UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCES

Age Seven and Being at Familial High Risk for Severe Mental Illness

– Emotion Regulation, Executive Functions, and Psychopathology

The Danish High Risk and Resilience Study - VIA 7 - a register-based cohort study of children with a familial high risk of schizophrenia or bipolar disorder and their matched controls

PhD Thesis

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This thesis has been submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen, April 30, 2020

Title: Age Seven and Being at Familial High Risk for Severe Mental Illness – Emotion Regulation, Executive Functions, and Psychopathology: The Danish High Risk and Resilience Study - VIA 7 - a register-based cohort study of children with a familial high risk of schizophrenia or bipolar disorder and their matched controls

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Preface

This thesis was submitted April 30, 2020, to attain the PhD degree in Psychiatry at the Graduate School of Health and Medical Sciences, University of Copenhagen, Denmark. The content of this thesis is based on data from The Danish High Risk and Resilience Study – VIA 7, a prospective familial high-risk study.

"It's a dangerous business, Frodo, going out your door.
You step onto the road, and if you don't keep your feet,
there's no knowing where you might be swept off to."
— J.R.R. Tolkien, The Lord of the Rings

I am afraid to admit that I ended up in research by chance. I salute chance as it has brought me to where and who I am today. For some (I have heard) their research follows a straight line from start to finish. I cannot say the same. The original purpose and focus of this study were to "narrowly" research emotion regulation in children with a familial risk of schizophrenia or bipolar disorder. As time progressed, we found that, with the current assessments, we were missing out on essential aspects of emotion regulation. Using the instruments and measures at hand, we did our best to resolve this within the restraints of an ongoing pre-planned study. The focus on emotion regulation remained, but the method was expanded to include broader areas of general and specific functioning related to emotion regulation, namely executive functions and dimensionally assessed psychopathology, and not the least, the construction of a novel instrument of clinician-rated emotion regulation. My hope with this thesis is to succeed in elucidating how these broader goals are relevantly interconnected and help carry forth the understanding of emotion regulation. This, with an overarching focus of aiding those who suffer the consequences of inadequate emoting regulation. This journey is nearing its end, but the interest in research and specifically research in child and adolescent mental health has settled root. With the aid of chance, I hope to continue in the field of research.

Katrine Spang

Katrine Søborg Spang
Copenhagen April 30, 2020

Acknowledgements

This work was supported by TrygFonden which funded the PhD scholarship. The 'Danish High Risk and Resilience Study -VIA 7' was additionally funded by the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH); Mental Health services of the Capital Region of Denmark, Aarhus University Psychosis Research Unit, Aarhus University Hospital, and the Beatrice Surovell Haskell Fund for Child Mental Healh Research of Copenhagen.

Numerous fantastic people deserve acknowledgement and my deepfelt appreciation.

First and foremost, I want to acknowledge all the families who participated in The Danish High Risk and Resilience Study – VIA 7. Without their commitment and willingness to let researchers into their lives this study had not been possible - Thankyou.

I wish to extend a special gratitude towards my principal supervisor Anne Amalie Elgaard Thorup, thank you for always being there whenever I needed your guidance. To my co-supervisor Jens Richardt Møllegaard Jepsen, thank you for your thoroughness, dedication and support and not least the countless hours you spend with me to go through parts of my writings. Carsten Obel, thank you for sharing your experience and your valuable feedback . A further acknowledgement and recognition go to my two unofficial supervisors to Merete Nordentoft, for your great knowledge, your optimism and dedication and to Kerstin Jessica Plessen, thank you for believing in me and for your valuable insight and guidance when you were my official supervisor and your continued support hereafter

I would also like to express my deepfelt appreciation of my close colleagues (and friends), as well as thank both current and former colleagues without whom this thesis and the whole VIA study had not existed. Thank you also to new colleagues and collaborators and all the other wonderful people I have been blessed to meet through the course of this work. A special thank you to Signe Vangkilde og Thomas Habekost and the researchers at Center for Visual Cognition, Department of Psychology for providing shelter closer to home and allowing focused attention on my studies, and to Julie Hagsrøm for collaboration in the development of TEC-M.

Last but definitely not least I would like to thank my beloved family. My husband, Jannik, for his endless love, support, patience and encouragement. My children Tjalfe, Sigurd and Magne for your patience, and much needed distractions. To my parents and mother-in-law for all your assistance and support.

List of papers

This Ph.D. study have resulted in the following papers:

Paper I. **The Strengths and Difficulties Questionnaire; Seven-year-old children with familial high risk of schizophrenia or bipolar disorder and controls**
- The Danish High Risk and Resilience Study - VIA 7; a population-based cohort study
Katrine Søborg Spang, Anne A. E. Thorup, Ditte Ellersgaard, Nicoline Hemager, Camilla Christiani, Birgitte Klee Burton, Ditte Gantriis, Aja Neergaard Greve, Maja Gregersen, Ole Mors, Merete Nordentoft, Jens Richardt Møllegaard Jepsen, Carsten Obel* & Kerstin J. Plessen*
(Manuscript)

Paper II. **Executive functions in seven-year-old children of parents with schizophrenia or bipolar disorder compared with controls compared with controls**
- The Danish High Risk and Resilience Study - VIA 7, a register-based cohort study
Katrine Søborg Spang, Ditte Ellersgaard, Nicoline Hemager, Camilla Christiani, Birgitte Klee Burton, Aja Neergaard, Greve, Ditte Gantriis, Jessica Ohland, Marianne Giørtz Pedersen, Ole Mors, Merete Nordentoft, Kerstin J. Plessen, Carsten Obel, Jens Richardt Møllegaard Jepsen, Anne A. E. Thorup
(In Review)

Paper III. **Emotion regulation in 7-year-old children with familial high risk for schizophrenia or bipolar disorder compared to controls**
- The Danish High Risk and Resilience Study - VIA 7, a register-based cohort study
Katrine Søborg Spang, Julie Hagstrøm, Ditte Ellersgaard, Camilla Christiani, Nicoline Hemager, Birgitte Klee Burton, Aja Neergaard Greve, Ditte Gantriis, Signe Vangkilde, Ole Mors, Merete Nordentoft, Carsten Obel, Kerstin Jessica Plessen, Jens Richardt Møllegaard Jepsen, Anne A.E. Thorup
(Submitted)

*Shared last co-authorship

Thesis summary

Executive functions and appropriate emotion regulation are crucial for adaptive everyday functioning and these functions develop vastly throughout childhood, and problems herewith may underlie problematic behaviour in some children. Schizophrenia spectrum disorder and bipolar disorder are severe mental illnesses with documented problems of emotion regulation and executive functions in the affected individuals. Studying childhood offspring of individuals diagnosed with a schizophrenia spectrum disorder or bipolar disorder gives valuable information regarding early developmental processes and symptoms which may inform early intervention programs.

The primary aim of this thesis is to assess emotion regulation, executive functions, and the occurrence of behaviour indicative of mental illness, in children with a familial predisposition for schizophrenia and bipolar disorder. The second aim is to assess whether a brief measure of behavioural difficulties can function as a screening tool to identify mental illness in children with familial high-risk of severe mental illness. This study, of children at seven-years of age, is a part of 'The Danish High Risk and Resilience Study – VIA 7', the first wave of a longitudinal, register-based cohort study of 522 children with familial high-risk of schizophrenia spectrum disorder (N= 202) or familial high-risk of bipolar disorder (N=120) and matched controls (N=200). Due to the lack of standardized behaviour-based observational measures of emotion-regulation rated by the clinician, a third aim was to develop and apply such a measure.

The method in focus in this thesis is behavioural-based observational assessment. We assessed executive functions with 'The Behavior Rating Inventory of Executive Functions' (BRIEF) questionnaire, rated by the child's primary caregiver and schoolteacher. Psychopathology was assessed dimensionally with 'The Strengths and Difficulties Questionnaire' (SDQ), also rated by the primary caregiver and the schoolteacher. Finally, we assessed emotion regulation with 'The Tangram Emotion Coding Manual' (TEC-M) the newly developed clinician-rated observational measure of emotion regulation and by emotion regulation related scales from both the BRIEF and SDQ.

We found that children with a familial high-risk of either schizophrenia or bipolar disorder had a higher occurrence of behavioural difficulties and more frequently at a level indicative of mental illness compared to control children. They also exhibited significant executive functions problems compared to control children. According to primary caregiver and teacher ratings, both high-risk groups displayed emotion regulation related difficulties; however, this did not reflect in the clinician-rated emotion regulation measure results. Finally, investigations of a brief measure of behaviour problems indicated that it could function well as a screening tool for the identification of mental illness in this high-risk population as it exhibited respectable discriminatory abilities.

These findings, of significant everyday life difficulties and significant psychopathology at the early age of seven in children with familial high-risk, warrant further investigation and targeted intervention.

Resumé (Danish summary)

Eksekutive funktioner og adækvat følelsesregulering er afgørende for at kunne tilpasse sig i forhold til hverdagslivets varierende krav. Disse funktioner udvikler sig betydeligt gennem barndommen, og problemer hermed kan være en medvirkende årsag til problemadfærd hos børn. Skizofreni og bipolar sygdom er alvorlige psykiske sygdomme med dokumenterede relaterede problemer i forhold til følelsesregulering og eksekutive funktioner hos de berørte personer. At undersøge børn, af forældre med skizofreni eller bipolar sygdom, i en tidlig alder giver værdifuld information om tidlige udviklingsprocesser og symptomer, som igen kan danne grundlag for tidlig intervention.

Det primære formål med denne afhandling er at måle og sammenligne følelsesregulering, eksekutive funktioner og adfærd, der potentielt er indikativ for psykisk sygdom, hos børn med en familiær disposition for skizofreni eller bipolar sygdom. Det andet formål er at vurdere, om et kortfattet adfærdsmål kan fungere som et screeningsværktøj til at identificere psykisk sygdom hos børn med familiært betinget høj risiko for alvorlig psykisk sygdom. Denne undersøgelse af syvårige børn er en del af 'The Danish High Risk and Resilience Study – VIA 7', den første i en planlagt række af undersøgelser af en registerbaseret kohorte af 522 børn af forældre med skizofreni forstyrrelse (N = 202) eller bipolar sygdom (N = 120) og matchede kontrolbørn (N = 200). Det tredje mål er at udvikle og applicere et klinikerbedømt, standardiseret observationsmåler af adfærd med henblik på at vurdere følelsesregulering.

Denne afhandling metodefokus er således observationsvurdering af adfærd. Vi undersøgte eksekutive funktioner med spørgeskemaet 'The Behaviour Rating Inventory of Executive Functions' (BRIEF) udfyldt af barnets primære omsorgsperson og barnets skolelærer. Dimensional psykopatologi blev vurderet med spørgeskemaet 'The Strengths and Difficulties Questionnaire' (SDQ), ligeledes udfyldt af den primære omsorgsperson og barnets skolelærer. Endelig undersøgte vi følelsesregulering med 'The Tangram Emotion Coding Manual' (TEC-M), som er et nyudviklet kliniker-scorede observationsmål for følelsesregulering, samt via følelsesreguleringsrelaterede skalaer fra BRIEF og SDQ.

Vi fandt, at børn med en familiær høj risiko for enten skizofreni eller bipolar sygdom havde en øget forekomst af adfærdsmæssige vanskeligheder og hyppigere på et niveau, der indikerer tilstedeværelsen af psykisk sygdom sammenlignet med kontrolbørn. Ligeledes udviste de betydelige problemer med eksekutive funktioner sammenlignet med kontrolbørn. Begge grupper af børn med familiær risiko vurderes af deres primære omsorgspersoner og lærere at have flere vanskeligheder med følelsesregulering end kontrolbørn, om end dette ikke afspejledes i den klinikerbedømte standardiserede observation af følelsesregulering. Endelig så vi, at et mål for adfærdsmæssige problemer viste sig at have gode diskriminatoriske egenskaber og potentiale for at fungere godt som et screeningsværktøj til identifikation af psykisk sygdom i denne gruppe af børn med høj risiko for alvorlig psykisk sygdom.

Disse fund af betydelige dagligdags vanskeligheder samt øget forekomst af psykopatologi i en ung alder hos børn med familiær høj risiko for alvorlig psykisk sygdom bør give anledning til yderligere undersøgelser samt fokuseret tidlig intervention.

Thesis structure

This thesis consists of some partially overlapping parts and verbatim overlap inevitable may occur between papers and thesis.

Chapter 1. Introduction, Concepts and Considerations

Presents a general introduction to schizophrenia spectrum psychosis and bipolar disorder and related subjects relevant for the field of research. Hereafter follows aspects relevant to the focus areas of executive functions, emotion regulation and behavioural signs of psychopathology.

Chapter 2. Objectives and hypotheses

This chapter presents the thesis' overall aims and the aims and hypothesis of the three individual papers.

Chapter 3. The Danish High Risk and Resilience Study

Gives a detailed overview of the Danish High Risk and Resilience Study that provided the materials for this thesis as well as common analyses strategy of the study.

Chapter 4. Materials and methods specific to the studies of the present thesis

Chapter 4 specifies participants, measures and analyses of the three papers of this thesis.

Chapter 5. The Tangram Emotion Coding Manual (TEC-M)

Describes the development of TEC as a measure of emotion regulation as well as the specifics of the manual and its application.

Chapter 6. Results

Present results from previous studies on the same study population of The Danish High Risk and Resilience Study and results from the four papers.

