stability of the cognitive functions
311 measured by the task (shown by the test-retest correlations), and the ability to disentangle and sensitively
312 measure distinct attentional processes unconfounded by motor abilities. Nonetheless, limitations also exist.
313 First, we had a high rate (33%) of missing data and therefore considered the option of imputation. Reasons
314 against imputation included the high rate of missing data as well as evidence for data missing not at random
315 and the lack of available auxiliary variables that could be used for imputation (Jelicic *et al.*, 2009, Nicholson
316 *et al.*, 2016). Of the total drop-out group (N=44), 47% did not participate in the entire project, for which we
317 do not know the reason. 25% did not participate on the TVA-test day, possibly caused by the other
318 (neuroimaging) assessments that were planned that day. Another 15% was not assessed due to the lack of
319 time or energy and 13% was invited at the other research site (in Aarhus). Therefore, to rule out that our
320 findings were based on the attrition bias, we performed the drop-out analysis as well as the comparison of the

baseline performance of the children of the follow-up subsample (N=89). Second, the linearity of the developmental trajectories of visual attention shown in our figures is unlikely. However, limited knowledge is currently available about these, more likely, non-linear pathways and therefore we need follow-up studies better characterize the exact shape of the trajectories. Such studies may enable to discriminate children with FHR that will develop typically from those that will not. Further, in the current study we used a whole-report, however, a partial-report design in which *selective* attention can be directly assessed in addition to the parameters described in this study may be interesting for future studies. Specifically, this would enable the estimation of two additional parameters; α which is a measure of top-down-controlled selectivity and w_{index} which indicates the lateralized allocation of attention (see (Vangkilde *et al.*, 2011)).

Our findings reveal that, at age 12, children with FHR-SZ or FHR-BP perform similarly to children of parents without these disorders in a visual attention task. Also, the performance of visual attention in these children improves at the same rate comparing age 7 with 12, which indicates that visual attention does not follow a developmental lag or deficit trajectory in children with FHR-SZ or FHR-BP.

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Conflicts of interest

HRS has received honoraria as speaker from Sanofi Genzyme, Denmark and Novartis, Denmark, as consultant from Sanofi Genzyme, Denmark and as senior editor (NeuroImage) and editor-in-chief (Neuroimage Clinical) from Elsevier Publishers, Amsterdam, The Netherlands. HRS has also received royalties as book editor from Springer Publishers, Stuttgart, Germany and Gyldendahl Publishers, Copenhagen, Denmark.

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Table 1. Characteristics of 133 12-year-old children from the VIA 11 study across three groups of FHR-SZ, FHR-BP, and PBC.

Demographics		FHR-SZ (N=50)		FHR-BP (N=43)		PBC (N=40)	Statistics (p-value)	FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
Age, years (s.d.)*		12.14 (0.23)		12.20 (0.29)		12.21 (0.31)	0.388 ^a			
Male, N (%)		22 (44)		22 (55)		20 (46.5)	0.565 ^b			
Clinical characteristics	N		N		N					
IQ (RIST), mean (s.d.)	50	97.78 (10.02)	40	100.15 (7.77)	42	98.40 (8.92)	0.452 ^a			
CBCL total, mean (s.d.)	48	19.17 (17.69)	40	16.15 (13.73)	42	11.62 (11.59)	0.193 ^c			
CBCL int, mean (s.d.)	48	6.23 (5.59)	40	5.38 (4.67)	42	4.12 (4.44)	0.116 ^c			
CBCL ext, mean (s.d.)	48	4.48 (6.79)	40	3.70 (4.18)	42	2.40 (3.26)	0.068 ^c			
ADHD-RS total, mean (s.d.)	49	10.57 (9.90)	40	7.70 (5.12)	43	6.72 (5.66)	0.536 ^c			
ADHD-RS hyper-impuls, mean (s.d.)	49	4.59 (4.79)	40	3.48 (3.04)	43	2.51 (3.13)	0.021 ^c	0.009 ^d	0.040 ^d	0.514 ^d
ADHD-RS inattent, mean (s.d.)	49	5.98 (5.75)	40	4.23 (3.64)	43	4.21 (3.32)	0.241 ^c			
CGAS, mean (s.d.)	47	67.30 (15.36)	40	70.93 (13.95)	42	75.67 (13.60)	0.018 ^c	0.006 ^d	0.079 ^d	0.298 ^d

^a One-way ANOVA; ^b Pearson Chi-Square test of independence; ^c Kruskal-Wallis test; ^d Mann-Whitney U test; Abbreviations: FHR-SZ, familial high-risk for schizophrenia; FHR-BP, familial high-risk for bipolar disorder; PBC, population-based children; s.d., standard deviation; N, number; RIST, Reynold's Intellectual Screening Test; CBCL, Childhood Behavior Checklist; ADHD-RS, Attention Deficit Hyperactivity Disorder – Rating Scale; CGAS, Children's Global Assessment Scale. * The childrens' age is calculated based on actual test date, instead of the date-of-inclusion in the entire project, which could be weeks earlier. Thus, though the project is called the VIA 11 study, the children are often 12 years of age.

Table 2. Characteristics of the follow-up subsample (N=89) that completed the TVA-based whole report test at age 7 and at age 12.

		FHR-SZ (N=32)	FHR-BP (N=22)	PBC (N=35)	Statistics (p-value)	FHR- SZ vs PBC	FHR- BP vs PBC	FHR- SZ vs FHR- BP
Child characteristics								
Male, N (%)		14 (43.8)	11 (50)	17 (48.6)	0.883 ^a			
Age, years (s.d.)	VIA 7 ^c	7.77 (0.18)	7.86 (0.17)	7.74 (0.23)	0.083 ^b			
	VIA 11	12.17 (0.25)	12.30 (0.35)	12.22 (0.30)	0.323 ^b			
Inter-session interval, years (s.d.)*		4.41 (0.19)	4.44 (0.35)	4.49 (0.22)	0.408 ^b			
IQ (RIST), mean (s.d.)	VIA 11	98 (11)	99 (7)	99 (7)	0.742 ^b			
CBCL total, mean (s.d.)	VIA 11	16.07 (15.08)	17.36 (14.83)	11.2 (10.89)	0.264 ^d			
CBCL int, mean (s.d.)	VIA 11	5.37 (5.49)	5.59 (4.81)	4.26 (4.76)	0.392 ^d			
CBCL ext, mean (s.d.)	VIA 11	3.63 (4.93)	4.27 (5.15)	2.09 (2.29)	0.434 ^d			
ADHD-RS total, mean (s.d.)	VIA 11	9.29 (7.29)	7.91 (5.99)	6.43 (5.06)	0.310 ^d			
ADHD-RS hyper-impuls, mean (s.d.)	VIA 11	4.10 (3.90)	3.23 (3.26)	2.43 (2.95)	0.109 ^d			
ADHD-RS inattent, mean (s.d.)	VIA 11	5.19 (4.13)	4.68 (3.93)	4.00 (3.10)	0.623 ^d			
CGAS, mean (s.d.)	VIA 11	72 (14)	68 (11)	76 (13)	0.026 ^d	0.185 ^e	0.005 ^e	0.233 ^e

^a Pearson Chi-Square test of independence; ^b One-way ANOVA; ^c see Hemager et al. (2018); ^d Kruskal-Wallis test; ^e Mann-Whitney U test. Abbreviations: FHR-SZ, familial high-risk for schizophrenia; FHR-BP, familial high-risk for bipolar disorder; PBC, population-based children; s.d., standard deviation; N, number; RIST, Reynold's Intellectual Screening Test; CBCL, Childhood Behavior Checklist; ADHD-RS, Attention Deficit Hyperactivity Disorder – Rating Scale; CGAS, Children's Global Assessment Scale. *Inter-session interval is calculated from the date-of-inclusion in the VIA 7 study up until the TVA-test day.

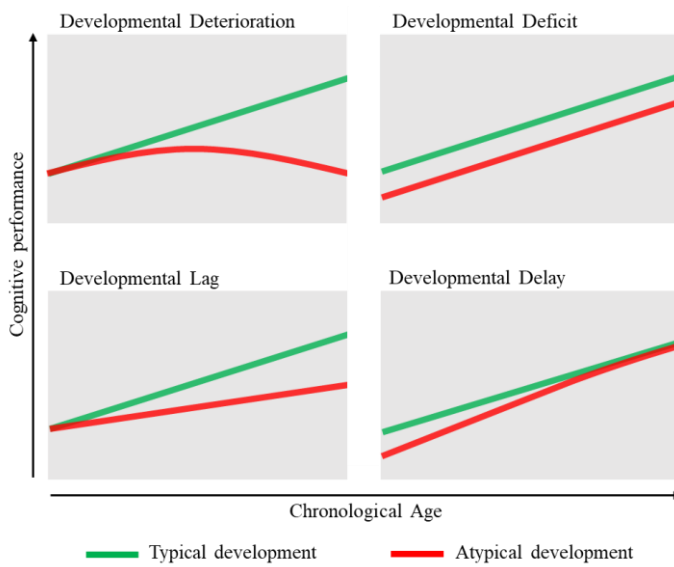


Figure 1. Four theoretical developmental trajectories of cognition described by Reichenberg et al. (2010) and Dickson et al. (2018).

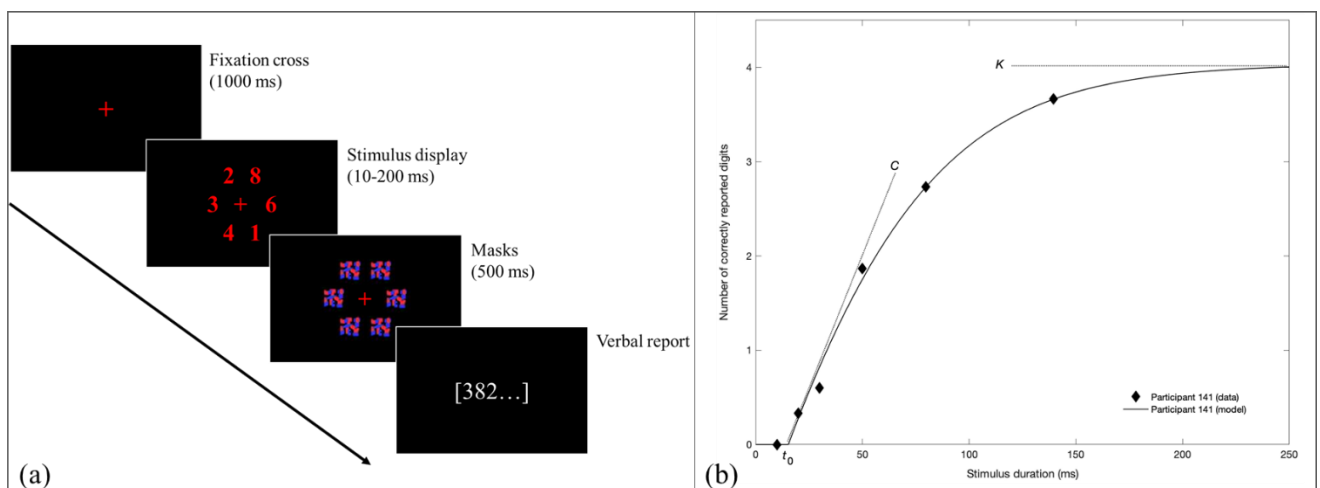


Figure 2. Schematic of the TVA-based whole report paradigm in the VIA 7 and VIA 11 studies (panel a) and the observed performance (filled circles) and fitted model (smooth line) of a representative single participant with familial high-risk for schizophrenia (FHR-SZ) (panel b). The main parameters derived from the paradigm are the perceptual threshold, t_0 , visualized as the point at which performance increases from zero; the visual processing speed, C , indicated by the slope of the curve at t_0 ; and the capacity of visual short-term memory, K , as the asymptote of the curve.