Chapter 7. Results from relevant or related papers and dissertations

Present results of previous studies relevant for framing the results of this thesis. This includes two dissertations based on data from The Danish High Risk and Resilience Study, and results from two papers related to The Tangram Emotion Coding Manual.

Chapter 8. Discussion

Provides a summary of the main findings followed by a discussion of methodology and findings.

Chapter 9. Conclusions and perspectives

Contains final remarks.

Table of content

Chapter 1. Introduction, concepts and considerations

Schizophrenia spectrum disorder, bipolar disorder and major depressive disorder are frequently referred to collectively as severe mental illness. Severe mental illness impacts the mental wellbeing and functioning of the affected individuals, and often also their physical health (including a reduced lifespan) as well as their social and work performance. Thus, severe mental illness can have detrimental effects not only for the individual affected by severe mental illness but also for both their close and professional relations. In addition to the consequences on the individual level, severe mental illness causes massive societal and economic disruptions, mainly through indirect economic costs, primarily caused by loss of productivity, and to a lesser degree direct toll on healthcare systems (Gustavsson et al., 2011; Trautmann, Rehm, & Wittchen, 2016).

Alleviation or prevention of severe mental illness could thus help both the individual, their social relations as well as the economy of the society. The first step towards this could be more exact knowledge achieved by research into the identification of risk factors eligible for intervention. Offspring of parents with severe mental illness have an approximately 10-fold increased risk of developing the concordant disorder relative to controls and further they also have a significantly increased risk of developing one of the two other severe mental illnesses as well as any other mental disorders (Gottesman, Laursen, Bertelsen, & Mortensen, 2010; Rasic, Hajek, Alda, & Uher, 2014). Thus, studying children of parents with severe mental illness is advantageous as these children constitute an enriched population allowing the study of antecedents, trajectories, common risk factors, and both genetic and environmental factors. Self-regulatory and behavioural problems are possible antecedents or indicators of, as well as risk factors for developing mental illness and thus one of many relevant areas to study closely.

The following sections of this chapter will briefly elaborate on the mentioned topics, starting with an introduction of the heritability of schizophrenia spectrum disorder and bipolar disorder, the two severe mental illnesses of focus in this thesis. This is followed by a discussion of the advantages of familial high-risk studies in general and hereafter a short outline of schizophrenia spectrum disorder and bipolar disorder together with topics and concepts relevant for framing the results presented in this thesis. Lastly, is an introduction to the primary focus of this thesis; dimensionally assessed psychopathology as well as executive functions and emotion regulation that will be introduced within the overarching umbrella concept of self-regulation.

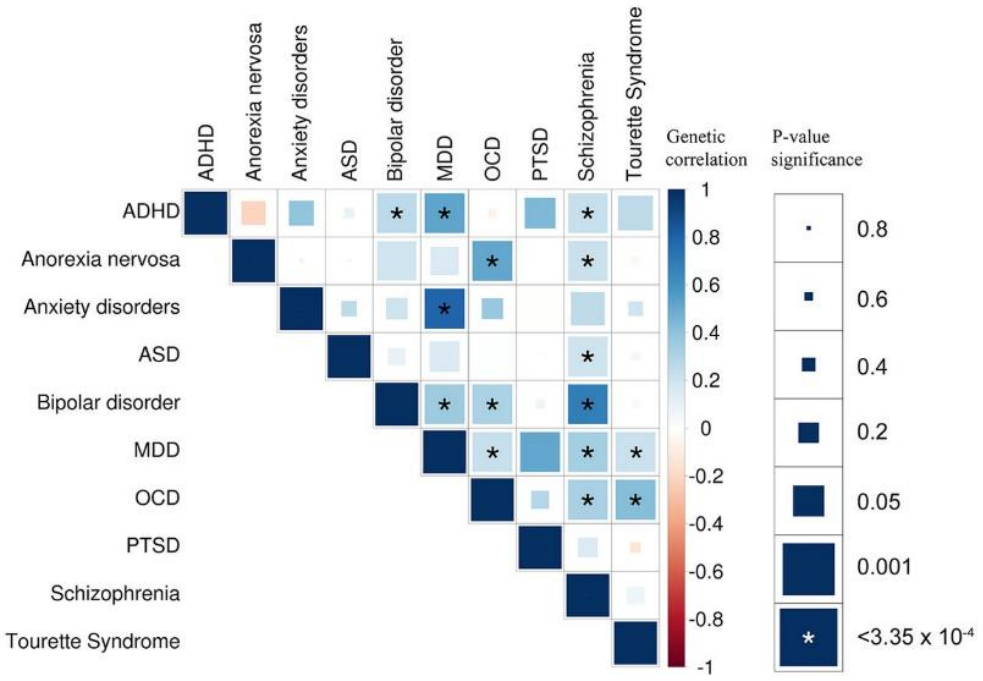
'Schizophrenia' will in this thesis be used synonymously with schizophrenia spectrum disorder.

Heritability of schizophrenia and bipolar disorder

Studies have found that children of parents diagnosed with either schizophrenia or bipolar disorder have a roughly 10% risk vs a 1% risk in the background population of developing the concordant disorder (Rasic et al., 2014). Genetic and environmental factors both contribute to this familial heritability and based on Danish National registers, the heritability attributed genetic factors has been estimated to be 0.67 for

schizophrenia and 0.62 for bipolar disorder (Wray & Gottesman, 2012). This is supported by other studies that likewise suggest that the genetic contribution accounts for the majority of the familial transmission (Lichtenstein et al., 2009; Walder, Faraone, Glatt, Tsuang, & Seidman, 2014; Wray & Gottesman, 2012). Schizophrenia and bipolar disorder are highly polygenic, and studies have found a significant genetic overlap of the two disorders (Figure 1.1) (Brainstorm Consortium, 2018; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Seidman & Mirsky, 2017; The International Schizophrenia Consortium, 2009; Wray & Gottesman, 2012). This overlap is supported by offspring studies which find that having a parent with schizophrenia or bipolar disorder not only increase the risk of developing the concordant disorder, but also the risk of developing the non-concordant disorder (Rasic et al., 2014). The high incidence of concordant disorders found in offspring of individuals diagnosed with severe mental illness, constitutes the offspring population a scientifically highly interesting study population.

Figure 1.1. Genetic correlations across psychiatric phenotypes.



Hue indicates the magnitude of the correlation and size indicates significance (LDSC). Asterisks indicate significance after Bonferroni correction. (Brainstorm Consortium, 2018).

Familial high-risk studies

As indicated by the nomenclature, 'familial high-risk studies' involve the study of relatives of individuals with a defined condition. Choosing the term 'familial' rather than 'genetic' in this study is a conscious choice as even though it is, as described earlier, well recognized that schizophrenia and bipolar disorder have a genetic component of heritability causation, the heritability is not purely genetic but also has an environmental component. Likewise, an individual with severe mental illness may have genetic markers for the illness without having first-degree relatives with severe mental illness. Thus, one can be at genetic risk

without having affected relatives (L. K. Phillips & Seidman, 2008). This said, schizophrenia and bipolar offspring studies exploit the fact that a family history of schizophrenia or bipolar disorder is the single most influential individual risk factor, presently known, for developing the concordant disorder (Mortensen et al., 1999). The cumulative incidence of schizophrenia and bipolar disorder have been found to be 1.12 % and 0.63 % in the general Danish population, versus 7.0 % and 4.4 % respectively for offspring with one parent ever having been admitted for the same disorder (Gottesman et al., 2010). Offspring cohorts thus constitute an enriched population for studying the aetiology, early antecedents, and pathological trajectories of an illness. This increased risk of the offspring developing the disorder is consequently advantageous for both practical and financial reasons. Familial high-risk studies also enable comparisons between those who convert to disorder with those who do not, thus, allowing the study of potential protective factors.

Familial high-risk studies have generated numerous important insights into severe mental illness. However, depending on the purpose of the familial high-risk study some considerations are necessary. It is important to keep in mind that the majority of individuals who develop schizophrenia or bipolar disorder have no family history of severe mental illness (Gottesman & Erlenmeyer-Kimling, 2001; Wray & Gottesman, 2012). Accordingly, familial high-risk studies include a sub-population of individuals with a risk profile that might not be equivalent to affected individuals without a familial disposition, and consequently, the familial high-risk method is strictly only generalizable to individuals who have a genetic relationship with an individual with severe mental illness (L. K. Phillips & Seidman, 2008).

Schizophrenia spectrum disorders

Schizophrenia spectrum disorders comprise a heterogeneous and multifaceted group of brain disorders recognized as progressive neurodevelopmental disorders. Active schizophrenia is characterized by an array of symptoms, including delusions, hallucinations, disorganized communication, and behaviour as well as negative symptoms such as loss or decrease of initiation, speech, emotions, and movement and impaired cognition. Collectively these symptoms attribute a detrimental effect on functioning. Schizophrenia thus constitutes a severe and disabling disorder with profound consequences. Schizophrenia afflicts approximately 1 % of the population and most often emerges in adolescence or young adulthood (Gogtay, Vyas, Testa, Wood, & Pantelis, 2011) with premorbid deficits discerned already in childhood (Shah, Tandon, & Keshavan, 2013). There is well-established consensus that neurocognitive deficits constituting a core feature of schizophrenia (Reichenberg & Harvey, 2007), and characterization of schizophrenia spectrum disorder is increasingly focusing on cognitive deficits as a robust characteristic of the disorder (Michie et al., 2008). This, however, is not reflected in the description of schizophrenia (F20) in the diagnostic manual ICD-10: *"Clear consciousness and intellectual capacity is usually preserved, although certain cognitive defects may develop over time."*[1] and the diagnosis of schizophrenia is still based on specific criteria being fulfilled,

[1] Unofficial English translation by Katrine Søborg Spang of the Danish version of the ICD-10 (World Health Organization Collaborating Centre for Research and Training in Mental Health, 1994)

with very little emphasis and attention to the underlying neurobiology and cognitive deficits of the disorder.

Bipolar disorder

Bipolar disorder refers to a group of disorders characterized by pathological fluctuations in mood from depressive to (hypo)mania, most often in alteration with periods of euthymia (M. L. Phillips & Kupfer, 2013). Depressive mood is associated with symptoms such as loss of pleasure and energy, sleep disturbances, and altered cognition. Mania is associated with e.g. irritability, inflated self-esteem, reduced sleep, distractibility, increased activity, and psychomotor agitation.

As a diagnostic category, bipolar disorder exhibits considerable heterogeneity both with regards to illness course, comorbidity, degree of intermittent recovery, functional and cognitive implications, and age of onset. Age of onset, defined as the age at first treatment or first hospitalization (Leboyer, Henry, Paillere-Martinot, & Bellivier, 2005), has been found to have three peaks; early onset with a mean age of 17, intermediate onset at mean age of 27, and late onset with a mean age of 46 (Leboyer et al., 2005). The first mood symptoms of bipolar disorder most often debut before the age of 21 years (Birmaher et al., 2009) and typically with a (mild) depressive episode followed years later by the first (hypo)manic episode (Drancourt et al., 2013). Children at familial high-risk who themselves develop bipolar disorder, most often have their first mood episode before the age of 12 years (Birmaher et al., 2009; Duffy, Goodday, Keown-Stoneman, & Grof, 2018). Early onset bipolar disorder is associated with more psychotic features, higher prevalence of comorbidity, and lower treatment responses. Bipolar disorder is often initially misdiagnosed with a delay of the bipolar disorder diagnosis of up to ten years (Fritz et al., 2017; L. V. Kessing et al., 2017). Early onset bipolar disorder is especially associated with protracted time from first episode to treatment (Drancourt et al., 2013; Suominen et al., 2007).

It is generally agreed that bipolar disorder is progressive in nature, which has led to the proposal of staging models that resemble models widely used in other medical specialties such as oncology. Some models focus on the clinical course of bipolar disorder (Berk, Hallam, & McGorry, 2007) while others focus more on functional impairment along with psychiatric symptomatology (Kapczinski et al., 2009). Both models are for the majority based on cross-sectional and retrospective studies, and results should therefore be interpreted with caution, but overall, results point towards that prognosis and treatment response deteriorate with progression of the disorder (Kapczinski et al., 2014). As the early stages of bipolar disorder are still poorly defined, both models highlight the need for identification and study of at-risk individual to further knowledge and contribute to the refinement of clinical staging. This, as a mean to enhance future early and appropriate intervention.

Diagnostic criteria (and the name) of bipolar disorder has changed over time and has likewise differed between diagnostic systems, as exemplified by the two main classification systems; 'the International Classification of Diseases and Related Health Problems' and 'the American Psychiatric Associations Diagnostic and Statistical Manual of Mental Disorders'. These systems have though, gradually converged to

very similar classifications; 'The ICD-10' (World Health Organization, 2004) and 'DSM-IV' (Morosini, Magliano, Brambilla, Ugolini, & Pioli, 2000). These differences and changes in diagnostic criteria have without doubt contributed to the differences in scientific results through the years.

The neurodevelopmental hypothesis

The neurodevelopmental model of schizophrenia is widely accepted and has been the most influential theory in schizophrenia during the last three decades (J. J. McGrath, Féron, Burne, Mackay-Sim, & Eyles, 2003). The neurodevelopmental hypothesis of schizophrenia first appeared in the 1980s and suggests that a disruption of typical brain development during early life underlies the development of psychosis later in life (Murray & Lewis, 1987). The brain development disruption, portrayed in the neurodevelopmental model, is depicted to happen years before clinical illness onset; often during foetal life, birth and the neonatal period and could be of genetic as well as environmental origin (Rapoport, Giedd, & Gogtay, 2012). Whether a neurodevelopmental model also applies to bipolar disorder, or if it is neuro-progressive is still much debated (Schneider, DelBello, McNamara, Strakowski, & Adler, 2012). However, cumulative evidence from genetic and familial studies, supporting a neurodevelopmental contribution to bipolar disorder has instigated a gradual shift, from seeing bipolar disorder as a neurodegenerative disorder, towards considering neurodevelopmental mechanisms as the underlying cause of bipolar disorder (O'Shea & McInnis, 2016). Overall, further research in the premorbid states of both schizophrenia and bipolar disorder are still much needed.

Endophenotypes

Endophenotypes is a concept that embodies a highly heritable characteristic which approximates the genetic liability of a complex disorder. As such, endophenotypes are defined by being disease-associated traits that are illness-state independent, highly heritable, and with both the trait and illness co-segregating within families. Thus, the trait is more frequent in unaffected relatives of individuals with the illness, than in the general population (Bora, Yucel, & Pantelis, 2009; Gershon & Goldin, 1986). Endophenotypes hereby provide a unique opportunity for exploring early signs of disorder in individuals with the endophenotype but not (yet) presenting the disorder. Endophenotypes could possibly aid the identification of individuals with high risk of developing the disorder and predict the development, as they must be state-independent and hence present in the premorbid phase. Identifying specific endophenotypes for psychiatric disorders might help differentiate between disorders and, with this, ensure appropriate and specific intervention in the early phase of disorder. Examining profile differences between related disorders, such as schizophrenia and bipolar disorder, may contribute with information valuable for diagnosis and targeted treatment.

Assessing signs of psychopathology within a familial high-risk perspective

In child and adolescent familial high-risk studies, psychopathology is often assessed with categorical measures such as semi-structured interviews. The gold standard and also most often used semi-structured

interview in familial high-risk studies is the 'Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version' (K-SADS-PL, (Kaufman et al., 1997)) administered to both the child and the parent. Dimensional measures are likewise often used, mainly comprehensive validated rating-scales such as the empirically based 'Child Behavior Checklist' (CBCL, (Achenbach & Edelbrock, 1983)). In familial high-risk bipolar studies, this practice of using semi-structured interviews or validated rating scales is frequent but less prevalent in familial high-risk schizophrenia studies (Ellersgaard, 2018). Differences in the methodology of psychopathological assessment challenge the comparison of findings between studies. However, an overall higher occurrence of a broad range of psychopathology, both in offspring with familial high-risk of schizophrenia and offspring with familial high-risk of bipolar disorder, has been documented through analyses of register data of in- and outpatient of psychiatric hospitals as well as results from categorical and dimensional measures of psychopathology (Ellersgaard, 2018). Depending on the purpose of assessment, it can be relevant to utilize shorter, less time-consuming assessment measures of psychopathology. Short questionnaires are one possibility, as they are often more accessible and acceptable in broad and more extensive epidemiological investigation, e.g. in large community assessments in school settings. However, this necessitates high reliability and validity of the measures used. One measure which is increasingly used, is 'The Strength and difficulties questionnaire' (SDQ, (Goodman, 1997)). The SDQ has in several studies been assessed to be a reliable tool for assessing psychopathology dimensionally (Goodman & Scott, 1999; Heuvel et al., 2017; Niclasen et al., 2012; Stone, Otten, Engels, Vermulst, & Janssens, 2010).

Cognitive impairments

Cognitive impairments are considered a core feature of schizophrenia (Mesholam-Gately, Giuliano, Faraone, Goff, & Seidman, 2009), with impairments in multiple cognitive domains including working-, verbal- and visual memory, attention, processing speed, social cognition, and executive functions(Bora, 2016). Likewise, cognitive dysfunctions are well-established features of bipolar disorder and evidence suggests that the profile of cognitive impairments is similar to that found in schizophrenia, albeit, dysfunctions are generally less severe (Bora, 2016). While premorbid cognitive deficits are ingrained features of schizophrenia, evidence suggests that premorbid cognitive dysfunction is not a dominant feature of bipolar disorder (Sudhir Kumar & Frangou, 2010). Contrary, studies on bipolar disorder have found evidence for the existence of both below and above-average cognitive performance premorbid, and both variants as a risk factor for developing bipolar disorder(Lima et al., 2019; Sudhir Kumar & Frangou, 2010). Thus, Both disorders are associated with various cognitive impairments however for bipolar disorder the impairments are repeatedly found to be less severe than in schizophrenia (Bortolato, Miskowiak, Köhler, Vieta, & Carvalho, 2015). The severity and type of cognitive impairments likely play a key role in the severity of both prodromal and active phase and likewise has been shown to substantially affects remission, rehabilitation, vocational function, and quality of life in euthymic phases and recovery (Fett et al., 2011; Green, Kern, & Heaton, 2004; K. W. Miskowiak et al., 2018).

Self-regulation, executive functions and emotion regulation

Self-regulation, executive functions and emotion regulation are crucial for overall functioning and well-being of the individual. But, like most (all) psychological concepts, the concepts of self-regulation, executive functions and emotion regulation are subject to vast disagreement and debate. The following will not dare the attempt of presenting the multiple notions of these concepts, but solely provide an overview of the definitions of concepts and model of emotion regulation utilized in the present thesis.

Self-regulation

The construct of self-regulation is much debated both in terms of its definition and how-to asses it (Vohs & Baumeister, 2011). However, there is an overall agreement of self-regulation as a multidimensional construct that broadly includes the individual's ability to regulate cognition, emotion, and behaviour, and that self-regulation has important implications for health and well-being (McClelland et al., 2018).
Self-regulation necessitates a mental representation of a goal; a goal here denoting a representation of both a desired immediate state of self, including both physical and emotional states, and also for one's near or more distant future (Baumeister & Heatherton, 1996). Self-regulation thus refers to, and is reliant upon, the ability to monitor self and environment, as well as the initiation, extinction, and modification of one's own cognition, behaviour, and emotions. Accordingly, self-regulation is heavily dependent on cognitive abilities including, among other, attentional control, working memory, initiation, and inhibition; as it is necessary to be able to inhibit an automated response and to initiate modification. Cognitive abilities of attentional control, inhibition, and working memory among other, are part of another collective concept; executive functions. According to Lezak (1995), executive functions correspond to the mental capabilities necessary for formulating an objective, planning, and implementing actions to achieve that objective, and then intervening in the performance of complex tasks (Lezak, 1995). In this way self-regulation is dependent on and assisted by executive functions (Blair & Ursache, 2011).
Yet another concept which is overlapping and heavily intertwined with both self-regulation and executive functions, is the concept of emotion regulation. Emotions are suggested to correspond to the motivational aspect of cognition (Zelazo & Cunningham, 2007) and hereof emotion regulation serves as a modulator of motivated cognition. As indicated, processes and concepts associated with and necessary for self-regulation are numerous and the following will only focus on the concept of executive functions and emotion regulation.

Executive functions

Executive functions are a collective of separate but interrelated cognitive control processes that are important for the monitoring of self and environment as well as the management and integration of information. The term 'executive functions' is thus used to generally indicate the most abstract functional levels of analysis. Executive functions enable future-directed thinking and planning, and herewith the formulation of goals. Equally important, executive functions enable the ability to pursue, maintain and

modify these goals according to changing circumstances (Banich, 2009; Blair & Ursache, 2011; Lezak, 1995). Executive functions are utilized in a wide range of everyday situations when, e.g. overriding habits (*Driving straight to work when you should have dropped off a letter at the post office' is an example of executive functions failure*) or dealing with novelty (*Driving a new route* (passing the post office) *you have not driven before*). Thus, executive functions are a prerequisite for successfully navigating daily life activities through regulation of other cognitive processes and thereof enablement of self-regulation of thoughts and behaviour (Miyake & Friedman, 2012; Snyder, Miyake, & Hankin, 2015).

The importance and general function of executive functions are over-all agreed upon, nonetheless, the precise components of executive functions are still debated (Nyongesa et al., 2019). Even so, it is mostly agreed that some of the primary elements of executive functions are attentional control/attention deployment, mental flexibility, working memory, initiation, and inhibition of activity (Anderson, 2002; Diamond, 2013). Executive functions develop from infancy and during the course of childhood, adolescence and young adulthood (Anderson, 2002; Best & Miller, 2010; Diamond, 2013; Seidman et al., 2006). Research points towards an expeditious development of executive functions before the age of five, with rapid developmental spurts occurring again around the age of seven years, around age 10 years, and also in adolescence (Brocki & Bohlin, 2004). The progression of executive functions maturation differs between individuals; this may both be due to individual genetic predispositions, pathophysiological mechanisms, as well as to external environmental stimulation and demands that the individual is exposed to; all of which can affect the structure and reorganisation of connective neural networks of the brain and hereby executive functions' networks (Best & Miller, 2010; Friedman et al., 2008; Keshavan, Giedd, Lau, Lewis, & Paus, 2014; C. R. Reynolds & Horton, 2008). The influence of an executive common factor has been found to be 99% heritable (Friedman et al., 2008) constituting executive functions ability highly heritable and mainly mediated by genetic predispositions. This however, does not rule out environmental effects on executive functions and the possibility of enhancing executive function ability by practice (Friedman et al., 2008).

Executive function in schizophrenia and bipolar disorder

As noted, generalized cognitive impairments are often reported in unaffected relatives of individuals with schizophrenia and executive functions impairments are the most commonly observed cognitive deficits of schizophrenia, and indicated as a key feature of cognitive impairment in schizophrenia (Li, Cao, Shao, & Xue, 2014; Orellana & Slachevsky, 2013; Raffard & Bayard, 2012). Some argue that executive functions deficits are purely reflective of a general intellectual decline (Chan, Chen, & Law, 2006). However, several studies find specific executive functions deficits confined to single executive functions domains and further, differential impairments of executive functions have been found in individuals with schizophrenia with seemingly preserved overall intellectual functioning. Collectively, this is difficultly explained by an overall cognitive impairment (Chan et al., 2006; Raffard & Bayard, 2012). Executive functions deficits are detectable early in life in individuals who later develop schizophrenia (Reichenberg & Harvey, 2007) as well as in first degree relatives, including offspring of parents diagnosed with schizophrenia (Bora, 2017; Burton

et al., 2018; Christiani et al., 2019; Hemager et al., 2018; Orellana & Slachevsky, 2013). Relevantly, executive dysfunction has been associated with the observed psychosocial impairments of individuals diagnosed with schizophrenia (Orellana & Slachevsky, 2013). Executive functions in relation to bipolar disorder is less examined and results are somewhat conflicting. Some evidence indicate impaired executive function prior to bipolar disorder illness onset (Bora & Pantelis, 2015; Meyer et al., 2004) while studies of offspring of parents diagnosed with bipolar disorder convey conflicting results, with some finding significant executive functions impairments, while others do not (Bora, 2017; Burton et al., 2018; Hemager et al., 2018; K. W. Miskowiak et al., 2017).

Assessing executive functions

Executive functioning is most commonly assessed by neuropsychological tasks in experimental conditions (performance-based), designed to tap into one or more components of executive functions, or by questionnaires designed to measure components of executive functions by assessing complex real-world behaviour (behaviour-based) (Gerst, Cirino, Fletcher, & Yoshida, 2017). The validity, utility, and diagnostic value of lab-based neuropsychological assessment instruments of executive functions have been thoroughly supported through decades of research across a wide range of disorders and in both children and adults (Castellanos, Kronenberger, & Pisoni, 2018; Lezak, 1995). A review (Toplak, West, & Stanovich, 2013) focusing on executive functions in individuals with attention-deficit/hyperactivity disorder (ADHD) examined to which extent performance-based and ecologically valid, behaviour-based executive functions assessment reflect the same underlying construct and found quite consistent small and mostly non-significant correlations. Thus, the authors suggest that both measurement types contribute independently with valuable information, by assessing different aspects of executive functions. Further, behaviour-based assessments might differ from performance-based assessments due to the context and complexity of the assessed behavioural situations. Where behaviour-based measures assess complex multi-component executive functions' tasks, performance-based assessments can both assess separate executive function components and multicomponent task performance. Evidence based on investigations of children with autism spectrum disorder indicate that differences could result from executive function difficulties being related to the simultaneous execution of multiple executive functions and not to poor functioning of one specific executive functions (Gardiner, Hutchison, Müller, Kerns, & Iarocci, 2017). This aspect further underscores the value of behaviour-based assessments of executive functions.