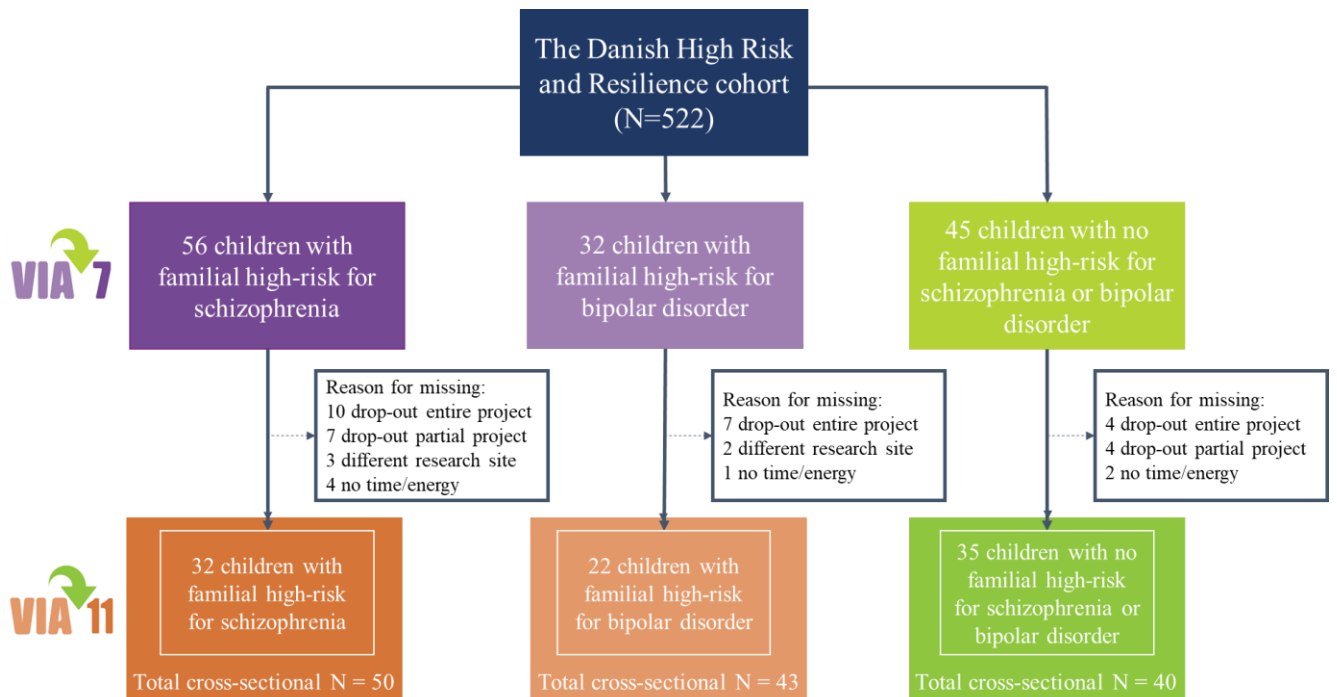


Figure 3. An overview of the number of participants that completed the TVA-based whole report in the VIA 7 and VIA 11 studies. Reasons for missing from the follow-up are (1) drop-out entire project: no participation in the VIA 11 study; (2) drop-out partial project: no participation on the particular TVA-test day; (3) different research site: the research site in Aarhus had no access to the TVA-based task; and (4) no time/energy: test was omitted out of consideration for the child. As additional participants completed the test in the VIA 11 study, the number of total participants for the cross-sectional part is stated for each group.

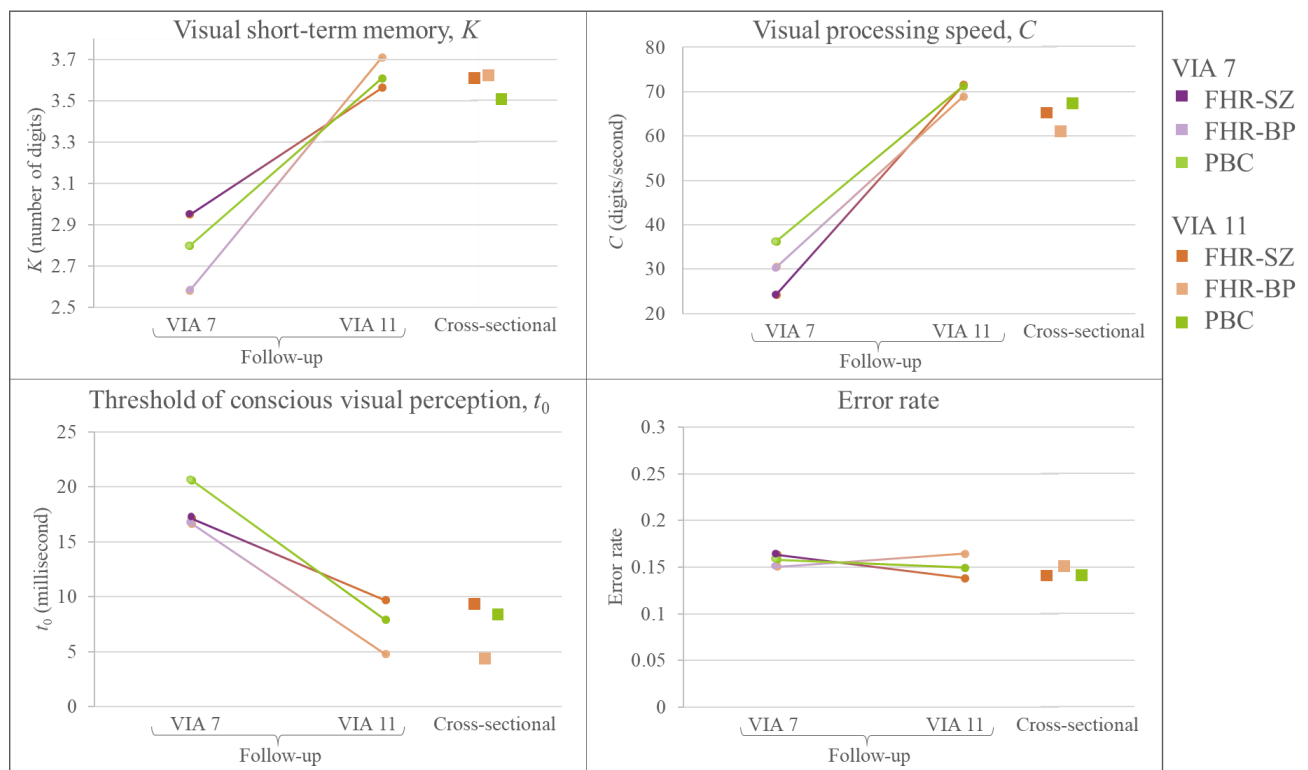


Figure 4. Developmental trajectories of visual short-term memory, processing speed, threshold for conscious visual perception, and error rate among 89 children with FHR-SZ, FHR-BP, and PBC as measured by the TVA-based whole report. For the exact values of the follow-up and cross-sectional analyses, see supplementary material 2 and 3.

Supplementary Material

Supplementary material 1. Cross-sectional results from performance on the TVA-based whole report in 133 12-year-old children with FHR-SZ, FHR-BP, and PBC.

TVA measures	FHR-SZ (N=50)	FHR-BP (N=40)	PBC (N=43)
Visual short-term memory capacity, <i>K</i> (digits), mean (s.d.)	3.61 (0.46)	3.64 (0.51)	3.50 (0.51)
Visual processing speed, <i>C</i> (digits/second), mean (s.d.)	65.12 (30.54)	61.90 (38.32)	67.34 (28.20)
Threshold of visual conscious perception, <i>t</i> ₀ (millisecond), mean (s.d.)	9.50 (7.04)	6.82 (8.18)	8.82 (7.14)
Error rate, mean (s.d.)	0.14 (0.04)	0.15 (0.06)	0.14 (0.06)

Abbreviations: FHR-SZ, familial high-risk for schizophrenia; FHR-BP, familial high-risk for bipolar disorder; PBC, population-based children; s.d., standard deviation; TVA, theory of visual attention; *K*, capacity of visual short-term memory; *C*, visual processing speed; *t*₀, threshold for conscious visual perception; *N*, number of participants.

Supplementary material 2. Characteristics and TVA-performance at age 7 of 44 participants tested in the VIA 7 study but not in the VIA 11 study.

	FHR-SZ			FHR-BP			PBC		
	Drop-out (N=24)	Stay-in (N=32)	Statistics (p-value)	Drop-out (N=10)	Stay-in (N=22)	Statistics (p-value)	Drop-out (N=10)	Stay-in (N=35)	Statistics (p-value)
Child characteristics									
Age, years (s.d.)	7.81 (0.22)	7.77 (0.18)	0.361 ^a	7.79 (0.32)	7.86 (0.17)	0.421 ^a	7.77 (0.14)	7.74 (0.23)	0.638 ^a
Male, N (%)	17 (70.8)	14 (43.8)	0.044 ^b	3 (30.0)	11 (50.0)	0.290 ^b	6 (60.0)	17 (48.6)	0.524 ^b
Psychiatric (axis 1 ^c) disorder at age 7, N (%)	8 (33.3)	7 (21.9)	0.338 ^b	3 (33.3)	4 (18.2)	0.454 ^b	1 (10.0)	3 (8.6)	0.889 ^b
Parameter estimates, mean (s.d.)									
<i>K</i> (maximum span length)	2.60 (0.90)	2.95 (0.91)	0.164 ^a	2.17 (0.68)	2.58 (0.65)	0.109 ^a	2.98 (1.04)	2.80 (0.54)	0.465 ^a
<i>C</i> (digits/second)	25.15 (9.12)	24.24 (11.00)	0.745 ^a	19.98 (9.38)	30.48 (14.15)	0.041 ^{a*}	36.10 (25.07)	36.27 (17.97)	0.981 ^a
<i>t</i> ₀ (millisecond)	13.86 (15.58)	17.15 (9.95)	0.340 ^a	15.72 (17.07)	16.67 (15.94)	0.880 ^a	15.36 (10.79)	20.62 (16.68)	0.354 ^a
Error rate	0.18 (0.11)	0.16 (0.08)	0.533 ^a	0.21 (0.07)	0.15 (0.07)	0.039 ^{a*}	0.19 (0.05)	0.16 (0.08)	0.143 ^a

^a One-way ANOVA; ^b Pearson Chi-Square test for independence; ^c Any axis 1 psychiatric disorder (without elimination disorder, see also Ellersgaard et al. (2018)). FHR-SZ, familial high-risk for schizophrenia; FHR-BP, familial high-risk for bipolar disorder; PBC, population-based children; s.d., standard deviation; TVA, theory of visual attention; *K*, capacity of visual short-term memory; *C*, visual processing speed; *t*₀, threshold for conscious visual perception; *N*, number of participants. * Significant at the 0.05 level.

Supplementary material 3. Follow-up subsample (N=89) with TVA-results at age 7 and at age 12.

Primary TVA outcome measures	FHR-SZ (N=32)			FHR-BP (N=22)			PBC (N=35)		
	VIA 7	VIA 11	Δ^a	VIA 7	VIA 11	Δ^a	VIA 7	VIA 11	Δ^a
Visual short-term memory capacity, <i>K</i> (digits), mean (s.d.)	2.95 (0.91)	3.56 (0.49)	0.61*	2.58 (0.65)	3.71 (0.51)	1.13*	2.80 (0.54)	3.61 (0.53)	0.81*
Visual processing speed, <i>C</i> (digits/second), mean (s.d.)	24.24 (11.00)	71.49 (34.90)	47.25*	30.48 (14.15)	68.95 (40.64)	38.47*	36.27 (17.97)	71.28 (28.49)	35.01*
Threshold of visual conscious perception, <i>t</i> ₀ (millisecond), mean (s.d.)	17.15 (9.95)	9.67 (7.72)	-7.48*	16.67 (15.94)	4.77 (6.23)	-11.89*	20.62 (16.68)	7.90 (6.59)	-12.71*
Error rate, mean (s.d.)	0.16 (0.08)	0.14 (0.04)	-0.03	0.15 (0.07)	0.16 (0.06)	0.01	0.16 (0.08)	0.15 (0.06)	-0.01

^a Paired t-test. Abbreviations: FHR-SZ, familial high-risk for schizophrenia; FHR-BP, familial high-risk for bipolar disorder; PBC, population-based children; s.d., standard deviation; TVA, theory of visual attention; *K*, capacity of visual short-term memory; *C*, visual processing speed; *t*₀, threshold for conscious visual perception; N, number of participants. * $p < 0.001$

Supplementary material 4. Performance on TVA-based whole report at age 7 of the follow-up group (N=89).