Emotion regulation

Emotion regulation (ER) has received increasing scientific interest with an explosive upsurge of publications on the topic since the mid-nineties (Cole, Martin, & Dennis, 2004; Gross & Feldman Barrett, 2011). Emotion regulation, which is the term chosen for this work, is often used interchangeably with other terms such as emotional control, affect-regulation, mood-regulation, and affective control. Likewise, both study method, focus, and interpretation of the concept varies greatly (Cole et al., 2004). Thus, to ensure comparability and understanding it is necessary to thoroughly define both the construct of emotion regulation, as elusive as it

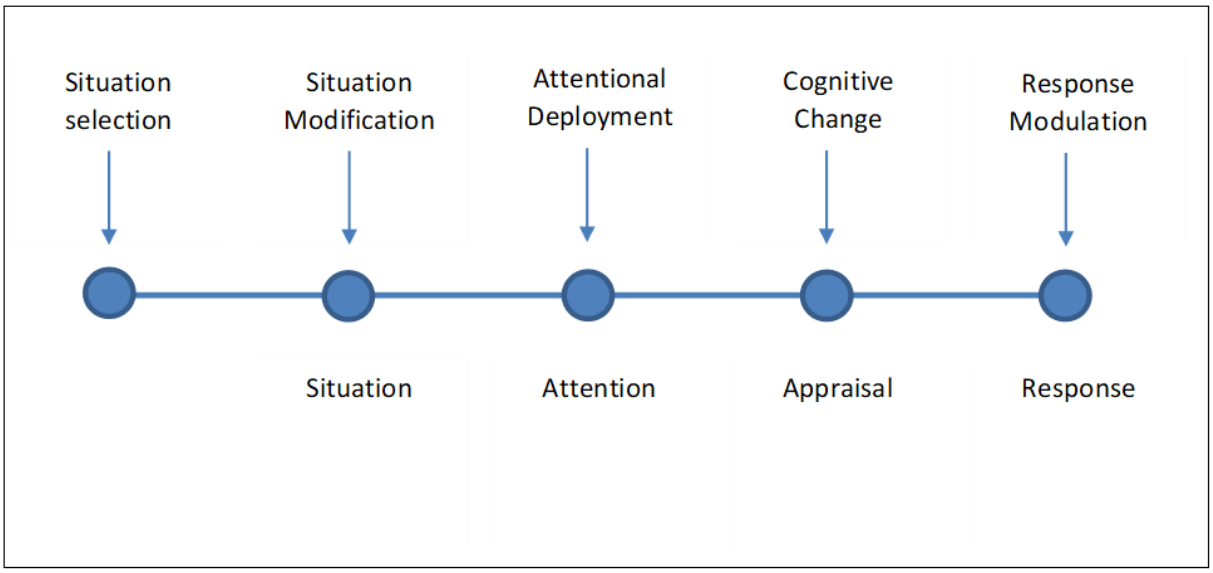
might be, and the method of investigation applied in a study. The following subsections of this thesis will present different aspects related to emotion regulation as well as the theoretical framework leading to the definition of emotion regulation applied in this thesis. Before going into depth with emotion regulation it is necessary first to conceptualize the focus point of regulation, namely emotions.

*Emotion*s are generated when a situation is interpreted as relevant for the individual's conscious or non-conscious goals (Gross & Feldman Barrett, 2011). In this way emotions serve as important indicators of goal relevant situations and motivators for action. The emotion is represented by a change of mental state and often also as behavioural and physiological changes e.g. change in facial expression and change in heart rate (Fredrickson, 2001; Sheppes, Suri, & J Gross, 2015). Emotions may influence the subjective experience of a situation and may lead to action. Emotions are thus multifaceted and include both mental and physical changes (Gross, 2014) and will in this thesis be defined as valenced reactions, that arise in an individual when attending to and appraising an event and giving it a valenced meaning. (Sheppes et al., 2015).

The Process Model of Emotion Regulation

The concept of emotion regulation will in this thesis be set in the theoretical framework of the widely used and recognized 'Process Model of Emotion Regulation' (Gross, 2014) (Figure 1.2). The model's first version 'The Modal Model of Emotion' was introduced by James Gross in 1998 in hopes of aiding future research in a complicated and entangled study field (Gross, 1998). The Process Model of Emotion Regulation gives a detailed account of how emotion regulation unfolds dynamically over time and accentuates that emotion regulation processes occurs in the individual in relations to the social and cultural contexts in which the individual is embedded. Importantly, 'The process model of Emotion Regulation' should be seen as a circular process so that emotion regulation can at any stage in the process elicit a change and hereby start over the process.

Figure 1.2. The Process Model of Emotion Regulation (Adapted from (Gross, 2015a))



The Process Model of Emotion Regulation highlights five families of emotion regulation processes; 1) 'Situation Selection' refers to choosing whether to engage in a situation expected to elicit specific emotions. Situation selection can thus be applied to induce or prevent future emotions. 2) 'Situation Modification' refers to actively changing a situation to alter the emotional outcome. 3) 'Attention Deployment' refers to redirecting attention towards or away from an emotion eliciting stimuli. This includes e.g. the strategy of distraction. 4) 'Cognitive Change' refers to making or altering a subjective evaluation of an emotional stimulus in order to change the elicited emotion. 5) 'Response Modulation' refers to directly influencing experiential, behavioural, and physiological components of the emotional response (Gross, 2014).

This model implicates multiple emotion modulation opportunities and emotion regulation can co-occur in the different processes, as well as that emotions themselves can serve as a regulatory factor within the five processes. Also importantly, according to Gross' model, emotion regulation can thus take place even before the arise of emotion, this by actively modifying current or future environment as well as the mindset towards a situation (Gross, Uusberg, & Uusberg, 2019).

The following text gives a short example of the five emotion regulation families of Gross' model:

> Morgan is going to a job interview on a job he applied for *(situation selection: he chose to apply for the job and go to the interview)*. He is nervous and doubts his qualifications. He remembers his friend's advice and before going in, he boosts his own self-confidence by reminding himself that he was top of the class and has done similar assignments *(cognitive change)*. At the interview he feels his chair is awkwardly placed and asks to change the seating slightly *(situation modification)*. Morgan feels that one of the interviewers seems discontent with him. To overcome the feeling of unease this elicits, he focuses his attention on the main interviewer *(attention deployment)*. During the interview Morgan gets increasingly angry towards the discontent interviewer as he continuously yawns, frown and makes disturbing comments. Morgan asks for a cup of water and uses the pause to take some deep breaths which he knows will calm his feelings *(response modulation)*. (*Addendum: He got the job.*)

The Process Model of Emotion Regulation has since been elaborated by James J Gross 'The Extended Process Model of Emotion Regulation' which includes more detailed models of each of the five regulatory processes and concurrent subprocesses (Gross, 2015a, 2015b).

Emotion dysregulation

Dysregulation is not just lack of regulation, as well as lack of regulation is not necessarily dysregulation (Ramani, Brownell, & Campbell, 2010). Emotions and emotion regulation must always be understood and

interpreted in relation to the personal, relational and societal context. Both vague and strong emotions can be both appropriate or dysregulated according to the prevailing situation, and the internal goals of the individual having the emotions. Thus, emotions regardless of valence and intensity are not maladaptive in themselves, but deficient emotion regulation or dysregulation can lead to both maladaptive emotions and maladaptive responses to normal emotions. Emotion dysregulation can be and will in this work, be defined as 'the inability to appropriately regulate emotions to meet the internal or external situational demands' (Cole et al., 2004). In the light of Gross' Process Model of Emotion Regulation, emotion dysregulation can occur at all five families of emotion regulation processes if the individual fails to implement relevant mechanisms or implements maladaptive processes. The definition of emotion dysregulation will in the following be used to include both mal-regulation and lack of regulation where regulation would have been appropriate.

A definition of emotion regulation

Emotion regulation can have both short-and long-term goals and can be as simple as feeling better in a discrete moment (increasing positive emotions and decreasing negative emotion) or more complex instrumentally motivated in order to achieve a more long-term outcome (e.g. Enduring a poor work-environment in order to obtain a promotion including a higher salary, which in turn enables a down payment on a desired house) (Gross, 2014). In short, emotion regulation can be described as and will in this work be defined as *'a continuous regulatory process (voluntary and involuntary) modulating the occurrence, intensity and duration of behavioural, physiological, and emotional reactions across physiological, neurological and socioemotional dimensions'* (Bernabei et al., 2018; Fogleman, Leaberry, Rosen, Walerius, & Slaughter, 2018).

The developmental trajectory of emotion regulation

Adaptive emotion regulation develops through the social interaction between individuals. This fundamental developmental process advances from infancy, through childhood and adolescence, and even extends into old age (Burr, Castrellon, Zald, & Samanez-Larkin, 2020; Charles & Carstensen, 2009; Plessen & Kabicheva, 2010; Schweizer, Gotlib, & Blakemore, 2020). From birth, infants look towards their caregivers and in the first years of life interaction with caregivers is crucial for children's emotion regulation development. Emotion regulation progresses from being primarily non-conscious and externally regulated, to being primarily internally regulated and a more conscious and deliberate process (Plessen & Kabicheva, 2010). Thus, one of many major tasks for the young child is to gradually internalize emotion regulation. The ability to do so is dependent on inborn traits but influenced by the environment around the child potentially from even before the child is born (Bale, 2015; Curley, Jensen, Mashoodh, & Champagne, 2011).

Emotion regulation and psychopathology

Behaviours associated with emotion dysregulation are seen in various psychiatric illnesses and disorders and emotion dysregulation is considered as a core symptom or a frequent comorbidity in multiple

psychiatric illnesses, including bipolar disorder and schizophrenia spectrum disorders, attention deficit/hyperactivity disorder (ADHD), disruptive behaviour disorder, autism spectrum disorder (Aldao, Gee, Reyes, & Seager, 2016; Fernandez, Jazaieri, & Gross, 2016; Kring & Werner, 2004; Sheppes et al., 2015), anxiety, depressive disorder, and borderline personality disorder (Daros & Williams, 2019; Klemanski, Curtiss, McLaughlin, & Nolen-Hoeksema, 2017; Sheppes et al., 2015). Although emotional disturbances play a central role in these disorders, the underlying pathophysiological mechanisms may be different (Delvecchio, Sugranyes, & Frangou, 2013; Rowland et al., 2013), and emotion regulation difficulties possibly mediate some of the vulnerability to psychopathology (Nimarko, Garrett, Carlson, & Singh, 2019). Studies in offspring of mothers with bipolar disorder suggest that problems with emotion regulation are present from infancy (Johnson, Brennan, Stowe, Leibenluft, & Newport, 2014). The capacity of emotion regulation is less studied in offspring of parents with schizophrenia, but studies imply that problems with emotion regulation are present from early childhood (4 and 7 years of age; 4-17 years of age) (Díaz-Caneja et al., 2018; Donatelli, Seidman, Goldstein, Tsuang, & Buka, 2010).

Assessing emotion regulation

Emotion regulation is, as described above, closely related and inherently coupled with other emotional processes such as emotion recognition and to other self-regulatory and cognitive functions. This renders emotion regulation a difficult territory of investigation and assessment. Searching the literature identifies several questionnaires and only a few experimental tests designed to measure aspects of emotion regulation (Hagstrøm, 2019). Questionnaires can be roughly divided into three categories: self-reports, reports by others e.g. parent- or teacher reports on a child's emotion regulation, and lastly clinician-ratings which will often be scored following direct interaction with the child or in relation to observations of child behaviour in e.g. their normal classroom setting. Furthermore, exists the method of clinician rated emotion regulation based on standardized experimental settings. An example of this is 'The Clean Up Task' (Ramani et al., 2010) where the child is placed in a common situation with their parents and 'The Mistaken Gift Paradigm' (Tobin & Graziano, 2011) where children are presented with a reward that they have earlier identified not to want. Lastly, objective measures of physiological responses such as heart rate variability are used as a measure of emotion regulation. Questionnaires such as self-, parent-, and teacher-reports are usually cheap and easy to administer and are widely used. Nonetheless there are several disadvantages of this method, one being the risk of rater-bias as studies have shown that e.g. the parent's own mental state can affect their report regarding their own offspring (Maoz et al., 2014). Experimental tasks most often focus on assessing emotion regulation while applying specific emotion regulation strategies such as suppression or reappraisal and outcome measures are often a combination of self-reports and clinician ratings. Despite their disadvantages, the existing measures contribute with valuable information on emotion regulation. However, it has been highlighted that there is a need for emotion regulation assessment methods that focus on spontaneous emotion regulation in ecologically valid settings (Aldao, Nolen-Hoeksema, & Schweizer, 2010) and translate to emotion regulation in everyday situations.

Deficit of self-regulation, executive functions and emotion regulation and their impact

Research indicates that self-regulation, including executive functions and emotion regulation, besides the specific regulatory processes, also require a form of resource capacity and that this resource is depletable. Moreover, individual differences in resource capacity seem to exist as well as differences in the expenses of different regulatory processes (Baumeister, 2003; Hagger, Wood, Stiff, & Chatzisarantis, 2009, 2010). In addition, research point to that different executive functions and different forms of emotion regulation are dependent on different cognitive function domains (including emotion regulation being dependent on executive functions and vice versa) and that these likewise expend differential resource capacities (Schmeichel, 2007; Schmeichel, Volokhov, & Demaree, 2008; Urry & Gross, 2010). Collectively, this highlights the interrelationship of cognitive functioning, self-regulation, executive functions and emotion regulation, but also that identified deficits can be due to underlying dysfunctions and mechanisms.

With this in mind research has identified that impaired executive functions negatively impacts several aspects of daily life functioning, including both interpersonal relationships, academic performance, and occupational functioning and overall life functioning and outcomes (Castellanos et al., 2018; Green et al., 2004). Impaired executive functions are also associated with both physical and mental health problems counting a wide range of psychopathology here including schizophrenia and bipolar disorder (Snyder et al., 2015). Likewise, emotion regulation has immense effect on an individual's overall functioning and wellbeing. The capacity to effectively regulate emotion is essential for psychological health both in typically developing children without familial high-risk of severe mental illness and especially in children with this risk factor (Eisenberg, Spinrad, & Valiente, 2018; Fogleman et al., 2018).