	FHR-SZ (N=32)	FHR-BP (N=22)	PBC (N=35)	Statistics (p-value)	FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
Visual short-term memory capacity, <i>K</i> (digits), mean (s.d.)	2.95 (0.91)	2.58 (0.65)	2.80 (0.54)	0.191 ^a			
Visual processing speed, <i>C</i> (digits/second), mean (s.d.)	24.24 (11.00)	30.48 (14.15)	36.27 (17.97)	0.006 ^a	0.004 ^b	0.466 ^b	0.399 ^b
Threshold of visual conscious perception, <i>t</i> ₀ (millisecond), mean (s.d.)	17.15 (9.95)	16.67 (15.94)	20.62 (16.68)	0.503 ^a			

^a One-way ANOVA; ^b Calculated with Scheffé post hoc test. For full group-analysis, see Hemager et al. (2019). Abbreviations: FHR-SZ, familial high-risk for schizophrenia; FHR-BP, familial high-risk for bipolar disorder; PBC, population-based children; s.d., standard deviation; TVA, theory of visual attention; *K*, capacity of visual short-term memory; *C*, visual processing speed; *t*₀, threshold for conscious visual perception; N, number of participants.

Appendix 4: Odor identification in 7-year-old children at familial high risk of schizophrenia or bipolar disorder - the Danish high risk and resilience study VIA

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Odor identification 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: Odor identification deficits occur in individuals with schizophrenia and their unaffected first-degree relatives, while deficits are less pronounced in individuals with bipolar disorder. We hypothesized that children at familial high-risk for schizophrenia (FHR-SZ) show odor identification deficits compared to population-based controls and that children at familial high-risk for bipolar disorder (FHR-BP) perform intermediate.

Methods: Odor identification was assessed at age 7 in 184 children with FHR-SZ, 106 children with FHR-BP, and 186 population-based controls with the Brief Smell Identification Test. Dimensional and predefined categorical outcomes were used in the analyses. Potential relationships with psychopathological, cognitive, and home environmental variables were conducted using hierarchical and logistic multiple regression analyses.

Results: ANOVA revealed no between-group differences in odor identification. Using the recommended cut-off (below 5), we found a significantly greater proportion of boys at FHR-SZ than population-based boys with an abnormal odor identification ($p = .013$). However, a supplementary analysis using a Danish-based cut-off (below 4) did not support this. All children showed significant, positive associations of odor identification with female gender, social responsiveness, and verbal working memory. Lower social responsiveness predicted abnormal odor identification in boys at FHR-SZ, only using the recommended cut-off.

Conclusions: Odor identification efficacy and risk status appear independent in this early developmental phase. Using the recommended threshold, abnormal odor identification is more frequent in young boys at FHR-SZ than in population-based boys and is linked to lower social responsiveness. The validity of these results is questioned by non-significant differences in the rates when using an exploratory Danish-based threshold.

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1. Introduction

Schizophrenia (SZ) and bipolar disorder (BP) are severe mental disorders that are intricately connected partially through shared genetic risk factors (Brainstorm et al., 2018). Both are considered as neurodevelopmental disorders, with social, emotional, and cognitive deficits that start long before the onset of the illness (Insel, 2010), although some of the findings regarding the neurodevelopmental

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nature of BP are still contradictory (Sanches et al., 2008). To study the developmental trajectories prior to illness onset, one can examine children of patients with SZ or BP. Children of a parent with SZ or BP carry the genetic liability for these disorders and are therefore at familial high-risk (FHR) to develop such illnesses themselves (SZ: 12% and BP: 6%) (Rasic et al., 2014). By investigating relatively young children at FHR for SZ (FHR-SZ) and BP (FHR-BP), we can provide evidence of distinct or shared developmental pathways of two severe mental disorders at an early phase, without the consequences of having the illness.

Impairments of olfaction is a likely endophenotype for SZ (Moberg et al., 2014; Turetsky et al., 2008). A recent meta-analysis comparing olfaction in patients with chronic SZ to that in healthy controls found a medium-large effect size for odor identification deficits in patients with SZ, the highest effect size among other aspects of olfaction (e.g. odor detection threshold and odor discrimination) (Moberg et al., 2014). Unaffected FDR of patients with SZ primarily show deficits in odor identification (Cohen's d : 0.25–0.69) (Compton et al., 2006; Kamath et al., 2014; Kopala et al., 2001; Turetsky et al., 2008) while individuals with first-episode psychosis (Kamath et al., 2018) and individuals at clinical high-risk (CHR) for psychosis (Turetsky et al., 2018) also show deficits in odor discrimination. This may underline that identification deficits precede further deterioration of olfactory functioning once the illness has commenced. Despite olfactory studies in other neurodevelopmental disorders (Kronenbuerger et al., 2018; Muratori et al., 2017), little is known about odor identification in patients with BP. One study found odor deficits in both psychiatric groups, however, deficits were more pronounced in patients with SZ than in those with BP (Cumming et al., 2011).

Odor identification deficits in SZ are consistently present irrespective of illness phase, age, smoking status, task complexity, or medication status (Kopala et al., 1995; Moberg et al., 2014). Despite observations of odor identification deficits in both males and females with SZ, some found more pronounced deficits in male patients with SZ (Malaspina et al., 2012; Seidman et al., 1997). Also, odor identification deficits are correlated with negative symptoms (Pearson's r : 0.43–0.47) (Brewer et al., 1996; Corcoran et al., 2005; Goudsmit et al., 2003), but not with positive symptoms (Corcoran et al., 2005; Malaspina and Coleman, 2003; Malaspina et al., 2012; Seidman et al., 1997). In individuals with CHR of psychosis, odor identification deficits are suggested to predict transition to psychosis (Brewer et al., 2003) and in individuals with first-episode psychosis, deficits predict the persistence of negative and cognitive/disorganized symptoms after 1 year (Good et al., 2006).

In addition, cognitive links to olfaction exist because successful identification of odors partially relies on semantic and olfactory knowledge obtained through prior experience with these odors. Accordingly, odor identification is associated with intelligence, verbal memory, and conceptualization (the ability to form abstract concepts) (Pearson's r : 0.28–0.58) (Brewer et al., 1996; Compton et al., 2006; Corcoran et al., 2005). Moreover, lower social drive (defined as less interest in and initiation of social interaction) accounts for 23% of the variance of odor identification in SZ and explains the relationship between odor identification deficits and negative symptoms (Malaspina and Coleman, 2003). This suggests common pathophysiology and perhaps shared neurobiological mechanisms that underlie olfaction and social functioning in SZ.

Finally, the olfactory bulbs, important for their direct connections to the primary olfactory cortex, have been implicated in the psychopathology of SZ; patients with SZ show reduced volumes of the olfactory bulbs (Turetsky et al., 2000). Notably, smaller olfactory bulb volumes are reported in their unaffected first-degree relatives (FDR) (Turetsky et al., 2003) and also in male adolescents, but not female, with CHR for psychosis whose reduced volumes correlate with negative symptoms (Turetsky et al., 2018). Therefore, the smaller olfactory bulb volume observed both in patients with SZ as well as their unaffected FDR might represent a risk indicator for SZ.

The current study assessed whether two FHR groups for SZ or BP show common impairment in odor identification. Therefore, we compared children at FHR-SZ, children at FHR-BP, and population-based controls (PBCs) on a test of odor identification (Doty, 2001). We hypothesized that both FHR groups would demonstrate significant odor identification deficits compared to the controls, with more pronounced deficits for children at FHR-SZ than for children at FHR-BP. Additionally, we exploratively analyzed whether odor identification is differentially associated with other cognitive functions in the three groups. The choice of cognitive functions was based on previously observed associations between odor identification and cognition (Compton et al., 2006; Larsson et al., 2004) as well as on earlier studies of cognitive deficits in children at FHR-SZ or FHR-BP (Burton et al., 2018; Christiani et al., 2019; Hemager et al., 2018). Cognitive functions were expected to relate positively with olfaction. Exploratively, this study also included demographic, psychopathological, and home environmental characteristics to provide a comprehensive identification of potential cross-sectional relations to the child's odor identification. We expected less symptomatology and a more stimulating and stable home environment to be positively associated with olfaction.

2. Methods

2.1. Study design and participants

This study is part of the Danish High Risk and Resilience Study - VIA 7 which is a nationwide population-based cohort study of 522 children. The cohort was collected from the national population of 7-year-old children with a parent diagnosed with schizophrenia spectrum psychosis, defined as schizophrenia, delusional disorder or schizoaffective disorder (ICD 10-codes: F20, F22, F25 or ICD 8-codes: 295, 297, 298.29, 298.39, 298.89, 298.99), or bipolar disorder (ICD 10-codes F30 or F31 or ICD 8-codes 296.19 or 296.39), and a control group with none of these two disorders (other diagnoses were allowed). The VIA 7 study design is described elsewhere (Thorup et al., 2015). The project was approved by The Danish Data Protection Agency. The study procedures were aligned with the guidelines of the National Committee for Health Research Ethics, although formal ethical approval was not required due to its observational design. With the help of the Danish Civil Registration System (Pedersen et al., 2006) and The Danish Psychiatric Central Research Register (Mors et al., 2011), data from 202 children at FHR-SZ, 120 children at FHR-BP, and 200 PBC children were collected; controls were matched on age, sex, and municipality to the children at FHR-SZ. Controls were not matched to children at FHR-BP, however, the groups were comparable on the parameters in question. Data were collected between January 1st, 2013 and January 31st, 2016. Legal guardians of the children gave written informed consent to participate after receiving a thorough oral and written explanation of the study. Participants were required to have Danish as their first language. <2% of the participants decided to stop study participation after giving written informed consent.

2.2. Procedures

Odor identification was assessed as part of a comprehensive assessment battery by trained psychologists, medical doctors, and nurses. While most of the assessments took place at the research sites in Copenhagen and Aarhus, Denmark, in few cases the test was performed in the child's homes (only if there was a quiet room with no distractions). Child assessors were blinded to the risk status of the children. Caregivers were asked about the child's health, for example, current nasal infections, allergies, sinus operations, or other complications that may have a negative impact on the child's olfaction.

2.3. Measures

2.3.1. Odor identification testing

To assess odor identification, we used the Brief Smell Identification Test (BSIT) (Version A, Danish version) which is a validated, standardized, non-invasive, and quantitative test for all ages above 5 years (Doty, 2001). With its 12 items (menthol, soap, gasoline, rose, cherry, cloves, leather, strawberry, lilac, pineapple, smoke, and lemon), BSIT is a shorter version of the 40-item University of Pennsylvania Smell Identification Test (UPSIT) (Doty et al., 1984) and contains items based upon world-wide reports (e.g. from France, Sweden, Russia, China, and Japan) to broader cross-cultural familiarity (Doty, 2001). Items were presented as micro-encapsulated odorant strips in a "scratch 'n sniff", forced multiple-choice format; each odor corresponds to one of four odors names. To avoid potential bias from differences in the reading ability of these young children, the assessor neutrally read out the four multiple-choice options to all children. After the assessor scratched and the child sniffed, the options were repeated and thereafter the child verbally reported her/his choice which was registered by the assessor. The assessor repeated the four multiple-choice options as many times as the child wanted.

The primary outcome is the sum of correctly identified odors, providing a total score ranging from 0 up to 12. Thus, a higher BSIT total score reflects better odor identification. The secondary outcome is the recommended sex- and age-based cut-off scores to distinguish individuals with normosmia (normal olfaction) from those with microsmia, defined as a significant impairment in odor identification which interferes with functioning. The cut-off score for microsmia is a BSIT total score below 5 for boys at ages 5–9 and a BIST total score below 4 for girls at ages 5–9 (Doty, 2001).

2.3.2. Psychopathological measures

The Child Behavior Checklist (CBCL) (Achenbach and Rescorla, 2001) and the Attention Deficit/Hyperactivity Disorder – Rating Scale (ADHD-RS) (Makransky and Bilenberg, 2014) assessed the severity of dimensions of psychopathology. These questionnaires were accomplished by the primary caregiver. The child's teacher filled in the Social Responsiveness Scale (SRS), providing an index of social reciprocity reflective of the severity of potential autistic traits (Constantino and Gruber, 2005). (The study cohort's dimensional psychopathology is described elsewhere (Christiani et al., 2019; Ellersgaard et al., 2018).

2.3.3. Cognitive functioning

The Reynold's Intellectual Screening Test (RIST) (Reynolds and Kamphaus, 2003) assessed intelligence. Verbal memory was assessed with two subtests of Test of Memory and Learning, 2nd version (TOMAL-2) (Reynolds and Voress, 2007), Memory for Stories (MFS) and Word Selective Reminding (WSR; the immediate and delayed conditions in both). MFS measures a verbal free-recall of orally presented stories while WSR is a verbal learning test requiring participants to recall an orally presented list of words. MFS and WSR assess different aspects of verbal memory; semantic recall (MFS) and learning and immediate recall functions (WSR), and these test scores were kept separate in the analyses (Reynolds and Bigler, 1996). Processing speed was assessed with the subtests Coding and Symbol Search from the Wechsler Intelligence Scale for Children – fourth edition (WISC-IV) (Wechsler, 2003); the subtest Letter-Number Sequencing was used to assess verbal working memory. The Rapid Visual Information Processing (RVP) A' (A prime) from the Cambridge Neuropsychological Test Automated Battery (CANTAB) assessed sustained attention (Sahakian and Owen, 1992). (The study cohort's neurocognitive functioning is described elsewhere (Hemager et al., 2018).)

2.3.4. Environmental exposure

To evaluate the child's home environment of potential relevance for olfaction we choose one subscale ("Active Stimulation") of the Middle Childhood – Home Observation for Measurement of the Environment

(MC-HOME) (Bradley et al., 1988). The Active Stimulation Subscale evaluates whether the family actively stimulates the child broadly. To illustrate, one item asked whether the child is taken on trips outside their home, village, or city, which would potentially increase the chance of smelling new odors. The primary caregivers social functioning was assessed with the Personal and Social Performance scale (PSP) (Morosini et al., 2000).

2.4. Statistical analyses

To compare the demographic, psychopathological, cognitive, and home environmental characteristics of the three study groups (FHR-SZ, FHR-BP, and PBC), we used parametric and non-parametric statistical methods as appropriate. We compared continuous variables across the risk groups using univariate analysis of variance (ANOVA) or Welch's ANOVA in case of heterogeneity of variance. We performed post-hoc multiple comparisons by means of Bonferroni corrections and Games-Howell (following the Welch's ANOVA). We compared the binary variable and the categorical outcome measure across the risk groups using chi-square tests for independence.

All test scores were standardized into z-scores with the mean and standard deviation of the PBCs as reference. A negative z-score reflect poorer performance. Two composite verbal memory z-scores were constructed (the MFS immediate and delayed scores as well as the WSR immediate and delayed scores) and one composite z-score for processing speed (the WISC-IV subtests Coding and Symbol Search scores). Composite z-scores were re-standardized.

Odor identification was analyzed 1) using the primary dimensional outcome (BSIT total score) with a two-way ANOVA with group and sex as fixed factors to examine the potential between-group differences and 2) using the secondary categorical outcome with a chi-square test of independence to examine the distribution of normosmic versus microsmic. We also performed separate one-way ANOVA's stratified for sex. Exploratively, we used the psychopathological, cognitive, and home environmental variables as predictors in the hierarchical multiple regression analysis on the dimensional outcome, including their interaction with group. Additionally, we conducted a sex-specific multiple logistic regression analysis. All basic assumptions of regressions analyses were checked. The hierarchical multiple regression analysis was conducted with risk status, sex, and age entered in the first step (Model 1), psychopathological and cognitive variables in the second step (Model 2), and home environmental variables in the third step (Model 3) (Table 4). Interaction terms with FHR*variables were included but did not reach statistical significance (data not shown). The sex-specific multiple logistic regression analysis on the categorical outcome was conducted with "normosmic" and "microsmic" as dependent variable. Due to lack of power, three predictors that were theoretically most relevant were selected: verbal memory, social reciprocity, and verbal working memory. As the means of the Danish PBC boys (Cohen's $d = 1.07$) and girls (Cohen's $d = 0.78$) were unexpectedly low compared to the normative data of the American boys and girls, we exploratively defined microsmia as a score <1.5 SD below the mean of the Danish PBC boys and girls. Using this definition, both boys and girls who scored below 4 were identified as microsmic, i.e. no change in the threshold for girls compared to the American threshold. We did all analyses in SPSS Statistics software (version 22.0).

3. Results

3.1. Cohort and demographic characteristics

The entire VIA 7 study cohort included 522 children (202 (39%) children at FHR-SZ, 120 (23%) at FHR-BP, and 200 (38%) PBC). BSIT data of 46 children (non-significantly differently distributed across the groups) were not analyzed due to either missing data (3 FHR-SZ, 4 FHR-BP, and 3 PBC) or excluded because sickness may have influenced olfaction (15

Table 1
Demographic, psychopathological, cognitive, and home environmental characteristics of 7-year-old children at familial high-risk for schizophrenia (FHR-SZ), bipolar disorder (FHR-BP), and population-based control (PBC) presented in raw scores and pairwise comparisons between groups.

Variables, mean (SD)	Assessed function	N	FHR-SZ	N	FHR-BP	N	PBC	P-value	Pairwise Comparisons (P value)		
									FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
Demographics											
Children		184		106		186					
Female %			46.7		43.4		46.2	0.067 ^a			
Age - years at inclusion			7.8 (0.2)		7.8 (0.2)		7.8 (0.2)	0.850			
Dimensions of psychopathology											
CBCL Internalizing subscale	Internalizing problem behavior	179	6.5 (6.0)	99	6.4 (6.4)	180	4.9 (4.5)	0.007 ^b	0.010	0.104	0.983
CBCL Externalizing subscale	Externalizing problem behavior	178	7.7 (7.3)	100	6.2 (6.8)	180	4.1 (4.8)	<0.001 ^b	<0.001	0.022	0.182
ADHD-RS Inattention subscale	Inattentive symptoms	179	6.8 (5.3)	102	6.6 (5.5)	180	4.8 (4.2)	<0.001 ^b	<0.001	0.016	0.933
ADHD-RS Hyperactive-impulsive subscale	Hyperactive-Impulsive symptoms	179	7.0 (5.7)	102	6.4 (5.2)	180	5.4 (4.5)	0.016 ^b	0.014	0.271	0.669
SRS	Social Responsiveness	157	37.3 (26.1)	93	33.7 (32.3)	159	24.9 (20.6)	<0.001 ^b	<0.001	0.052	0.640
Cognition											
RIST	Intelligence	184	102.5 (11.5)	106	104.1 (9.0)	184	105.1 (10.0)	0.067 ^b	0.053	0.715	0.335
MFS Immediate	Verbal memory (immediate)	183	19.3 (10.1)	106	20.7 (10.0)	185	19.8 (9.4)	0.534	1.00	1.00	0.790
MFS Delayed	Verbal memory (delayed)	183	14.9 (9.1)	106	17.0 (9.3)	185	15.4 (8.4)	0.149	1.00	0.425	0.163
WSR Immediate	Verbal memory (immediate)	177	38.6 (5.7)	105	39.7 (4.7)	185	39.0 (5.0)	0.246	1.00	0.944	0.283
WSR Delayed	Verbal memory (delayed)	176	6.1 (2.0)	104	6.4 (1.5)	182	6.2 (1.6)	0.326	1.00	0.913	0.407
Coding	Processing speed	183	26.6 (7.7)	104	28.9 (7.3)	186	29.4 (7.1)	0.001	0.001	1.00	0.037
Symbol Search	Processing speed	179	15.5 (5.3)	104	17.4 (4.9)	181	17.2 (5.3)	0.001	0.005	1.00	0.008
Letter-Number Sequencing	Verbal working memory	181	12.5 (4.1)	105	13.8 (3.9)	186	13.8 (3.5)	0.001	0.003	1.00	0.014
RVP A'	Attention	173	0.89 (0.06)	104	0.90 (0.06)	180	0.90 (0.05)	0.038	0.032	1.00	0.557
Home environment											
Active Stimulation	Stimulating home environment	179	5.6 (1.5)	105	5.6 (1.4)	185	5.9 (1.5)	0.061	0.078	0.293	1.00
PSP	Parental personal and social functioning	182	73.4 (14.3)	106	74.9 (14.1)	185	84.3 (9.2)	<0.001	<0.001	<0.001	0.989

^a Pearson chi-square.

^b No homogeneity of variance thus Welch's ANOVA and multiple comparisons with Games-Howell. Abbreviations: A', A prime; ADHD-RS, Attention Deficit/Hyperactivity Disorder-Rating Scale; CBCL, Child Behavior Checklist; FHR-BP, Familial high-risk for bipolar disorder; FHR-SZ, Familial high-risk for schizophrenia; MFS, Memory for Stories; PSP, Personal and Social Performance; PBC, Population-Based Controls; RIST, Reynold's Intellectual Screening Test; RVP, Rapid Visual Information Processing; SRS, Social Responsiveness Scale; SD, standard deviation; WSR, Word Selective Reminding. See (Christiani et al., 2019; Ellersgaard et al., 2018; Hemager et al., 2018) for results on the full cohort.

FHR-SZ, 10 FHR-BP, and 11 PBC). Thus, data from 476 children were analyzed and there were no significant group differences on age or sex (Table 1).

3.2. Odor identification

The main effect of group in the two-way ANOVA conducted on the primary dimensional outcome (the BSIT total score) showed no significant difference ($F = 0.94, p = .390$) while the main effect of sex showed a significant difference ($F = 25.00, p < .001$) (Table 2). The interaction effect was not significant ($F = 0.962, p = .383$) (supplementary material: Sex-stratified ANOVA's on BSIT total score). The secondary categorical outcome showed no significantly different distribution of normosmic versus microsmic across the groups including both sexes ($\chi^2 = 2.05, p = .36$). However, a significantly greater proportion of boys at FHR-SZ (27 out of 98; 28%) than PBC boys (13 out of 100; 13%) was classified as microsmic ($\chi^2 = 6.48, p < .05$) (Table 3). The proportion of boys at FHR-BP that fell into the microsmic group (21%) was in between boys at FHR-SZ and PBC boys but these differences were non-significant in both directions (see Fig. 1). We found no significant differences in distributions across groups for girls ($\chi^2 = 3.10, p = .21$). Using the microsmic threshold based on the Danish PBC boys' mean and SD, there was no significant between-group difference in the proportion rates for boys, with 11% of the boys at FHR-SZ, 8% of boys at FHR-BP, and 7% of PBC boys having microsmia ($p = .571$). The distribution of the test scores can be found in the supplementary material (Box-and-whisker plots of test scores of total group, boys, and girls).

3.3. Psychopathological, cognitive, and home environmental characteristics

The ANOVA showed significant differences in psychopathological, cognitive, and home environmental measures across the three groups

(Table 1). Results on the full cohort are published elsewhere (Christiani et al., 2019; Ellersgaard et al., 2018; Hemager et al., 2018) and thus not replicated here (supplementary material: Results on psychopathological, cognitive, and environmental exposure variables).

3.4. Potential relationships between odor identification and aspects of psychopathology, cognitive functioning, and the home environment

The exploratory hierarchical regression analysis on potential associations between variables on psychopathology, cognition, and the home environment and odor identification revealed that BSIT total score was only significantly associated with sex, efficacy of social responsiveness, and verbal working memory functioning ($R^2 = 0.17, p < .001$) (Table 4). The likelihood of falling into the American-based microsmic group was, for boys at FHR-SZ, significantly associated with less social reciprocity (pseudo $R^2 = 0.10, p = .023$) whereas there was no significant association for verbal working memory or verbal memory (Table 5). A supplementary analysis was performed using the Danish-based threshold for microsmia, which showed no significant association between social reciprocity and microsmia ($p = .984$) (supplementary

Table 2

Two-way ANOVA on a dimensional score of odor identification in 7-year-old children with familial high-risk group and sex as fixed factors.

	Parameter estimate (B)	Confidence interval (95%)	p-value
Intercept	6.250	5.930–6.570	<0.001
FHR-SZ versus PBC	−0.274	−0.667–0.118	0.170
FHR-BP versus PBC	−0.129	−0.588–0.331	0.583
Female versus male	0.958	0.611–1.306	<0.001

Abbreviations: FHR-BP, Familial high-risk for bipolar disorder; FHR-SZ, Familial high-risk for schizophrenia; PBC, Population-Based Controls.

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Table 3

Categories of normal and abnormal olfaction of 7-year-old children at familial high-risk for schizophrenia (FHR-SZ), bipolar disorder (FHR-BP), and population-based control (PBC).

Categorical, abnormal odor identification ^a	N	FHR-SZ	N	FHR-BP	N	PBC	P-value	Chi-square tests (P value)		
								FHR-SZ vs PBC	FHR-BP vs PBC	FHR-SZ vs FHR-BP
All children, %	29	15.8	15	14.2	20	10.8	0.358 ^b	0.013	0.185	0.455
Boys, %	27	27.6	13	21.7	13	13.0	0.039 ^b			
Girls, %	2	2.3	2	4.3	7	8.1	0.213 ^b			

^a Abnormal odor identification boys, BSIT total score < 5; girls, BSIT total score < 4 (Doty, 2001).^b Pearson chi-square test; Abbreviations: FHR-BP, Familial high-risk for bipolar disorder; FHR-SZ, Familial high-risk for schizophrenia; PBC, Population-Based Controls.

material: Univariate Logistic Regression Analysis of social responsiveness on odor identification of boys at FHR-SZ).