Chapter 2. Objectives and hypotheses

Psychopathology, cognition, and aspects of self-regulation have been studied extensively in individuals diagnosed with schizophrenia spectrum psychosis and bipolar disorder, but to a lesser degree, and for some aspects not at all, in their biological offspring during childhood. Increased insight into the developmental processes and symptoms that precede illness is crucial for understanding and identifying early stages of the illness. Studying child offspring at familial high-risk for schizophrenia simultaneously with offspring at familial high-risk for bipolar disorder in the same prospective study and including a control group is unique. It enables the mapping of both shared and distinct characteristics.

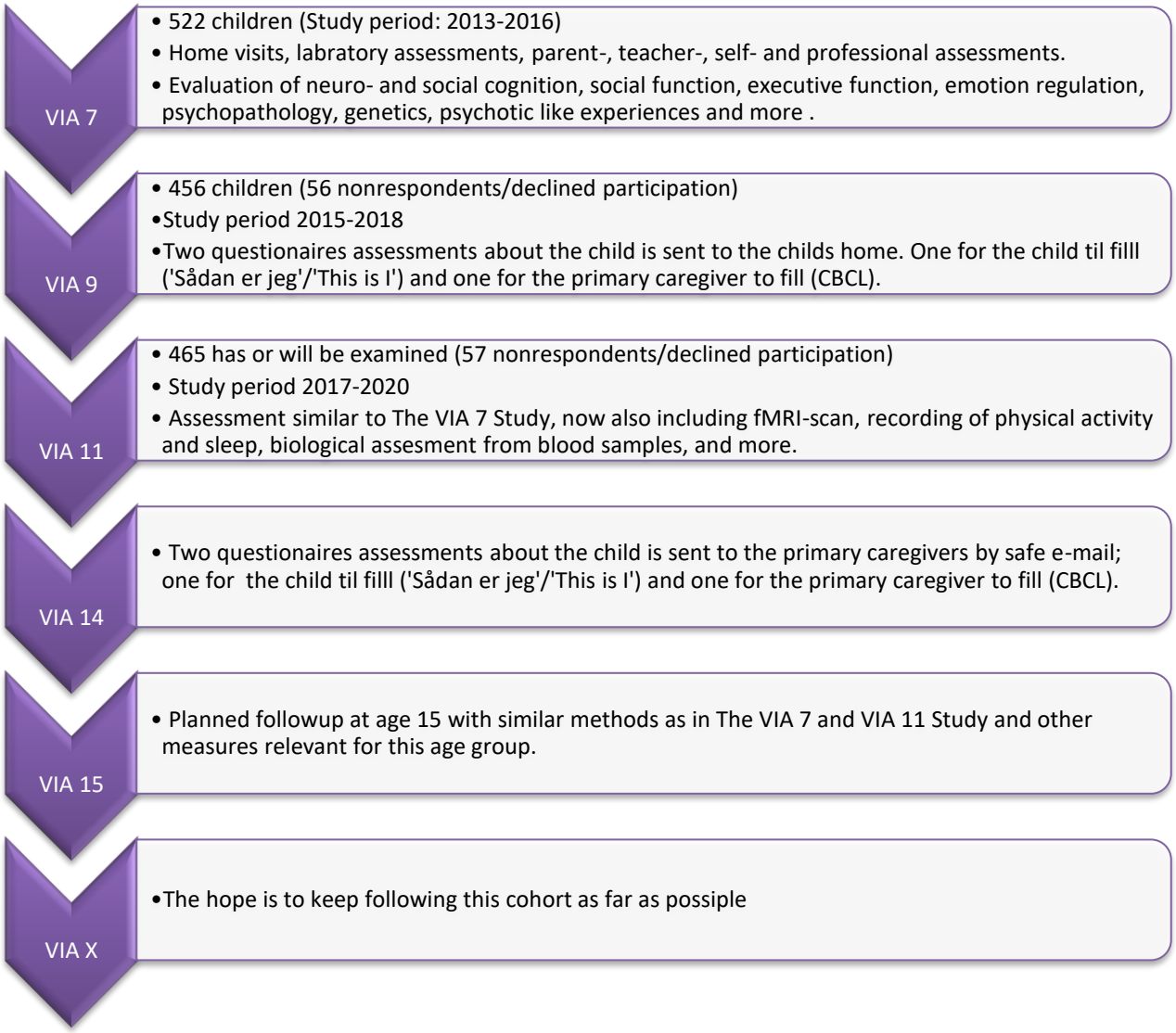
The focus of this thesis is dimensionally measured psychopathology and behaviour-based assessments of executive functions and emotion regulation. We investigated this using a cross-sectional study design within a prospective study cohort of seven-year-old children with a parental diagnosis of schizophrenia spectrum psychosis or bipolar disorder or neither of these two severe mental illnesses.
The overall aim of this thesis is to add knowledge and hopefully contribute to prevention or at least lessening the severity and adverse consequences of severe mental illness and this, preferably at an early-age time-point.

Within **Paper I** the focus is dimensionally measured psychopathology and early detections of mental illness in familial high-risk children. We hypothesized that children with a familial predisposition of schizophrenia or bipolar disorder would have significantly more behavioural difficulties than control children, and more often to a degree indicative of mental illness. Considering the familial high-risk study design of The VIA 7 Study, we aimed to compare the proportion of children in each risk group identified with difficulties to a degree indicative of mental illness. Further, we aimed to assess if a short and accessible measure of childhood difficulties; 'the Strengths and Difficulties Questionnaire' (SDQ) (Goodman, 2001; Obel, Dalsgaard, Stax, & Bilenberg, 2003), could identify children with mental illness and to compare the discriminatory qualities of the SDQ to those of the likewise highly used and extensively validated, 'Child Behavior Checklist' (CBCL) (Achenbach & Edelbrock, 1983). The main focus was reporting's from the child's primary caregiver and secondary teachers' reports.

The aim of **Paper II** is to compare behaviour rated executive functions between the three risk groups. We hypothesized that children of parents diagnosed with either schizophrenia or bipolar disorder would have more inferior executive functions and more often have impairments above the threshold for clinically significance compared to control children. Finally, we expected that children with familial high-risk of schizophrenia would show impairments across all executive functions but with a jagged pattern of impairment. In contrast, children with familial high-risk of bipolar disorder would primarily display impairment of executive functions related explicitly to emotional processing.

The focus of **Paper III** is emotion regulation. As we discovered the lack of standardized ecologically valid assessments of emotion regulation, it became a primary objective of this PhD study to develop a behaviour-based clinician-rated measure for evaluating emotion regulation ability in children. This was done in collaboration with clinical psychologist Julie Hagstrøm, a co-PhD student (now PhD) who studied emotion regulation in children with Tourette's syndrome and/or ADHD. This resulted in the Tangram Emotion Coding Manual (TEC-M) which is described in detail in chapter 5. A published paper on the validation of the TEC-M is available (Hagstrøm et al., 2019). Utilizing the TEC-M, Paper III aims to compare emotion regulation between risk groups. A further aim is to investigate potential associations between emotion regulation of the child and dimensional measures of child psychopathology, psychopathological symptom severity, daily life functioning, and the categorical defined emotional and behavioural dysregulation profile from The Child Behavior Checklist (CBCL-DP, (Achenbach & Rescorla, 2001; Althoff, 2010)). We hypothesized that children with familial high-risk of schizophrenia or bipolar disorder would display more inadequate emotion regulation than children without familial high-risk. We further hypothesized that an increased dimensional psychopathological load and the presence of a dysregulation profile would be negatively associated with emotion regulation.

Figure 2.1. Flowchart of The Danish High Risk and Resilience Study



Chapter 3. The Danish High Risk and Resilience Study

The Danish High Risk and Resilience Study (the VIA Study) is the result of a successful collaboration between child- and adolescent mental health center, research unit, Capital Region of Denmark and two mental health centers for adults; The Copenhagen Research Centre for Mental Health - CORE, Capital Region of Denmark and The Psychosis Research Unit, Aarhus University Hospital. The VIA Study is designed as a prospective population-based cohort study and aims to conduct a thorough examination of biological children born to parents diagnosed with schizophrenia spectrum psychosis (Familial High-Risk Schizophrenia **(FHR-SZ)**) and children born to parents diagnosed with bipolar disorder (Familial High-Risk Bipolar Disorder (**FHR-BP**)) and a group of matched control children with neither parent diagnosed with schizophrenia nor bipolar disorder. The aim was to recruit a cohort which was representative of the whole Danish population, and this would be accomplished by utilizing information from the Danish National Registers.

The first assessment took place when the children were seven years of age (the VIA 7 Study) (Thorup et al., 2015). A brief follow-up when the children were nine years of age (the VIA 9 Study) included only two questionnaires sent to the home of the child. The second thorough assessment of the children at age 11 years (the VIA 11 Study) (Thorup et al., 2018) is currently underway and almost finalized. The next short follow-up at age 14 (the VIA 14 Study) and next thorough assessment when the children are 15 years old (the VIA 15 Study) is presently in preparation (Figure 2.1).

Main objective

The main objectives of the Danish High Risk and Resilience Study - VIA 7 were to analyse influences of familial risk of schizophrenia and bipolar disorder, including both genetic and environmental factors and focusing on behaviour, cognition, psychopathology, emotional symptoms, and neuromotor abilities of the child while also investigating the rearing environment and characteristics of the adults around the child. This, as part of the second objective aiming to identify early risk markers of severe psychopathology and possible protective factors.

A derived goal became to get an overview of the nature of help and support the families had received up until age seven of the child, and what help the families felt was lacking. This eventually led to a related intervention study the 'VIA Family'(Müller et al., 2019).

Collectively, this information would aid to establish a basis for preventive interventions premorbid by focusing both on impairments and boosting protective factors and overall use this knowledge as a framework for creating improved support programmes in the future (Thorup et al., 2015).

Why age seven

The optimal study of children at familial high-risk of severe mental illness would commence if not before conception then at least at the prenatal stage, but all scientific studies must make financial considerations and The VIA Study is no exception. Thus, age seven was chosen as the start point of investigation after thorough consideration of several facets. Firstly, in Denmark children start school the calendar year they turn six years of age, children will thus usually have attended school one to two years when they are seven years of age. Starting and attending school, pose both cognitive and social challenges that often exceed those posed in the home and kindergarten environment. These higher requirements on the child can potentially expose latent challenges within the child. School attendance also renders the possibility of retrieving information on the child in a social setting of peers and from the perspective of the teacher. Secondly, the assumption was that the early development of the child as well as information regarding pregnancy was not too distant to be recollected adequately by the parent. Finally, age seven would give the possibility to retrieve information directly from the child, which would less attainable at an earlier developmental stage (Thorup et al., 2015).

Recruitment

The Danish national registers

The Danish Civil Registration System (DCRS) was established in 1968 and contains detailed information on all individuals residing in Denmark including e.g. sex, date of birth, identity of parents and children, vital status, and place of residence (full address). All persons registered in DCRS are assigned a unique personal identification number (CPR-number) (Pedersen, 2011). The DCRS data have high accuracy and are effectively complete (Schmidt, Pedersen, & Sørensen, 2014). The CPR-number is used in all Danish national registers and in this way information regarding health, school attendance, income, residence and much more is linked to the individual person through the CPR-number.

The Danish Psychiatric Central Research Register (DPCRR) was established in 1969 and contains nationwide information on all hospital in- (valid data from 1970 and onwards) and outpatient (from 1995 and onwards) contacts, including all diagnoses. Until January 1994 diagnoses were based on ICD-8 (Sundhedsstyrelsen, 1971), hereafter diagnoses were based on ICD-10 (World Health Organization Collaborating Centre for Research and Training in Mental Health, 1994). If approved by the Danish Data protection Agency and the National Board of Health, person identifiable data can be retrieved from DPCRR for research purposes (Mors, Perto, & Mortensen, 2011). A registration of a diagnosis of schizophrenia in The Danish Psychiatric Central Research Register has been proven to have good diagnostic validity (Uggerby, Østergaard, Røge, Correll, & Nielsen, 2013) as has also a diagnosis of bipolar disorder (L. Kessing, 1998).

Register extract and matching with controls

By combining information from the DCPRR with data from the DCRS it is possible to extract a list of individuals with specific characteristics. To create the three groups (FHR-SZ, FHR-BP and controls) relevant for The VIA Study a list of individuals with the following characteristics was requested:

1. A full list of all children born between September 1. 2004 and August 8. 2009 with at least one parent ever diagnosed with schizophrenia spectrum psychosis defined as ICD 10 codes: F20 (Schizophrenia), F22 (Persistent delusional disorders) and F25 (Schizoaffective disorders) or ICD 8-codes: 295 (Schizophrenia), 297 (Paranoid states), 298.29 (Other psychoses, Reactive confusion), 298.39 (Other Psychoses, Acute paranoid reaction), 298.89 (Other psychoses, Reactive psychosis), 298.99 (Other psychoses, Reactive psychosis, unspecified).
2. A full list of all children born between September 1. 2004 and August 8. 2009 with at least one parent ever diagnosed with bipolar disorder defined as ICD 10-codes: F30 (Manic episode) and F31 (Bipolar affective disorder) or ICD 8-codes: 296.19 (Manic-depressive psychosis, manic type), 296.39(Manic-depressive psychosis, circular type)
3. A list of up to ten matched control children (PBC) per identified index child and fulfilling the following criteria:
    a. Sexr: The matched control child should be the same sex as the index child.
    b. Age: Born within a three-month interval of the index child.
    c. Municipality (the Danish administrative unit 'kommune'): The matched control should live in the same municipality as the index child.
    d. Neither parents diagnosed with schizophrenia spectrum psychosis or bipolar disorder.
    e. No siblings diagnosed with schizophrenia spectrum psychosis or bipolar disorder.
4. A list of all biological parents and custody holders to the above identified children including information on e.g. CPR-number, name, exact address, psychiatric contacts and diagnoses.