4. Discussion

The current study investigated odor identification in 7-year-old children at FHR-SZ or FHR-BP, and PBCs (their parents may have other diagnoses than SZ or BP). The three groups including both sexes did not differ significantly in odor identification efficacy (dimensional data). Analyses of the rates of normosmic versus microsmic (using recommended thresholds) of children in the risk groups showed that a significant higher percentage of boys at FHR-SZ (28%) were classified as microsmic compared to population-based boys (13%). The proportion of microsmic boys at FHR-BP was not significantly different from that of boys at FHR-SZ nor to that of population-based boys (Fig. 1). However, we did not find significant group differences in the rates of normosmic versus microsmic boys using a threshold of 1.5 SD below the Danish population-based boys' mean. No significant differences were found in the proportions of microsmic girls across the groups. The exploratory regression models indicated that better odor identification was positively related to being female, better social reciprocity (fewer autistic traits), and better verbal working memory, whereas we found no significant relationships with the other cognitive, psychopathological, and home environmental factors. Additionally, boys at FHR-SZ with higher levels of autistic traits were more likely to be classified as microsmic than those with lower levels of autistic traits whereas verbal working memory and verbal memory were both unrelated to microsmia in this group. However, this association was only observed using the

American-based threshold and not when using the Danish-based threshold for microsmia.

The results indicate that 7-year-old children at FHR-SZ or FHR-BP do not show odor identification deficits. Despite the results from the American-based threshold suggested that boys at FHR-SZ are more likely of having microsmia than population-based boys, this was not supported by findings based on a Danish-based threshold and it was not in line with the result of the dimensional analysis. The large difference (Cohen's $d = 1.07$) between means of odor identification of American boys and Danish population-based boys may question the cross-cultural validity of the BSIT.

First, our findings in young children at FHR-SZ or FHR-BP expand on the literature of olfactory functioning in the prodromal phase of psychosis-related disorders and in patients with SZ. Previous studies observed impaired odor identification in youth with CHR for psychosis (Brewer et al., 2003; Kamath et al., 2014; Keshavan et al., 2009; Woodberry et al., 2013). Interestingly, our finding shows that odor identification is not significantly impaired in young children at FHR-SZ or FHR-BP, suggesting that olfactory deficits may arise in the prodromal phase, which may have implications for the underlying origin of these deficits. Second, across the three groups, the efficacy of olfaction identification was associated with severity of autistic traits and verbal working memory while there were no associations to other cognitive or home environmental factors. The link between olfaction and social cognition may glean from common brain structures underpinning both areas of functioning (Malaspina and Coleman, 2003). Third, several studies involving unaffected FDR (including both sexes) observed dimensional olfactory differences compared to healthy controls (Kamath et al., 2014; Kopala et al., 2001; Turetsky et al., 2008). The discrepancy

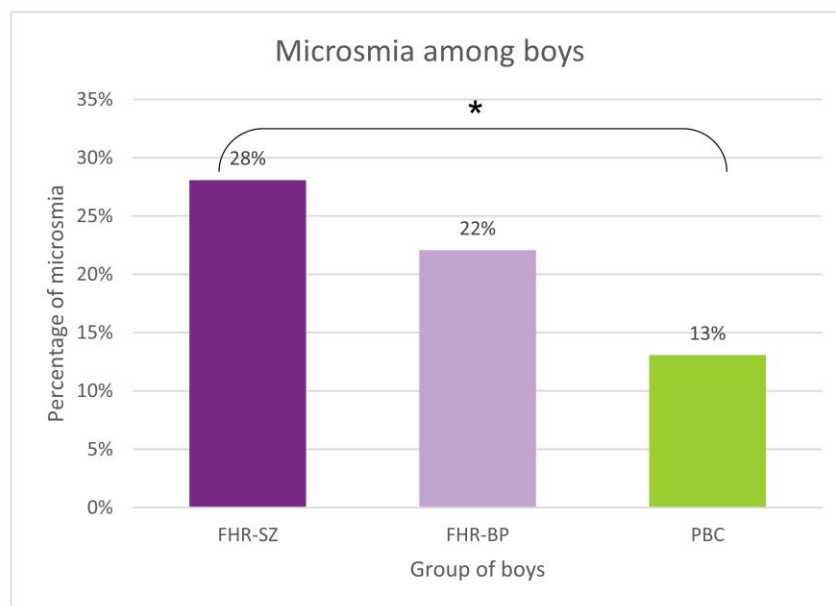


Fig. 1. Percentage of abnormal odor identification among boys at FHR-SZ, FHR-BP or PBC boys. Abbreviations: FHR-BP, Familial high-risk for bipolar disorder; FHR-SZ, Familial high-risk for schizophrenia; PBC, Population-Based Controls. * Significant at 0.05% level.

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Table 4
Hierarchical Regression Analysis of demographical, psychopathological, cognitive, and home environmental predictors on odor identification of 7-year-old children at familial high-risk for schizophrenia (FHR-SZ), bipolar disorder (FHR-BP), and population-based control (PBC).

Predictors	Assessed function	Model 1	95% CI	Model 2	95% CI	Model 3	95% CI
		Estimate		Estimate		Estimate	
Demographics							
High-risk status		0.06	−0.04; 0.18	0.02	−0.09; 0.14	0.01	−0.11; 0.13
Sex (boys)		−0.24*	−0.68; −0.29	−0.19*	−0.57; −0.18	−0.19*	−0.58; −0.18
Age		0.05	−0.24; 0.69	0.05	−0.22; 0.73	0.06	−0.21; 0.74
Dimensions of psychopathology							
CBCL Internalizing Subscale	Internalizing problem behavior			0.00	−0.10; 0.10	−0.01	−0.10; 0.09
CBCL Externalizing Subscale	Externalizing problem behavior			−0.12	−0.20; 0.02	−0.12	−0.20; 0.02
ADHD-RS Inattention Subscale	Inattentive symptoms			0.00	−0.10; 0.12	0.01	−0.10; 0.12
ADHD-RS Hyperactive-impulsive Subscale	Hyperactive- and impulsive symptoms			0.10	−0.03; 0.21	0.10	−0.03; 0.21
SRS	Social Responsiveness			0.18*	0.05; 0.23	0.17*	0.04; 0.22
Cognition							
RIST	Intelligence			0.02	−0.09; 0.13	0.01	−0.10; 0.12
MFS (composite)	Verbal memory			0.11	0.00; 0.20	0.10	−0.00; 0.20
WSR (composite)	Verbal memory			0.06	−0.05; 0.14	0.06	−0.05; 0.15
Processing speed (composite)	Processing speed			−0.01	−0.12; 0.10	−0.02	−0.13; 0.10
Letter-number sequencing	Verbal working memory			0.13*	0.02; 0.22	0.13*	0.02; 0.22
RVP A'	Attention			−0.02	−0.11; 0.08	−0.02	−0.11; 0.08
Home environment							
Active stimulation	Stimulating home environment					0.05	−0.06; 0.15
PSP	Parental personal and social functioning					0.03	−0.05; 0.10
Model squared R		0.064		0.168		0.172	
F change		8.870		4.290		0.781	
P-value		<0.001		<0.001		0.459	

Model 1: High-risk Status, sex, age; Model 2: High-risk Status, sex, CBCL Internalizing subscale, CBCL Externalizing subscale, ADHD-RS Inattention subscale, ADHD-RS Hyperactive-impulsive subscale, SRS, RIST, MFS (composite), WSR (composite), Processing Speed (composite), Letter-Number Sequencing, RVP A'; Model 3: High-risk Status, sex, CBCL Internalizing subscale, CBCL Externalizing subscale, ADHD-RS Inattention subscale, ADHD-RS Hyperactive-impulsive subscale, SRS, RIST, MFS (composite), WSR (composite), Processing Speed (composite), Letter-Number Sequencing, RVP A', Active Stimulation, PSP. Abbreviations: A', A prima; ADHD-RS, Attention Deficit/Hyperactivity Disorder-Rating Scale; CBCL, Child Behavior Checklist; CI, Confidence Interval; FHR-BP, Familial high-risk for bipolar disorder; FHR-SZ, Familial high-risk for schizophrenia; MFS, Memory for Stories; PSP, Personal and Social Performance; PBC, Population-Based Controls; RIST, Reynold's Intellectual Screening Test; RVP, Rapid Visual Information Processing; SRS, Social Responsiveness Scale; WSR, Word Selective Reminding.

* Indicates significance ($p < .05$).

between our results and that of others may be attributed to the older mean age in these studies (mean ages: 35 to 43 years) (Kamath et al., 2014; Kopala et al., 2001; Turetsky et al., 2008), as normal maturation of olfaction is rapid during adolescence (Doty et al., 1984), olfactory maturational impairments may evolve in the later developmental phase. According to the developmental lag hypothesis, neurocognitive functions may worsen with increasing age due to slower than normal maturational growth (Reichenberg et al., 2010). Longitudinal research of odor identification could potentially specify the time point when olfactory deficits would arise.

Our explorative regression model with significant effects of sex, severity of autistic traits, and verbal working memory explained 17% of the variance of odor identification. The observed association between verbal working memory and odor identification is consistent with a finding in adult, unaffected FDR of patients with SZ.⁹ Together this suggests that verbal working memory may be involved and thus impact odor identification in childhood and adulthood. Also, our results suggest that odor identification at this young age appears independent of intelligence, verbal memory, processing speed, sustained attention, and severity of ADHD-symptoms. This is in line with the lack of association

between odor identification and intelligence in 11-year-old children with ASD (Muratori et al., 2017). Similarly, odor identification was associated with social impairments but not ADHD, depression, nor anxiety symptoms nor with executive functioning in adult patients with Tourette's Syndrome (Kronenburger et al., 2018). While our findings indicate that more autistic traits predict microsmia in boys at FHR-SZ, supporting the idea that social and olfactory dysfunction share common pathophysiology (Brewer et al., 1996; Goudsmit et al., 2003), this finding is not supported when using the, more relevant, Danish-based threshold for microsmia.

Strengths of this study include 1) the large sample size of children examined at the same age, 2) the inclusion of both children at FHR-SZ and FHR-BP, 3) valid olfactory data through exclusion of children with medical conditions involving the respiratory tracts, and 4) the blind status of assessors. However, several limitations to this study need to be addressed. First, the cross-sectional nature limits the possibility to study the maturation of olfaction, which could characterize the maturational development of olfactory functioning. Second, the cross-cultural validity of the BSIT may be questionable, as the recommended microsmic threshold may not be applicable to young Danish boys.

Table 5
Multiple Logistic Regression Analysis of psychopathological and cognitive measures on odor identification of boys at familial high-risk for schizophrenia (FHR-SZ).

Covariates	Assessed function	Model 1		Model 2		Model 3	
		OR	95% CI	OR	95% CI	OR	95% CI
SRS	Social responsiveness	1.61*	1.06–2.45	1.62*	1.07–2.46	1.59*	1.07–2.38
MFS (composite)	Verbal memory	1.27	0.84–1.91	1.29	0.87–1.91		
Letter-Number Sequencing	Verbal working memory	1.08	0.65–1.80				

Model 1: SRS, MFS (composite), Letter-Number Sequencing; Model 2: SRS, MFS (composite); Model 3: SRS. Abbreviations: CI, Confidence interval, MFS, Memory for Stories; OR, Odds Ratio; SRS, Social Responsiveness Scale.

* Indicates significance ($p < .05$).

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Third, the restricted number of items of the BSIT (12 items) may have limited the sensitivity to detect subtle differences between the groups, especially because the majority of these children did not have any psychiatric diagnoses, and the test was originally designed for patient samples. Future studies should include tests that examine more aspects of olfaction to broaden its characterization, such as odor sensitivity and discrimination. Additionally, subthreshold symptoms of psychosis should be included in the analyses (Keshavan et al., 2009), as well as analyses of subgroups of parental clinical diagnoses.

In summary, no significant difference in odor identification was observed between children at FHR-SZ, children at FHR-BP and control children at age 7. Regarding previous studies reporting odor identification deficits in youth at CHR for psychosis, our finding indicates that olfactory dysfunction might be part of the prodromal phase or appear in a later developmental phase in older subjects at FHR-SZ and possibly FHR-BP, but olfactory dysfunction may not be part of the earlier developmental phase. Shared risk factors for SZ and BP may not be involved in odor identification at this young age. Further, our dimensional findings emphasize the link between olfaction and sex, social skills and verbal working memory in children at age 7, independent of risk groups.