The biological parents were also required to be born and living in Denmark. It was not an exclusion criterion if any of the biological parents neither index nor control, were registered with any other diagnosis of mental disorder. Individuals, who were registered with a diagnosis of both schizophrenia spectrum psychosis and bipolar disorder, were allocated to the schizophrenia spectrum psychosis group.

The Danish High Risk and Resilience study – VIA 7

Participant selection

The Initial aim of the VIA Study was to include 200 FHR-SZ children, 100 FHR-BP children and 100 control children. During the inclusion period, it was decided to take in an additional 20 FHR-BP children, because recruitment went well, and resources were available. Additionally, it was an expectation that a subgroup of approximately 30-40 children with "double high-risk status" due to both parents having a diagnosis of either schizophrenia or bipolar disorder would be included.

The aim was to include and test children while they were seven years of age. To ensure that the index and the matched child were as close to the same age as possible at time of assessment, it was sought to include a matched control child as quickly as possible after the inclusion of the index. Initially, we recruited one control child for every included familial high-risk child. However, due to lack of resources, it was decided not to continue including matched controls for FHR-BP children. At the point of the decision to discontinue to include FHR-BP matched controls, 38 control children matched to FHR-BP children had been included. These 38 children were kept in the study and re-matched as controls for FHR-SZ children. To begin with, more children living in the area of Greater Copenhagen were invited to participate, as opposed to more rural areas. This procedure was chosen to ensure a good flow at the beginning of the study and hereby optimize data quality by consolidating the trained assessment methods in the data collectors.

The final register extract contained only 45 children with two diagnosed parents. The research nurse made an extra effort in trying to contact and include these families but was unfortunately unsuccessful in many cases. We attempted to contact 25 eligible double high-risk families but only managed to establish contact with 16. Nine of the 16 double high-risk families declined participation.

Due to Danish Research Protection legislation, there was a period where we were not allowed to contact some of the families in the extract, due to the families having chosen research protection. During the study this legislation was changed in a way that it no longer affected our recruitment.

Younger siblings and twin-siblings were allowed to participate if they fulfilled the inclusion criteria of the study. While siblings from the familial high-risk groups were all in the register extracts, siblings from the control group were not, and thus represent an exception from the original recruitment strategy as they were matched subsequently to FHR-SZ children.

Families were included on account of the participation of the child. We always sought to include both biological parents as well as any other registered legal guardians and adults who were de facto functioning primary caregivers (e.g. foster parents, stepparents, grandparents) of the child or had lived with the child for a minimum of 12 months just prior to study inclusion. It was not an exclusion criterion if any or all adults refused participation in all or parts of the study. We waivered contact to any biological parents, if this was requested by the legal custody holder of the child. Children and adults could be part of The VIA 7 Study without accepting participation in The Gene Environment Study (see procedure and ethics section for description of The Gene Environment Study).

The Danish registration system registers legal parents, not only biological parents. This entails that it is not necessarily the child's biological parents that is registered as legal parents. Due to the dual interest of the study of both genetic inheritance as well as rearing environment, families where the child was a non-biological adopted child were excluded from the study. Further, both child and biological parents should be born and living in Denmark to eliminate effects of immigration (J. McGrath, Saha, Chant, & Welham, 2008).

Procedures and ethics

The Danish Data Protection Agency approved retrieval of data from The Danish Psychiatric Central Research Register and The Danish Civil Registration System and conduction of The VIA 7 Study (RHP-2012-06). The Danish Committee on Health Research Ethics was approached for approval of the study, but on account of the observational nature of the study, with no treatment or intervention, the committee deemed approval not necessary according to Danish legislation. The guidelines from the committee was followed, nonetheless.

One single primary research nurse coordinated all initial contact to the families and was the only person accessing the register extract of index and matched control families.

Contact to the families were initiated first through hard copy letters send to custody holders at the child's primary address. The letter shortly outlined the study and that participation was voluntary. Further, it was stated that the research nurse would contact them by telephone within a few days to tell them more and to arrange a meeting if they were willing to participate or just to hear more about the study. The families were always met with a high degree of flexibility and friendliness to ensure highest possible participation rates.

All adult participants received both verbal and written information about the study before they decided if they wanted to participate. A signed written consent form was retrieved for all adult participants and from custody holders of the child. This included consent to audio- and video-recordings. Further, if consent was given from the legal guardian of the child, the child's schoolteacher was asked to fill in a set of questionnaires about the child.

All legal guardians were offered verbal feedback on the child's general performance and if it was found urgently necessary and was wanted by the custody holders, we provided written referrals to child- and adolescent psychiatric facilities.

Studying and interacting with children entails several ethical considerations. Performing a detailed investigation of a child, where you want to create a safe and confidential arena for them to tell about themselves and their experiences, easily creates a delicate ethical dilemma. This, as legal guardians of a child have the right to be informed about their child. We sought to inform the parents that we would not tell them everything their child told us unless the child told us something very serious or worrying. Likewise, we told the children that our conversations with them would be confidential, but that we would have to inform their parents or the authorities if they told us anything where we deemed it necessary. We also told the children that we would not talk to their parents without informing and talking with the child about it

first. Danish legislation entails a strict reporting obligation for health professionals, this means that if we are seriously and acutely concerned for a child's health and wellbeing, we are obliged to inform the authorities. The families were informed that we, on account of our position as health professionals, would react if we found substantial grounds for concerns regarding the child's current wellbeing or future development. In case of concern it was always sought to report in cooperation with the parents. Further, not all children knew of their parent's (former or current) mental illness. We never discussed or told the children about their parents' mental illness and likewise did not discuss or tell the children about mental illness in general. The only exception to this was if a child themselves brought up the subject. If this happened, we would ask the parents how they wished us to talk with their children on the subject. Overall, we sought to create an open, warm and relaxed environment for both adults and children, and we tried to make it a positive and fun experience for the child. We discussed ethical matters within the group often, and whenever it was needed.

The Gene Environment Study

Part of the VIA Study concerns investigation of genetics related to psychiatric risk status and investigating hair cortisol levels of the children. In collaboration with the Psychiatric Genetics Consortium biological material was collected in form of either a saliva or blood sample from all participants and hair samples from child participants. Approval of this procedure as well as retrieving e.g. blood spot-samples from The Danish New-born Screening Biobank (Nørgaard-Pedersen & Hougaard, 2007) on all participating (and consenting) children, was part of the Gene Environment study protocol (00466 PSV-2009-07). A separate written and verbal informed consent was obtained for the Gene Environment part of the VIA Study and the families were given a minimum of 24 hours from receiving information on the study before they decided on participation.

Participation rates

Contact was attempted with 38% of the FHR-SZ children and 28% of the FHR-BP children identified as eligible for the VIA 7 study, through the Danish National Registries. It is important to note that it was never intended to include all identified children. Children were included ongoing according to the capacities of the study which entailed that some children would inevitably turn eight years of age without being contacted and thus become ineligible for the study.

Table 3.1. Participation rates where contact was attempted

	FHR-SZ	FHR-BP	Controls	Total
Unable to establish contact with the family	22.4%	18.7%	12.5%	17,9%
Participation rate where contact was attempted	49.3%	56.1%	62.7	56,0%
Participation rate where contact was established	63.5%	69.0%	71.2	67,9%

Verification of Group Affiliation and group reassignments

All adult participants were asked to complete a semi structured diagnostic interview (Schedules for Clinical Assessment in Neuropsychiatry (SCAN, (Wing et al., 1990) in order to confirm the register diagnosis of the index families and to assure that no control parents had a diagnoses of schizophrenia spectrum psychosis or bipolar disorder.

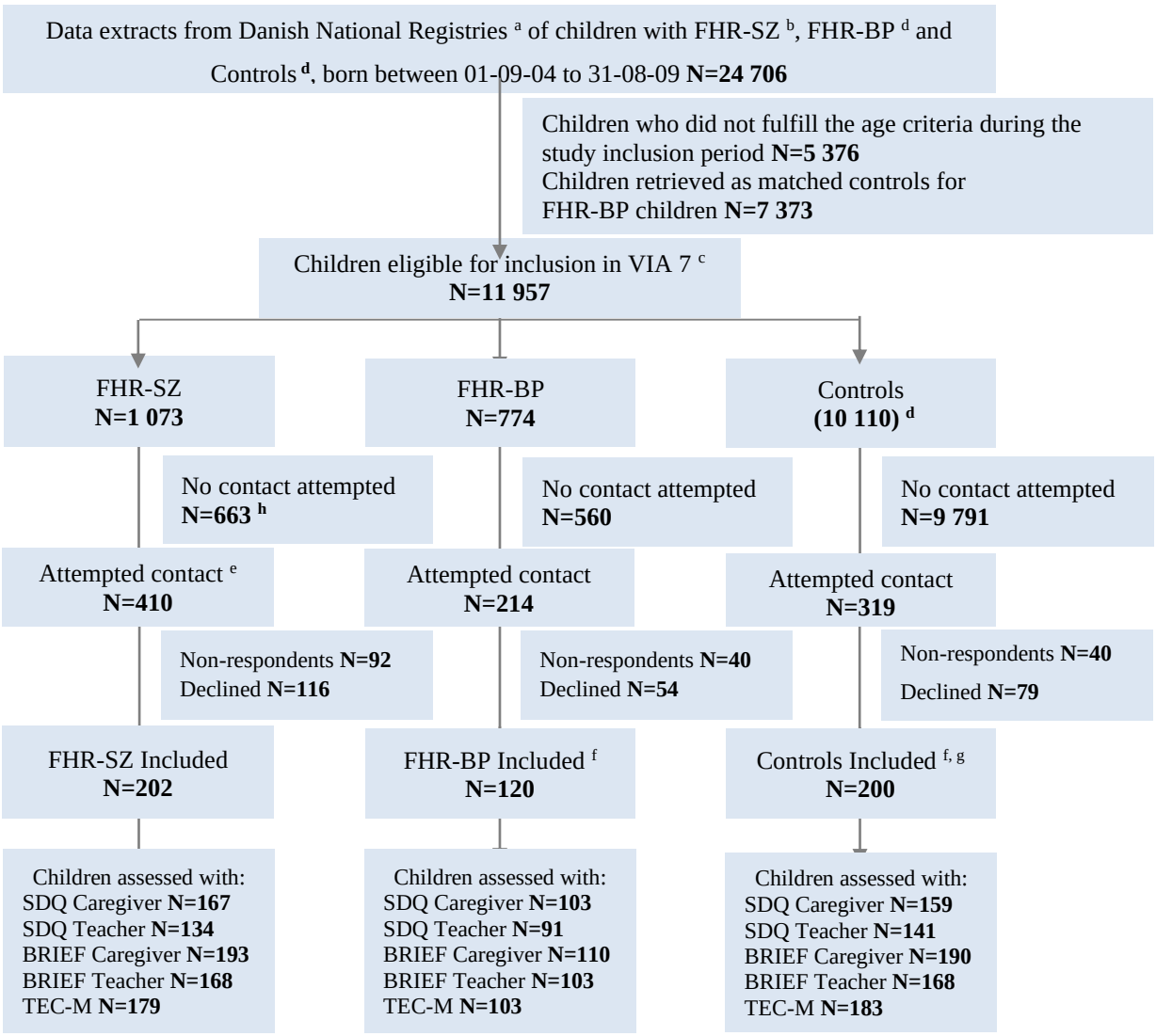
On account of the parental diagnostic interview's one control parent was found to have a diagnosis of bipolar disorder given by a private practicing adult psychiatrist. This family was therefore reassigned to the FHR-BP group. For one FHR-SZ sibling pair the non-index parent received a diagnosis of schizophrenia in a hospital setting after the assessment of the older sibling but before assessment of the younger sibling. The primary investigator group decided that only the younger sibling would be reassigned as a double high-risk schizophrenia child.

The Final VIA 7 Study Cohort

The final VIA 7 Study Cohort consists of 522 children; 202 FHR-SZ children, 120 FHR-BP children and 200 control children (Figure 3.1). Sixteen sibling pairs (FHR-SZ=9, FHR-BP=5, =Controls=2) hereof six twin-pairs (FHR-SZ=3, FHR-BP= 2, =Controls=1) were included, resulting in a total of 506 families (Table 1). Nine children with double high-risk status (7=FHR-SZ/SZ, 1=FHR-SZ/BP, 1=FHR-BP/BP) were included in the study. Two younger siblings from control families were included in the study. These were not in the original register extract and were pot hoc matched to included FHR-SZ children. Thirteen children had non-biological primary caregivers. 'Primary caregiver' was defined as the adult who, at the time of the study, knew the child the best and cared for the child on a daily basis.

One child did not participate in any testing due to very severe mental and physical retardation. Likewise, not all adults of an included child participated in all testing assigned for the parents (Table 3.2). Ten families choose to discontinue testing prior to completion of the full VIA 7 Study assessment, but no families discontinued completely from the study or withdrew their consent. We included and assessed a number (N= 58) of non-biological adults who lived with the included children, but we have not yet looked at this data in any way unless this non-biological adult was the primary caregiver of the child. For more details on the included and participating adults of The VIA 7 Study cohort.

Figure 3.1. Inclusion and participation of children in The Danish High Risk and Resilience Study VIA 7



FHR-SZ: Children of parents with schizophrenia spectrum disorders. FHR-BP: Children of parents with bipolar disorde SDQ: The Strengths and Difficulties Questionnaire (Obel et al., 2003). BRIEF: The Behavior Rating Inventory of Exec Functions(G. A. Gioia, Isquith, Guy, & Kenworhty, 2005). TEC-M: The Tangram Emotion Coding Manual (Hagstrøm 2019).

[a] Danish Civil Registration System and Danish Psychiatric Central Research Register. [b] Parents with both a diagnosis of schizophrenia and bipolar disorder were assigned to the schizophrenia high risk group as per the ICD-10 hierarchy. [c] As May 2011, legislation was enacted to protect individuals´ phone numbers from being called for participation in scientifi research. Therefore, there were eligible children who were not contacted and enrolled in VIA 7. [d] Controls were matche cases on sex, municipality, and exact age. 38 FHR-BP matched controls were re-matched as FHR-SZ controls. [e] Contac first attempted through letters sent to the child´s address. If the family did not respond, contact by telephone was attemp (calls and text messages), if a phone number could be found. [f] One control parent was found to have a diagnosis of bipo disorder made by a private practitioner. This family was therefore reassigned to FHR-BP group. [g] Two younger control siblings who were not in the original extract, but fulfilled the age criterion, were included in VIA 7.

Participation characteristics

The proportion of boys versus girls did not differ between the included and the non-included groups. However, significantly more participating children (46.6) than non-participating children (29.3%) lived in densely populated areas as opposed to intermediate and thinly populated areas (p<.001). The difference in population density living was equal across all three included risk groups.

Almost all biological mothers of included children participated. Biological index mothers in the schizophrenia high risk group had the lowest participation rate (94%). Participation rates of biological fathers of all groups were markedly lower than that of biological mothers from the concordant group. The lowest participation rate was found for schizophrenia biological index fathers (63%). In 79 % of all study families, the child and both the child's biological parents participated (Table 3.2).

Table 3.2. Participation of the included families in The Danish High Risk and Resilience Study VIA 7

	FHR-SZ	FHR-BP	Controls	Total
Included children	202	120	200	522
Participation:				
Biomothers, N (%)	184 (95)	112 (97)	196 (99)	490 (97)
Index biomothers, N (%)	104 (94)	62 (97)	114 (99)	280 (97)
Non-index biomothers, N (%)	80 (98)	50 (98)	82 (99)	212 (98)
Biofathers, N(%)	140 (73)	87 (76)	183 (92)	410 (81)
Index biofathers, N (%)	56 (63)	41 (79)	82 (92)	179 (78)
Non-index biofathers, N(%)	84 (81)	46 (73)	101 (93)	231 (84)
Child Only Participant [a], N	3 (1)	1 (1)	0 (0)	4
Child and Biomother Participating, N (%)	49 (24)	27 (23)	15 (8)	91 (17.4)
Child and Biofather Participating, N (%)	5 (2)	2 (2)	2 (1)	9 (1.7)
Child and Both Bioparents Participating, N(%)	144 (71)	90 (75)	183 (92)	417 (79)
Non-bioparent Primary Caregivers [b] Participating, N (%)	12 (100)	0 (100)	1 (100)	13 (100)
Primary Caregivers is Index Parents, N(%)	89	68	118	275

[a] One FHR-SZ child did not participate in any testing due to severe mental and physical retardation. Only register data was retrieved for the parents of this child.
[b] Primary caregiver is defined as the adult who, at the time of the study, knew the child the best and cared for the child on a daily basis.

Assessment procedures

Psychologists, medical doctors, and nurses performed all assessments under the supervision of a senior specialist in child neuropsychology (JRMJ) and a specialist in child and adolescent psychiatry (AT). All assessors were trained in all assessment procedures and instruments prior to data collection. Regular supervision and repetitions of assessment methods were held as well as regular reliability ratings throughout the data collection period. Child assessors were kept blinded to the risk status of the child.
The primary caregiver was defined as the adult who, at the time of the study, knew the child the best and cared for the child on a daily basis. We identified the primary caregiver in collaboration with the participating adults. The primary caregiver was not necessarily a biological parent of the child. The sex of the index parent in the familial high-risk group defined which of the parents in the matched control family were the index parent. In case of two index parents in a familial high-risk family, both parents in the control family would be defined as matched control index parents.
Assessments took place either in the families' homes or in the research facilities in Copenhagen and Aarhus. The research team met the families with a flexible approach both regarding time and place of the assessment. Because of the comprehensive assessment battery which entailed 2-3 days of testing for the child and 1-3 days of testing of the adult participants, finalizing an assessment could take from 3 days to several months, depending on the flexibility and special needs of the family.
Five hundred and twenty-two families were included in the study between January 2013 and January 2016.

Assessment of participating children

Children were assessed on multiple domains. Information regarding the child was attained through performance-based measures of the child him or herself as well as questionnaires and interviews with the child. Further information regarding the child was retrieved through interviews with the child's primary caregiver and through questionnaires filled by the child's primary caregiver and by the child's primary school teacher. Lastly, the child assessor also filled in a questionnaire about the child and assessed the child's current level of daily life functioning. Children's psychiatric DSM-IV past and present diagnoses were ascertained through semi-structured interviews with the Danish version of the Schedule for Affective Disorders and Schizophrenia for School-age Children -Present and lifetime Version (Kaufman et al., 1997). All child diagnoses were discussed and confirmed in group conference meetings according to the best estimate procedures and always with the presence of a child- and adolescent psychiatrist (AT). Both the case-presenting assessor and AT were always blind to the familial risk status of the child (Table 3.3, Table 3.4).

Assessments of participating adults

Index parents included in the study were assessed with a comprehensive test battery. Psychiatric symptoms were assessed with questionnaires as well as the semi structured diagnostic interview; Schedule for Clinical Assessment in Neuropsychiatry (Wing et al., 1990) in order to confirm the diagnosis of schizophrenia or bipolar disorder and any other psychiatric diagnoses including addictions. Daily life and

social functioning were assessed by questionnaires and semi structured interviews. Multiple cognitive domains were assessed by differential measures and demographic information were retrieved by interview (Table 3.5).

Non-index adults included in the study were likewise assessed with diagnostic interviews and any relevant psychopathological severity measures following the results of the interview. Further, non-index adults were also assessed regarding their daily life and social functioning and with a small cognitive test-battery and an interview regarding demographic information (Table 3.5).

Primary caregivers were assessed with the same test-battery as non-index parents and further they were given a full anamnestic interview regarding themselves and the child, as well as a few tasks and questionnaires related to child-caregiving and interaction (Table 3.5).

All parent and other adult caregiver diagnoses were made in group conference according to the best estimate procedures and always with the presence of a child- and adolescent psychiatrist (AT).

Table 3.3. Instruments used in the assessment of psychopathology, behavioural and environmental domains of children participating in the Danish High Risk and Resilience Study – VIA 7

Domains	Informant			
	Child	Primary Caregiver	Teacher	Research assessor
Psychiatric and emotional symptoms, social functioning and, behaviour, self-perception	K-SADS-PL	K-SADS-PL		K-SADS-PL
	CEMS	CBCL	TRF	TOF
	STAIC	SDQ	SDQ	CGAS
	Kidscreen-27	ADHD-RS	ADHD-RS	
	"Sådan er jeg"	BRIEF	BRIEF	
	DLSS	SRS	SRS	
	Tangram Puzzle	Tangram Puzzle		
		Vineland Adaptive Behavior Scales-I		
		Social contact at infancy from anamnestic interview		
Environment and emotional climate	Story Stem Assessment Profile (SSAP)	CHQ		
	HOME Inventory	HOME Inventory		
		Five Minute Speech Sample		
		Social Provision Scale		

All abbreviations and references can be found in the article 'The Danish High Risk and Resilience Study – VIA 7 - a cohort study of 520 7-year-old children born of parents diagnosed with either schizophrenia, bipolar disorder or neither of these two mental disorders' **(Thorup et al., 2015)**.

Table 3.4. Instruments used in the assessment of cognitive functioning, neuromotor and physical domains of children participating in the Danish High Risk and Resilience Study – VIA 7

Domain	Informant		
	Child	Primary Caregiver	Teacher
Cognitive functioning	Reynolds Intellectual Screening Test		
	Word Selective Reminding and Memory for stories from Tomal-2		
	Rey Complex figure test and recognition Trial		
	Rapid visual information processing;3-5- mode (RVP), Stocking of Cambridge (SOC), Intra-Extra Dimensional Shift test (IED), Spatial Span (SSP), Spatial Working Memory (SWM), Emotion Recognition Task (ERT), Cambridge Gambling Task (CGT) from CANTAB		
	Test for Reception of Grammar (TROG-II)		Children's Communication Checklist-II (CCC-II)
	Visual Attention Battery from University of Copenhagen		
	Verbal Fluency and TRAILS A/B from D-KEFS		
	Symbol Search, Coding, Letter-Number Sequencing, Arithmetic subtest from WISC-IV		
	Flanker Task		
	Revised Happé's Strange Stories		
	Animated Triangles		
	Pattern Meanings		
	Brief Smell Identification Test (B-SIT)		
Neuromotor and physical measures	Movement ABC	Motor milestones from Anamnestic interview	
	Height, weight, head circumference, arm span		
	Finger tapping		
	Grooved Pegboard		
	Waldrop Scale		
	3D photo		
	Hair cortisol		
	Saliva Sample (Genetics)		

All abbreviations and references can be found in the article 'The Danish High Risk and Resilience Study – VIA 7 - a cohort study of 520 7-year-old children born of parents diagnosed with either schizophrenia, bipolar disorder or neither of these two mental disorders' **(Thorup et al., 2015)**.

Table 3.5. Instruments used in the assessment of adults participating in the Danish High Risk and Resilience Study – VIA 7

Domains	Informant and instrument		
	Index	Non-Index	Primary Caregiver
Psychiatric symptoms and affect regulation	SCAN	SCAN	SCAN
	Schedule for Assessment of Positive Symptoms (SANS)	Schedule for Assessment of Positive Symptoms (SANS)	Schedule for Assessment of Positive Symptoms (SANS)
	Schedule for Assessment of Negative Symptoms (SAPS)	Schedule for Assessment of Negative Symptoms (SAPS)	Schedule for Assessment of Negative Symptoms (SAPS)
	Hamilton Rating Scale for Depression	Hamilton Rating Scale for Depression	Hamilton Rating Scale for Depression
	Young Mania Rating Scale	Young Mania Rating Scale	Young Mania Rating Scale
	Affective Lability Scale	Affective Lability Scale	Affective Lability Scale
Daily and social functioning	Social Provision Scale (SPS)	Social Provision Scale (SPS)	Social Provision Scale (SPS)
	Psychosis Attachment Measurement (PAM)	Psychosis Attachment Measurement (PAM)	Psychosis Attachment Measurement (PAM)
	Personal and Social Performance Scale (PSP)	Personal and Social Performance Scale (PSP)	Personal and Social Performance Scale (PSP)
Cognitive functioning	Reynolds Intellectual Screening Test (RIST)	Reynolds Intellectual Screening Test (RIST)	Reynolds Intellectual Screening Test (RIST)
	Letter-number sequencing and coding from WAIS	Letter-number sequencing and coding from WAIS	Letter-number sequencing and coding from WAIS
	Intra/extra Dimensional Set Shift, Spatial Working Memory, Cambridge Gambling Task and Rapid Visual Information Processing from the CANTAB		
	Brief Smell Identification Test (B-SIT)		
	D-KEFS Verbal Fluency		
Demographic information	Anamnestic interview (e.g. employment, education, income)	Anamnestic interview (e.g. employment, education, income)	Anamnestic interview (Full interview)
Social cognition	Animated Triangles		
	The Awareness of Social Inference Test – Revised (TASIT-R)		
	Emotion Recognition Task (ERT) from CANTAB		
Measures associated with caregiving			Caregivers Helplessness Questionnaire (CHQ)
			Five Minute Speech Sample
			Tangram puzzle
Genetic	Blood or Saliva sample	Blood or Saliva Sample	

All abbreviations and references can be found in the article 'The Danish High Risk and Resilience Study – VIA 7 - a cohort study of 520 7-year-old children born of parents diagnosed with either schizophrenia, bipolar disorder or neither of these two mental disorders' **(Thorup et al., 2015)**.

Common analyses strategy for the VIA 7 study cohort:

Only 9 children in the total cohort were double high-risk children. It was thus decided that the included children with double high-risk status would be analysed together with the single high-risk children without adjustment for the double high-risk status.

Siblings included in the study violate the assumption of independence of observations because of shared genetic and environmental factors that exceeds those between non-siblings. Despite this for most analyses of all studies it was decided to perform analyses without accounting for this factor.

Demographic and clinical characteristics were analysed by one-way analysis of variance (ANOVA), chi-square test or the Mantel-Haenszel linear-by-linear test of association, as appropriate (Table 6.1).

Summary of The Danish High Risk and Resilience Study VIA 7

The VIA 7 Study includes children of parents with either schizophrenia (N=202) or bipolar disorder (N=120) as well as a matched control group (N=200). This allows for comparison not only between children with familial high-risk and controls, but also between children at familial high-risk of two different severe mental illnesses. The cohort was uniquely created utilizing the Danish national registries.