Contributors

AAET, JRMJ, OM, MN, and KJP developed the study design, provided methodological advice, and supervised the conduct of the study. BKB, DE, KSS, CJC, NH, DG, AG collected the data. AHVT, JMD, and JRMJ made the statistical plans and performed the analyses. AHVT conducted the literature search and created the tables and figures. AHVT and JRMJ wrote the first draft. All authors interpreted data, commented on and edited the manuscript, and agreed on the final version.

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Declaration of competing interest

There are no conflicts of interest for any of the authors.

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Appendix A. Supplementary data

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Appendix 5: Event-related electroencephalographic responses in children at familial high risk for schizophrenia or bipolar disorder: a single-site EEG sub-study of the Danish High Risk and Resilience Study – VIA 11

Event-related electroencephalographic responses in children at familial high risk for schizophrenia or bipolar disorder: a single-site EEG sub-study of the Danish High Risk and Resilience Study – VIA 11

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Abstract

Aim: Studying children of parents with schizophrenia or bipolar disorder, i.e. who are at familial high-risk of developing similar disorders, offers the possibility to identify abnormalities preceding the emergence of mental health disorders during adolescence. This paper reports the rationale and methodology of a single-site electroencephalography-study of the register-based Danish High Risk and Resilience Study–VIA 11. Focusing on event-related electroencephalographic read-outs that have previously been proposed as endophenotypes for schizophrenia, we set out to retrieve these endophenotypes in children at familial high-risk.

Method: Event-related cortical responses to repetitive auditory stimuli or visuospatial flanker stimuli will be recorded with 128-channel electroencephalography in eleven-year-old children with one or two parents diagnosed with schizophrenia spectrum psychosis ($n > 40$) or bipolar disorder ($n > 40$) and control children without familial high-risk ($n > 40$). We will test for between-group differences in auditory processing, focusing on the auditory steady-state response and mismatch negativity. We will also assess between-group differences in visually evoked cortical activity implicated in the resolution of a visuomotor response conflict such as P3b potential and lateralized readiness potential. We will further examine whether the individual expression of these electroencephalographic read-outs scale with clinical characteristics.

Conclusions: The study will clarify whether potential electroencephalographic-derived endophenotypes are expressed in children of parents with schizophrenia and possibly also in children of parents with bipolar disorder. The multiple electrophysiological-based read-outs of brain reactivity will enable additional exploratory analyses. Together, the study will contribute to current attempts to validate and identify electroencephalographic-based endophenotypes of vulnerability for mental health disorders.

Keywords: Bipolar disorder, electroencephalography, endophenotypes, familial high-risk, offspring, schizophrenia.

Introduction

Schizophrenia (SZ) and bipolar disorder (BP) are among the most severe mental disorders imposing a huge impact on patients and their families (Millier et al., 2014) and show considerable overlap in their genetic, symptomatic and neurobiological characteristics (Purcell et al., 2009). Behavioural, cognitive and emotional abnormalities are present before the prodromal phases of both illnesses, though deficits are more severe in those who will develop SZ (Bora, 2016), which argues for a stronger neurodevelopmental nature in SZ compared to BP (Owen, O'Donovan, Thapar, & Craddock, 2011). Studies that include children born to parents with SZ or BP, which are at a familial high risk (FHR) for developing these disorders, provide the opportunity to investigate vulnerability and protective factors, as well as factors of resilience in those who present with the typical endophenotypes, but do not develop the disorder (Rasic, Hajek, Alda, & Uher, 2014).

Prospective longitudinal FHR-studies suggested several cognitive endophenotypes for both disorders (Bora & Ozerdem, 2017; Hameed & Lewis, 2016). Few studies included electroencephalography (EEG), a non-invasive and cost-effective technique to investigate early information-processing abilities (Friedman & Squires-Wheeler, 1994; Schreiber, Stolz, Rothmeier, Kornhuber, & Born, 1989). EEG provides a direct measure of electrical activity with high temporal resolution, which is essential to study oscillatory activity and event-related potentials (ERPs). Furthermore, EEG has greatly contributed to the search for endophenotypes in psychiatry; in SZ (Earls, Curran, & Mittal, 2016), BP (Ethridge et al., 2015) and in other psychiatric disorders (Riva et al., 2018). The following section describes three aspects of neural mechanisms being tested as part of the current study 1) auditory steady-state responses, 2) automatic cortical processing of changes in regularity of auditory input and 3) event-related cortical responses of visuomotor control.

Auditory steady-state responses

Auditory steady-state responses (ASSRs) are evoked by brief tones or clicks and provide readily available, noninvasive means of probing impaired neural gamma synchrony in the auditory system (Larsen et al., 2017; Thune, Recasens, & Uhlhaas, 2016). The ability to generate 40 Hz ASSR relies on the GABAergic interneurons (Bartos, Vida, & Jonas, 2007; Sohal, Zhang, Yizhar, & Deisseroth, 2009; Traub et al., 2003) by exerting a finely timed inhibition onto the pyramidal cells. ASSR at 40 Hz is well-studied in patients with chronic SZ; 17 out of 20 studies reported reductions in power

and phase-locking of 40 Hz ASSR compared to healthy subjects (Thune et al., 2016). Additionally, unaffected first-degree relatives (UFDR) of patients with SZ showed reduced 40 Hz ASSR (Rass et al., 2012). The few studies that investigated ASSR in patients with BP reported similar results (O'Donnell, Hetrick, et al., 2004; Rass et al., 2010) suggesting circuit dysfunctions in both disorders. Furthermore, evidence shows that deficits in early gamma-band responses arise after the onset of psychosis while the late gamma-band response is already premorbid impaired (Tada et al., 2016). These findings indicate its potential role as endophenotype for SZ whereas their potential role as an endophenotype of BP is not well elucidated.

Automatic cortical processing of changes in regularity of auditory input

The preconscious process of detecting change in regularity of auditory input is expressed by the mismatch negativity (MMN). MMN reflects an automatic predictive processing system that is evoked when an expectation regarding upcoming stimuli is violated. This results in a fronto-temporal negative deflection that peaks between 150-250 ms after the mismatching stimulus (Näätänen, 1990). MMN amplitude reductions are consistently found in patients with chronic SZ, with effect sizes (ES) between 0.95 and 0.99 and are greatest in response to duration-deviant tones (Earls et al., 2016; Umbricht & Krljes, 2005) and are also observed in UFDR of patients with SZ (Earls et al., 2016). MMN alterations are associated with poorer psychosocial functioning and ratings on global functioning in daily life (Light, Swerdlow, & Braff, 2007) and are also reported in children with autism (Vlaskamp et al., 2017) and adolescents with ADHD (Rydkjaer et al., 2017). Recent findings revealed that MMN amplitude reductions may be due to a decreased connectivity from higher to lower cortical areas, indicative of predictive processes going wrong (Larsen et al., 2018). Evidence of MMN changes in patients with BP is more controversial and meta-analyses reported moderate ESs between 0.37 and 0.45 (Chitty, Lagopoulos, Lee, Hickie, & Hermens, 2013; Erickson, Ruffle, & Gold, 2016). UFDR of patients with BP showed no MMN deficits compared to healthy subjects (Hall et al., 2009; Umbricht et al., 2003). These findings suggest MMN deficits as potential endophenotype for SZ, whereas this has not yet been documented for BP.

Event-related cortical responses of visuomotor control

In visuomotor tasks assessing interference control, e.g. the flanker task (Eriksen, 1995), cortical responses reflect higher cognitive processes. To investigate neural correlates of interference control, three ERP-components N200, P3b and the lateralized readiness potential (LRP) are of interest

(Coles, 1989; Eichele et al., 2016; Xie, Ren, Cao, & Li, 2017). N200 is a frontocentral negative peak at approximately 200 ms after stimulus onset and its amplitude is enhanced in tasks eliciting response conflict (Heil, 2000; Kopp, Rist, & Mattler, 1996). P3b is a parietal positive peak at approximately 300 ms after stimulus onset. P3b amplitude reflects the degree of cognitive demand during task processing and P3b latency reflects the time required to detect a target stimulus (Polich, 2007). Alterations in N200 and P3b amplitudes reflect impaired attention-dependent processing in higher cortical regions and are linked to other disorders with attention and inhibition disturbances, such as ADHD (Tsai, Hung, & Lu, 2012). Specifically, reductions in N200 amplitudes have been shown in patients with SZ, but not in patients with BP (O'Donnell, Vohs, Hetrick, Carroll, & Shekhar, 2004), whereas both patient groups show reduced P300 amplitudes and prolonged P300 latencies (Jahshan et al., 2012; O'Donnell, Vohs, et al., 2004), which also precede psychosis onset (Hamilton et al., 2019). UFDR of patients with SZ, compared to healthy subjects, display prolonged N200 latencies (Frangou et al., 1997; Schreiber et al., 1989), reduced P300 amplitudes (ES: 0.52-0.61) and prolonged P300 latencies (ES: 0.44-0.50) (Bramon et al., 2005; Earls et al., 2016). UFDR of patients with BP only show smaller P300 amplitudes (Hall et al., 2009; Schulze et al., 2008), though fewer studies have been conducted. Finally, the LRP reflects the difference in motor cortex activation between the two cerebral hemispheres and is related to response preparation and execution (Coles, 1989). Delayed onset of the LRP, i.e. lengthening of motor response selection and preparation processes, are present in both SZ and BP (Van Voorhis et al., 2019). When our cohort was aged 7, children with FHR-SZ showed motor impairments relative to control children (Burton et al., 2017), which gives reason to study the LRP. In addition to the stimulus-locked ERPs, response-locked ERPs such as the error-related negativity (ERN) and error positivity (Pe) allow us to study processes of error monitoring. Specifically, the ERN indexes automatic error detection and arises immediately after an erroneous response (Ford, Jorgensen, Roach, & Mathalon, 2009). Subsequently, Pe emerges approximately 300 ms after an erroneous response and reflects the evaluation and awareness of the incorrect response (Davies, Segalowitz, & Gavin, 2004).

We designed a study to identify potential electrophysiological endophenotypes for SZ and/or BP. Our primary aim is to clarify whether suggested electrophysiological-based endophenotypes can be retrieved in this FHR-cohort. Therefore, EEG will be recorded while children undergo a gamma entrainment paradigm to measure ASSR, an auditory oddball paradigm to measure MMN and a modified flanker task to measure the ERP-components N200, P3b and LRP. We hypothesize that

children at FHR-SZ relative to control children show (1) reductions in power and inter-trial phase coherence of the ASSR in response to regular auditory stimulation at 40 Hz, (2) reduced amplitudes of the MMN response, (3) altered N200, P3b and LRP in more attentional demanding conditions in the flanker task that require suppression of a prepotent response, and (4) altered ERN and Pe after the commission of an error. Given the overlap in SZ and BP, we expect that EEG outcome measures of children at FHR-BP will lie between those of FHR-SZ and control children. Further, we will perform exploratory analyses to identify novel endophenotypes related to GABAergic circuitry dysfunction through computational modelling (Shaw et al., 2019; Symmonds et al., 2018) within the network generating the ASSR as well as altered connectivity in the MMN network. Additionally, we expect associations between the individual EEG-outcomes and severity of behavioural problems, especially with symptomatology of autism and ADHD. Finally, we propose a combination of altered functional patterns constituting complementary network biotypes conferring risk for psychosis. This opens up for follow-up studies to investigate resilience factors.

Methods

Study design

This study was approved by The Danish Data Protection Agency as part of the Danish High Risk and Resilience Study - VIA 11 (Thorup et al., 2018). The Danish High Risk and Resilience Study - VIA 7 was initiated in 2013 when children were 7 years of age (Thorup et al., 2015) and a collaboration of two research sites in Denmark (Copenhagen and Aarhus). The EEG sub-study was added to the first follow-up (VIA 11) but only performed at the research site in Copenhagen, at the Danish Research Centre for Magnetic Resonance (DRCMR), Copenhagen University Hospital Hvidovre. Children of the cohort were evenly distributed over the two research sites based on place of residence, FHR status, and gender. EEG was performed by trained researchers who are blinded to the group status of the parent. Parents or legal guardians of participating children complete a written informed consent after written and oral explanation of the study procedures. Children receive a verbal, child-friendly explanation of the study. Although the current EEG study is cross-sectional, we plan to incorporate EEG in future waves of the Danish High Risk and Resilience Study that are intended to occur every four years.

Participants

This study will recruit at least 40 children at FHR-SZ, 40 children at FHR-BP and 40 control children. Eleven-year-old children with either zero, one, or two parent(s) diagnosed with schizophrenia spectrum psychosis (defined as SZ, delusional disorder and schizoaffective disorder; ICD 10-codes: F20, F22 and F25 or ICD 8-codes: 295, 297, 298.29, 289.39, 298.89, 298.99) or BP (ICD 10-code F30 and F31 or ICD 8-codes: 296.19, 296.39) were recruited from VIA 7 (Thorup et al., 2015) and testing commenced in May 2017. The original cohort of VIA 7 was recruited through the Danish Civil Registration System and the Danish Psychiatric Central Research register (Mors, Perto, & Mortensen, 2011) and was required to have Danish as native language. Children not at FHR (population-based controls; PBC) were matched to children at FHR-SZ on municipality, sex and age. Children at FHR-BP were comparable to the other groups in terms of age and gender. Power calculations for the EEG read-outs were difficult to make due to a low number (or lack) of previous studies including children with FHR-SZ and FHR-BP. Our sample size of at least 40 children per group (total N=120) is high compared to the existing studies (Friedman, Cornblatt, Vaughan, & Erlenmeyer-Kimling, 1988; Schreiber, Stolz-Born, Kornhuber, & Born, 1992) and compared to studies including young and adult individuals with CHR for psychosis (Bruggemann, Stockill, Lenroot, & Laurens, 2013; Lepock et al., 2018), although effect sizes may be different due to different clinical characteristics.

Procedure

After generally explaining EEG, participants are seated in a comfortable chair in a quiet room. Participants are carefully instructed about the experimental procedures. Three experimental tasks are presented in the following fixed-order; gamma entrainment paradigm, (2×6 minutes); modified flanker task (Eichele et al., 2016; Eriksen, 1995), (2×6 minutes); and an auditory oddball paradigm (MMN) (Düring, Glenthøj, & Oranje, 2016), (16 minutes). Training of the modified flanker task takes place prior to EEG testing, at an earlier MRI session in which the same task is also assessed (Thorup et al., 2018). In case children do not want to be scanned, the flanker-training is performed before the EEG session. The experimental part of the EEG takes approximately 45 minutes (including breaks).

Electroencephalography

EEG data is recorded with a Biosemi ActiveTwo (BioSemi, Amsterdam, Netherlands) 128-channel system at a sampling frequency of 4096 Hz. External electrodes record electro-oculography. Auditory stimuli are delivered binaurally via insert-earphones (E-ARTONE 3A). EEG signals will be pre-processed and analyzed using the FieldTrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011), SPM, Brain Electrical Source Analysis (MEGIS Software GmbH, Gräfelfing, Germany) and customized scripts.

Paradigms/tasks

- 1) ASSR: participants are presented with auditory stimuli containing sequences of 40 Hz click trains. One sequence' stimulation lasts one second, followed by a two-second pause. We use a regular and irregular condition, see Larsen et al. (2017). In the regular condition, clicks with the duration of one second are distributed regularly at a rate of 40 clicks per second, while clicks are distributed irregularly over the one-second stimulation period in the irregular (control) condition. Each condition is recorded in separate blocks of six minutes. Participants are asked to relax while fixating on a fixation cross (see Figure 1).
- 2) MMN: participants are presented with an auditory oddball paradigm (Düring et al., 2016). This paradigm consists of 1800 stimuli in total with standard tones (76% occurrence) and deviant tones (8% occurrence) of three kinds. The standard tone is a pure tone with a frequency of 1000 Hz, an intensity of 75 dB and a duration of 50 ms. Deviant tones differ either in frequency (1200 Hz, 75 dB, 50 ms), duration (1000 Hz, 75 dB, 100 ms) or its combination (1200 Hz, 75 dB, 100 ms). Participants are asked to relax while watching a muted movie.
- 3) Modified flanker task: participants perform a modified flanker task (Eichele et al., 2016; Eriksen, 1995) running in E-Prime 2 (Psychology Software Tools, 2012). Trials start with a 700 ms fixation dot at the center of the screen. Six flanking arrows appear for 100 ms followed by the target arrow, which is present for 1000 ms in the middle of the six flankers. Flanking and target arrows point in the same (congruent condition, 50%) or in the opposite direction (incongruent condition, 50%). Participants are instructed to press the left button with their left thumb when the target arrow points to the left and vice versa. Four-hundred trials are presented in two blocks in fixed-order between subjects each lasting six minutes. An exclamation mark appears when participants respond too slow, either because of exceeding the response window (1000 ms) or their personal threshold

calculated during the training, i.e. mean reaction time (RT) + 1.5 x SD of the mean RT on 10 incongruent trials.

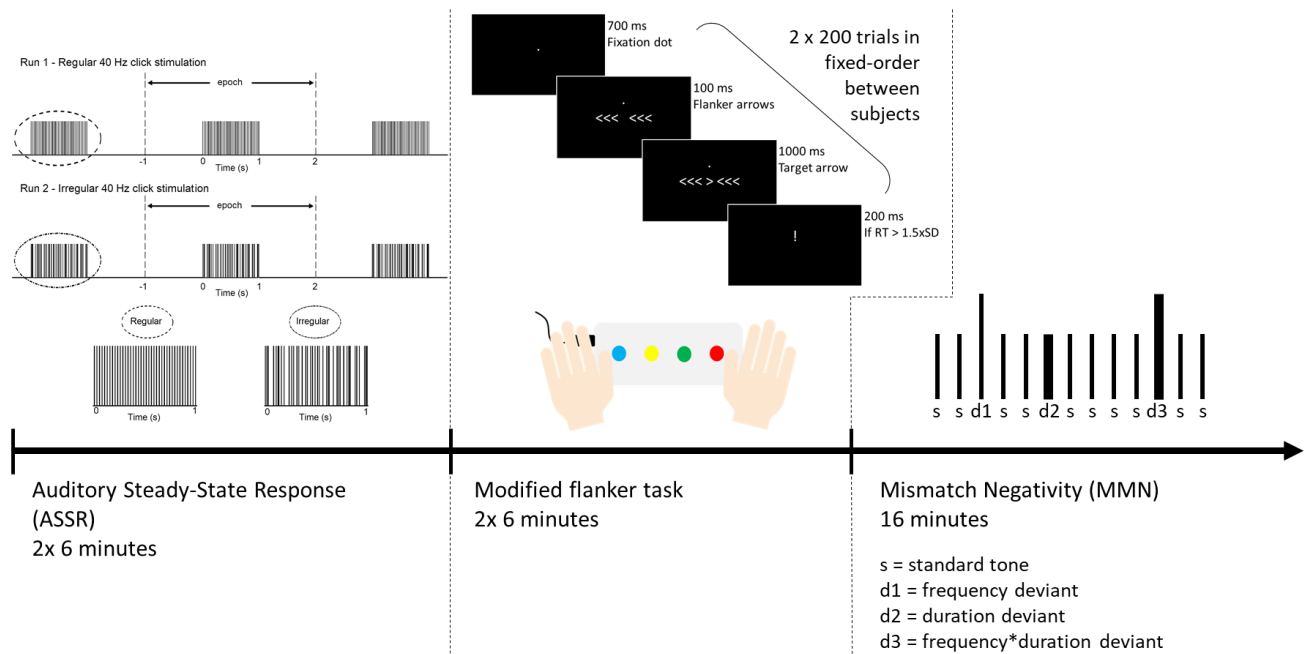


Figure 1. The paradigms presented during EEG recordings. From left to right, are the gamma entrainment paradigm (Larsen et al., 2017) to study the auditory steady-state response (ASSR), the modified flanker task (Eichele et al., 2016; Eriksen, 1995) to elicit N200, P3b and LRP, and an auditory oddball paradigm (Düring et al., 2016) to elicit mismatch negativity (MMN). The ASSR image is adapted with permission from (Larsen et al., 2017).

Functional and clinical measures

Children will be assessed with the Reynolds Intellectual Screening Test (RIST) (Reynolds, Kamphaus, & Lutz, 2003), for estimating IQ. The Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS) (Kaufman et al., 1997) will be used to ascertain presence of psychiatric disorders and subsyndromal symptomatology. We included the following measures to assess daily functioning, global problem behaviour, positive symptomatology and specific severity of autism and ADHD. The Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983) rates a child's psychological, social and daily functioning. The Childhood Behavior Checklist (CBCL) (Bilenberg, 1999) reports on various behaviours and emotions in children. Psychotic-Like Experiences (PLE) (Miller et al., 2003) assesses sub-threshold psychotic-like experiences. The Social Responsiveness Scale (SRS) (Constantino & Gruber, 2005) provides an index of the severity of autistic traits. The Attention-

Deficit/Hyperactivity Disorder – Rating Scale (ADHD-RS) (Makransky & Bilenberg, 2014) assesses the severity of ADHD-symptomatology.

Statistical analyses

Demographic and clinical characteristics will be analyzed by using parametric (one-way analysis of variance (ANOVA)) or non-parametric methods where appropriate. Behavioural performance on the flanker task will be evaluated following the statistical analyses in Ridderinkhof (2002). To assess group differences in the EEG outcome variables we will employ two different approaches; one hypothesis-driven approach assessing differences in prespecified channels known to produce highest responses for the given task (Handy, 2005) as well as a more unbiased assumption-free approach.

For the primary aim, we will test for group differences on the EEG outcome variables from the ASSR, MMN and flanker task by using a repeated-measures analysis of (co)variance (RM-AN(C)OVA) with the EEG outcome variable as the dependent variable, group-membership as between-subject factor (children at FHR-SZ, children at FHR-BP and PBC children) and condition as within-subject factor (i.e. congruent versus incongruent condition or correct versus incorrect for the flanker task). MMN is considered to show the highest amplitude at the frontal/midline EEG-channels (Hall et al., 2007; Light et al., 2007), whereas highest N200 and P3b amplitudes are typically found at frontal/midline and centro/parietal electrodes (Xie et al., 2017). Electrodes C3 and C4 will be used for the calculation of the LRP (Coles, 1989). ERN and Pe are considered maximal at frontal and central electrodes (Davies et al., 2004). Bonferroni correction for multiple comparisons will be applied to post hoc tests.

For the secondary aim, we will search for differences over the entire electrode-time (or frequency) volume and use random field theory to correct for multiple comparisons (Kilner & Friston, 2010). Using this approach, we can capture if differences are present outside of the expected component while still controlling for multiple comparisons. For the ASSR data we will use Dynamic Causal modelling (DCM) with the canonical microcircuit model to tap into potential GABAergic circuitry dysfunction (Shaw et al., 2019; Symmonds et al., 2018). For the MMN task we will employ DCM for ERPs (David et al., 2006) to infer on group differences in the connectivity of the underlying network generating the MMN responses. For each of the EEG outcome variables, we will explore how these are related to the clinical variables using either parametric or non-parametric correlation

methods. Finally, we will use a multivariate machine learning approach to merge all parameters to learn from the data by doing a cluster analysis to look at potential overlaps.

Age and sex will be included in all analyses if they covary significantly. We will conduct a post hoc test for the effect of IQ. P-values will be reported significant if below 0.05.

Discussion

This paper describes the rationale and methodology of an EEG-investigation of 11-year-old children at FHR-SZ and FHR-BP and PBC children. Evidence suggests a considerable overlap in genetic, neuropsychological and neurobiological characteristics between SZ and BP (Purcell et al., 2009). However, the search for endophenotypes that could identify those individuals at highest risk to develop these disorders remains ongoing. This study is the first EEG-investigation in a young, large FHR-sample of the same age assessing several electrophysiological measures within the context of a longitudinal cohort-study, namely ASSR, MMN, N200, P3b, LRP, ERN and Pe. By doing so, we aim to 1) identify potential electrophysiological endophenotypes for SZ and/or BP, 2) explore to what extent clinical characteristics correlate with these electrophysiological measures and 3) identify electrophysiological profiles that may distinguish children at FHR-SZ from children at FHR-BP, which can be validated in future follow-up studies.

We expect that our findings will contribute to gaining a deeper insight into potential electrophysiological endophenotypes for SZ and BP. Our findings may pave the way to follow-up studies on resilience factors because not all vulnerable children will develop the disorders. Finally, a better understanding of the underlying risk markers of SZ and BP may not only contribute to early diagnostic precision but also to the development of interventions designed to prevent or mitigate the individual expression of these severely disabling disorders.

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Conflict of interest statement

HRS has received honoraria as speaker from Sanofi Genzyme, Denmark and Novartis, Denmark, as consultant from Sanofi Genzyme, Denmark and as senior editor (NeuroImage) from Elsevier Publishers, Amsterdam, The Netherlands. He has received royalties as book editor from Springer Publishers, Stuttgart, Germany. The other authors declare they have no competing interests.

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Appendix 6: Co-authorship declarations



PHD-THESIS DECLARATION OF CO-AUTHORSHIP

The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

1. Declaration by	
Name of PhD student	Anna Hester Ver Loren van Themaat
E-mail	anna.hester.ver.loren.van.themaat.01@regionh.dk
Name of principal supervisor	Merete Nordentoft
Title of the PhD thesis	From early information processing to higher-order cognitive functioning in children with familial high risk for schizophrenia or bipolar disorder
2. The declaration applies to the following article	
Title of article	Normal Mismatch Negativity in 12-year-old Children with Familial High Risk of Schizophrenia or Bipolar Disorder
Article status	
Published ☐	Accepted for publication ☐
Date:	Date:
Manuscript submitted ☒	Manuscript not submitted ☐
Date: 27-02-2020	
If the article is published or accepted for publication, please state the name of Journal, year, volume, page and DOI (if you have the information).	
3. The PhD student's contribution to the article (please use the scale A-F as benchmark)	
Benchmark scale of the PhD student's contribution to the article	
A: Has essentially done all the work (> 90 %) B: Has done most of the work (60-90 %) C: Has contributed considerably (30-60 %) D: Has contributed (10-30 %) E: No or little contribution (<10 %) F: Not relevant	
1. Formulation/identification of the scientific problem	B
2. Development of the key methods	B
3. Planning of the experiments and methodology design and development	B
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	B
6. Interpretation of the results	B
7. Writing of the first draft of the manuscript	B
8. Finalisation of the manuscript and submission	B
Provide a short description of the PhD student's specific contribution to the article. ¹	
Anna collected data, analyzed the data, interpret the data, wrote first draft of the manuscript, submitted the manuscript.	

Latest update of the declaration: December 2018

4. Material from another thesis / dissertation¹

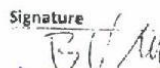
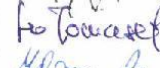
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?

Yes: ☐ No: ☒

If yes, please state name of the author and title of thesis / dissertation.

If the article is part of another author's academic degree, please describe the PhD student's and the author's contributions to the article so that the individual contributions are clearly distinguishable from one another.

5. Signatures of the co-authors^{1b}

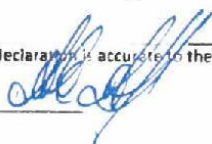
	Date	Name	Title	Signature
1.	11-02-2020	Bob Oranje	PhD	
2.	27/2/20	Leo Tomasevic	PhD	
3.	26/2/20	Kil Melissa Larsen	PhD	
4.	26/02/20	Line Korsgaard Johnsen	MSc	
5.	17/2/20	Anne Amalie Elgaard Thorup	MD, PhD	
6.	18/2/20	Kerstin Jessica Plessen	MD, PhD	
7.	21/2/20	Hartwig Roman Siebner	MD, PhD	
8.	24/2/20	Merete Nordentoft	MD, PhD	
9.				
10.				

6. Signature of the principal supervisor

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge

Date: 24/2-2020

Principal supervisor: Merete Nordentoft

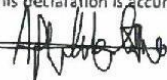


7. Signature of the PhD student

I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge

Date: 25-02-2020

PhD student: Anna Hester Ver Loren van Themaat



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PHD-THESIS DECLARATION OF CO-AUTHORSHIP

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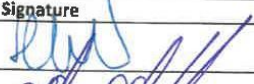
1. Declaration by	
Name of PhD student	Anna Hester Ver Loren van Themaat
E-mail	anna.hester.ver.loren.van.themaat.01@regionh.dk
Name of principal supervisor	Merete Nordentoft
Title of the PhD thesis	From early information processing to higher-order cognitive functioning in children with familial high risk for schizophrenia or bipolar disorder

2. The declaration applies to the following article	
Title of article	Behavioral performance and neural responses during a visuomotor conflict task in children with familial high risk for schizophrenia and bipolar disorder
Article status	
Published ☐	Accepted for publication ☐
Date:	Date:
Manuscript submitted ☐	Manuscript not submitted ☒
Date:	
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

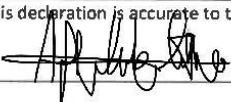
3. The PhD student's contribution to the article (please use the scale A-F as benchmark)	
Benchmark scale of the PhD-student's contribution to the article A. Has essentially done all the work (> 90 %) B. Has done most of the work (60-90 %) C. Has contributed considerably (30-60 %) D. Has contributed (10-30 %) E. No or little contribution (<10 %) F. Not relevant	
1. Formulation/identification of the scientific problem	B
2. Development of the key methods	B
3. Planning of the experiments and methodology design and development	A
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	A
6. Interpretation of the results	B
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A
Provide a short description of the PhD student's specific contribution to the article. Anna was responsible for data collection, data management, data analysis, data interpretation, writing first draft of manuscript, submit the manuscript.	

Latest update of the declaration: December 2018

4. Material from another thesis / dissertationⁱⁱ	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student's and the author's contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authorsⁱⁱⁱ				
	Date	Name	Title	Signature
1.	21/4/20	Hartwig Roman Siebner	MD, PhD	
2.	4/3/20	Merete Nordentoft	Prof	
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				

6. Signature of the principal supervisor
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date:
Principal supervisor: Merete Nordentoft 

7. Signature of the PhD student
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 25-02-2020
PhD student: Anna Hester Ver Loren van Themaat 

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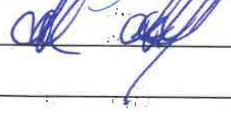
1. Declaration by	
Name of PhD student	Anna Hester Ver Loren van Themaat
E-mail	anna.hester.ver.loren.van.themaat.01@regionh.dk
Name of principal supervisor	Merete Nordentoft
Title of the PhD thesis	From early information processing to higher-order cognitive functioning in children with familial high risk for schizophrenia or bipolar disorder

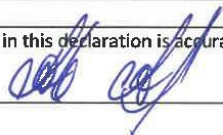
2. The declaration applies to the following article	
Title of article	Development of visual attention from age 7 to age 12 in children with familial high risk for schizophrenia or bipolar disorder
Article status	
Published ☐	Accepted for publication ☐
Date:	Date:
Manuscript submitted ☒	Manuscript not submitted ☐
Date: 25/02/2020	
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

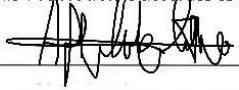
3. The PhD student's contribution to the article (please use the scale A-F as benchmark)	
Benchmark scale of the PhD-student's contribution to the article	
A. Has essentially done all the work (> 90 %) B. Has done most of the work (60-90 %) C. Has contributed considerably (30-60 %) D. Has contributed (10-30 %) E. No or little contribution (<10 %) F. Not relevant	
1. Formulation/identification of the scientific problem	B
2. Development of the key methods	B
3. Planning of the experiments and methodology design and development	B
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	A
6. Interpretation of the results	B
7. Writing of the first draft of the manuscript	B
8. Finalisation of the manuscript and submission	A
Provide a short description of the PhD student's specific contribution to the article. ¹	
Anna was responsible for data collection, analyzing the data, interpreting the data, writing the first draft of the manuscript, submitting the manuscript to journal.	

Latest update of the declaration: December 2018

4. Material from another thesis / dissertationⁱⁱ	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student's and the author's contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authorsⁱⁱⁱ				
	Date	Name	Title	Signature
1.	10/2 2020	Signe Vangkilde	Associate professor, PhD	
2.	24/2-2020	Merete Nordentoft	Prof	
3.				
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10.				

6. Signature of the principal supervisor
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date:
Principal supervisor: Merete Nordentoft 

7. Signature of the PhD student
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 25-02-2020
PhD student: Anna Hester Ver Loren van Themaat 

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1. Declaration by	
Name of PhD student	Anna Hester Ver Loren van Themaat
E-mail	anna.hester.ver.loren.van.themaat.01@regionh.dk
Name of principal supervisor	Merete Nordentoft
Title of the PhD thesis	From early information processing to high-order cognitive functioning in children with familial high risk for schizophrenia or bipolar disorder

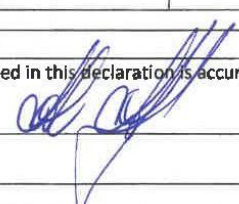
2. The declaration applies to the following article	
Title of article	Odor identification in 7-year-old children at familial high risk of schizophrenia or bipolar disorder - the Danish high risk and resilience study VIA 7
Article status	
Published ☒ Date: 08-01-2020	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☐
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	Schizophrenia research, https://doi.org/10.1016/j.schres.2019.12.028

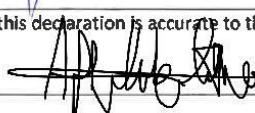
3. The PhD student's contribution to the article (please use the scale A-F as benchmark)	
Benchmark scale of the PhD-student's contribution to the article A. Has essentially done all the work (> 90 %) B. Has done most of the work (60-90 %) C. Has contributed considerably (30-60 %) D. Has contributed (10-30 %) E. No or little contribution (<10 %) F. Not relevant	A, B, C, D, E, F
1. Formulation/identification of the scientific problem	B
2. Development of the key methods	B
3. Planning of the experiments and methodology design and development	B
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	E
5. Conducting the analysis of data	A
6. Interpretation of the results	B
7. Writing of the first draft of the manuscript	B
8. Finalisation of the manuscript and submission	B
Provide a short description of the PhD student's specific contribution to the article. ¹	
Anna was responsible for data analyses, design statistical model, interpreting results, writing first draft, submitting the manuscript	

Latest update of the declaration: December 2018

4. Material from another thesis / dissertationⁱ	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student's and the author's contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authorsⁱⁱⁱ				
	Date	Name	Title	Signature
1.	10-01-20	Jens Richardt Møllegaard Jepsen	PhD	
2.	24-2-20	Merete Nordentoft	Prof	
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6.				
7.				
8.				
9.				
10.				

6. Signature of the principal supervisor I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge. Date: Principal supervisor: Merete Nordentoft	
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7. Signature of the PhD student I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge. Date: 25-02-2020 PhD student: Anna Hester Ver Loren van Themaat	
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PHD-THESIS DECLARATION OF CO-AUTHORSHIP

The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

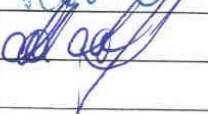
1. Declaration by	
Name of PhD student	Anna Hester Ver Loren van Themaat
E-mail	anna.hester.ver.loren.van.themaat.01@regionh.dk
Name of principal supervisor	Merete Nordentoft
Title of the PhD thesis	From early information processing to higher-order cognitive functioning in children with familial high risk for schizophrenia or bipolar disorder

2. The declaration applies to the following article	
Title of article	Event-related electroencephalographic responses in children at familial high risk for schizophrenia or bipolar disorder: a single-site EEG sub-study of the Danish High Risk and Resilience Study-VIA 11
Article status	
Published ☐	Accepted for publication ☐
Date:	Date:
Manuscript submitted ☐	Manuscript not submitted ☒
Date:	pre print to psyxiv
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

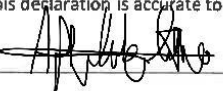
3. The PhD student's contribution to the article (please use the scale A-F as benchmark)	
Benchmark scale of the PhD-student's contribution to the article A. Has essentially done all the work (> 90 %) B. Has done most of the work (60-90 %) C. Has contributed considerably (30-60 %) D. Has contributed (10-30 %) E. No or little contribution (<10 %) F. Not relevant	
1. Formulation/identification of the scientific problem	C
2. Development of the key methods	C
3. Planning of the experiments and methodology design and development	C
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	F
6. Interpretation of the results	F
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A
Provide a short description of the PhD student's specific contribution to the article. Anna wrote first draft of the manuscript and submitted the manuscript. There was no data involved due to the descriptive character of the paper.	

Latest update of the declaration: December 2018

4. Material from another thesis / dissertationⁱ	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	
If the article is part of another author's academic degree, please describe the PhD student's and the author's contributions to the article so that the individual contributions are clearly distinguishable from one another.	

5. Signatures of the co-authorsⁱⁱⁱ				
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6. Signature of the principal supervisor
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date:
Principal supervisor: Merete Nordentoft 

7. Signature of the PhD student
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 25-02-2020
PhD student: Anna Hester Ver Loren van Themaat 

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