The VIA 7 study is to date the largest register based nationwide cohort study of children. The study applies a multi-method (performance tests, questionnaires, interviews) and multi-informant (self-, parent-, teacher-, health professional- reports) approach of assessment, and assessment covers multiple domains (neuro- and social cognition, social function, executive function, emotion regulation, psychopathology, genetics, psychotic like experiences and more).

Chapter 4. Materials and methods specific to the studies of the present thesis

Chapter 4 firstly describes the materials and methods used in one or more of the three studies of this thesis. Hereafter, specifics of each of the three studies are described, specifically when they differ between the three studies or from the overall VIA 7 study.

Participants, measures and analyses that apply for one or more of the three papers

Participants

The VIA 7 Study was the first wave of The Danish High Risk and Resilience Study and constituted the establishment of the prospective cohort. The cohort of 522 children (FHR-SZ=202, FHR-BP=120, Controls=200) forms the basis of the studies of this thesis (Figure 2.1).

Measures:

Best estimate present and lifetime DSM-IV children's psychiatric research diagnoses were determined on the basis of the semi-structured diagnostic interview; **Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL)** (Kaufman et al., 1997) which allows for the utilization of all available data on the child ascertained during the test-period. The K-SADS-PL interviews were as recommended firstly performed with the primary caregiver and subsequently with the child. Consensus diagnoses were for all children made at group conferences and always with the presence of a child- and adolescent psychiatrist (AT). Attendees at diagnostic conferences were kept blind to the psychiatric status of the parents to ensure unbiased assessment of the child. All diagnostic interviews were video recorded, and recordings could thus be consulted if needed and for reliability ratings. In case of doubt in scoring, scoring would be discussed on a consensus conference. From the K-SADS-PL we utilized the attention-deficit/hyperactivity disorder (ADHD) diagnosis and any Axis I diagnosis. We further utilized the conduct disorder and oppositional defiant disorder diagnoses to construct a disruptive behaviour disorder (DBD) diagnosis category. We included both definite and probable diagnoses in the analyses. Given the high rate of eliminations disorders (encopresis and enuresis) in all groups at this age, and the high possibility that this is not connected to a psychiatric disorder at this age, elimination disorders were excluded from the any Axis I diagnosis to prevent it from falsely influencing the results.
Regular diagnostic reliability ratings were completed to ensure agreement among raters.

Current level of daily functioning of the child was evaluated with **the Children's Global Assessment Scale (CGAS)** (Shaffer et al., 1983) as part of the K-SADS-PL interview. CGAS is global assessment of daily life functioning designed for children and adolescents aged 4-17 years and is completed by the clinician (researcher). CGAS is a single score on a numeric scale that ranges from 1 to 100 with higher scores

reflecting higher levels of functioning. Scores are defined within ten increment point intervals with a score that range from 1-10 classified as 'extremely impaired' and importantly scores between 91 and 100 indicating 'superior functioning' and should thus not normally be expected. Scores above 70 indicate normal functionality. CGAS is rated independent of specific mental health diagnoses and was scored on basis of the level of functioning within the last four weeks. The same procedures as described for K-SADS-PL likewise applied for CGAS.

The Child Behavior Checklist school-age version (CBCL) (Achenbach & Rescorla, 2001) is divided into two main sections. The first section; 'the competence section', taps into the child's social network, school performance and leisure activities. The second section includes 118 questions on problem behaviour that are rated on a Likert scale from zero (not true) to two (very true/often true). The CBCL total score is summed from the 118 problem behaviour items. Further an Internalizing and an Externalizing broad-band subscale can be computed, as well as six DSM-IV oriented subscales of which we utilize the Attention-Deficit/Hyperactivity Problems scale and the Conduct Problems scale. The CBCL is completed by the primary caregiver. **The Teacher's Report Form (TRF)** (Achenbach & Rescorla, 2001) with minor differences corresponds to the CBCL. The TRF is completed by the child's primary school teacher.

ADHD symptomatology of the child was assessed with the modified version of **The Attention Deficit/Hyperactive Disorder - Rating Scale (ADHD-RS)** (DuPaul, Power, Anastopoulos, & Reid, 1998) Danish version (Makransky & Bilenberg, 2014). The ADHD-RS comprises 18 items covering core symptoms of ADHD; nine items on behaviours related to inattention and nine items regarding behaviour related to symptoms of hyperactivity and impulsivity. The ADHD-RS further comprises eight items concentrating on behavioural disturbances. Higher scores on ADHD-RS reflect worse symptom severity. Both the primary caregiver and the child's teacher independently completed the ADHD-RS.

Current level of personal and social functioning of adult participants was assessed with **the Personal and Social Performance scale (PSP)** (Morosini et al., 2000). The PSP assesses functioning within the previous four weeks, in four main areas: Socially useful activities; personal and social relationships; self-care; and disturbing and aggressive behaviour. Each area is rated on a six-point scale from absent to very severe, where lower ratings indicate better functioning. A PSP global score ranging from 1 to 100, with higher scores reflecting higher level of functioning, is assigned by the interviewer at completion of the interview. The PSP global scores are defined in ten increment point intervals to aid the precision of the rating. A score above 90 is reflective of more than adequate functioning. The PSP is interviewer-administered and often conducted in relation to the diagnostic interview of adult participants (The SCAN interview). In case of doubt, scoring was brought up on a consensus conference. Regular reliability scorings were completed to secure agreement

Employment status and educational levels of adult participants were attained through anamnestic interviews.

Analyses

Between group differences regarding demographic and clinical characteristics were analysed by one-way analysis of variance (ANOVA), Pearson's Chi-Squared test of independence and Mantel-Haenszel linear-by-linear test of association with Least Significant Difference (LSD) post hoc test, as appropriate. These analyses were not adjusted for any covariates or multiple assessments (Table 6.1)
IBM SPSS Statistics, version 25.0 or 26.0 were used for all statistical analyses.

Paper I – Dimensionally assessed psychopathology

Participants:

The primary outcome measure of the study; The Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997) was unfortunately not included from the beginning of the data collection period, but was introduced six months into the study. This consequently resulted in a smaller (but unselected) total number of potential SDQ participants. A total of 448 children were assessed with the SDQ: 429 children were rated by their primary caregiver, 366 children were rated by their schoolteacher and, 347 children were rated by both their primary caregiver and their schoolteacher (Figure 2.1).

Measures:

The Strengths and Difficulties Questionnaire (SDQ) was developed as a brief behavioural screening tool to assess child and adolescent behaviours, emotions and relationships (Goodman, 1997). The SDQ consists of 25 questions selected on the basis of contemporary diagnostic criteria and factor analysis. The 25 items comprise five scales; four difficulties scales (Emotional Symptoms, Conduct Problems, Hyperactivity, Peer Problems) and one scale on Prosocial Behaviour, each scale of five items each. A Total Difficulties Scale score is generated by summing the four difficulties scales. All questions are identical for the parent and teacher version and have the following response options: "Not true", "Somewhat true" or "Certainly true" corresponding to a score of 0, 1 and 2 or reversed scores of 2, 1 and 0 for some items. For each scale, a score between zero and ten can be obtained. For the four difficulties scales, higher scores indicate more problem behaviour, whereas, for the prosocial scale, a higher score indicates better performance. The respondent is asked to consider the behaviour of the child during the previous six months period when rating the SDQ. The SDQ is widely used internationally, and satisfactory psychometric properties as well as the clinical utility of the questionnaire, have repeatedly been affirmed (Goodman, 2001; Heuvel et al., 2017; Mieloo et al., 2012; Niclasen et al., 2012). The SDQ can be used to approximately determine the probability of mental illness in a population with 80 percent of a population-based sample classified as 'unlikely' to have a mental illness, 10 percent as 'possibly' and lastly the 10^{th} percentile poorest scoring classified as 'probably' having a mental illness. Utilizing these classifications the SDQ has repeatedly been

found to discriminate well between clinical and non-clinical populations as well as having satisfactory predictive values in in population studies (Nielsen et al., 2019; Rimvall et al., 2014; Stone et al., 2010; Sveen, Berg-Nielsen, Lydersen, & Wichstrøm, 2013; Ullebø, Posserud, Heiervang, Gillberg, & Obel, 2011; Wolf et al., 2019).

Analyses

Descriptive SDQ mean values and between-group differences

SDQ scores were converted to Z-scores for boys and girls separately using the control group as the reference group. Hereafter Z-scores were computed into T-scores (mean=50 and SD=10) with higher T-scores indicating worse functioning in all scales. SDQ mean raw, and T-scores and comparisons of group differences analysed on T-scores by Welch ANOVA followed by Games-Howell post hoc tests are presented solely as descriptive illustrations of the data.

Prevalence of SDQ clinical range scores

We applied logistic regression analyses to compare the proportion of children from each high risk group that were classified within 'probably' category compared to the control group. Cut-off scores were calculated from the control group. Main results of group differences are reported as the proportion of children above cut-off and odds ratios (OR) between groups. We analysed differences in the proportion of boys and girls scoring above cut off in the individual groups with chi-square tests.

Difference in daily life functioning (CGAS) between children scored below and above the SDQ Total Difficulties Scale cut-off score

In order to qualify the assumption that an SDQ score above cut-off has an impact on daily life functioning we assessed differences in CGAS mean scores between the above and below cut-off groups by independent samples t-test.

The discriminatory ability of the SDQ compared to the CBCL and TRF

We applied receiver operating characteristics (ROC) curves to determine the ability of SDQ and the CBCL total scores to distinguish between familial high-risk children with and without any lifetime Axis I diagnosis. ROC curve analysis was further used to determine the ability of the SDQ and CBCL hyperactivity scale to distinguish between children with and without a lifetime ADHD diagnosis and the conduct scales for the presence of a disruptive behaviour disorder diagnosis Comparisons of the areas under the ROC curves for SDQ and CBCL respectively were performed using paired sample statistics. All ROC analyses were performed on outcome T-scores. Teachers' SDQ ratings and ROC curves compared to the TRF were examined by the same methods as described above.

Correlation of primary caregiver and teacher rated SDQ scores

Interrater agreement between the primary caregiver and teacher SDQ ratings and between primary caregiver and teacher rated CBCL and TRF were performed by intra-class correlation coefficient (ICC) with two-way random effect model on absolute agreement (Liu et al., 2016; Shrout & Fleiss, 1979).

Paper II – Executive functions

Participants

515 out of 522 children were assessed with the primary outcome measure of the study by either their primary caregiver (N=493), teacher (N=417) or both (N=439) (Figure 2.1).

Measures

We measured executive functions with **the Behavior Rating Inventory of Executive Function (BRIEF** (G. A. Gioia, Isquith, Guy, & Kenworthy, 2000)); Danish parent (rated by the primary caregiver) and teacher version (G. Gioia, Isquith, Guy, & Kenworhty, 2005). The BRIEF consists of 86 statements about executive function problem behaviours. Higher scores indicate worse functioning. Aspects of executive functions are reflected in eight non-overlapping clinical scales: Inhibit, Shift, Emotional Control, Initiation, Working Memory, Planning, Organization of Materials, and Monitoring. The eight clinical scales are summed into a Global Executive Composite (GEC) score. Cronbach's alpha on GEC for caregiver and teacher-rated BRIEF was calculated to be 0.97 and 0.98 respectively in the VIA 7 study cohort. We utilized the large population-based control group (N=190) to construct T-score reference group values adjusted for sex of the child. Effect of age was non-significant in all groups. Clinical cut-off scores were defined as 1.5 standard deviations above the mean (T-score>65) (G. Gioia et al., 2005).

Analyses

Between-group differences

Between group differences of BRIEF GEC scores were analysed by Welch ANOVA followed by Games-Howell post hoc test. The eight clinical scales were analysed jointly by MANOVA reporting Wilks' lambda statistics. In case of a significant result, Welch ANOVA was performed on each of the eight individual clinical scales with Games-Howell post hoc test.

Sex differences in executive functioning and executive functioning profiles

Exploratory analysis by one-way MANOVA with the child's sex as fixed factor and the eight clinical scales as dependent variables was performed to identify potential sex differences in executive functions associated with FHR-SZ and FHR-BP status. Pillai's trace results are reported. One-way repeated-measures ANOVA was performed to detect potential differences in executive functions profile shapes between the three groups. Group was set as between-subject factor, and the eight clinical scales were set as within-subject repeated measures. Greenhouse-Geisser corrections are reported. If deviations from flatness (in the BRIEF-clinical scales profiles of the FHR-SZ and FHR-BP group compared to the control group) was suggested by a significant group by BRIEF-clinical scale profile interaction, the individual clinical scales were assessed using paired-samples t-test to identify which executive functions were relatively differently impaired within each of the two high risk groups.

Prevalence of clinical range scores

Between-group differences in the proportion of children scoring above clinical cut-off were analysed by logistic regression with odds ratios reported as effect size measures. This analysis was performed to quantify the clinical significance of group differences by assessing the prevalence of potentially clinically relevant impairment in each of the three groups. An alpha level of 0.05 was set for analyses on GEC. The alpha level was adjusted to 0.00625 (Bonferroni adjustment) for the eight clinical scales to counter the risk of type I errors when performing multiple comparisons. All analyses were performed on BRIEF T-scores.

Paper III – Emotion regulation

Participants

The primary outcome measure of the study, EmReg, was ascertained for 465 children (Figure 2.1). TEC-M data of 57 children was not included in the study. Technical and administration problems accounted for 43.9 % of missing data (N=28; lack of sound or picture, inappropriate film angle etc.), but missing data was also due to, e.g. refusal to be videotaped or dis-participation. Missingness analyses revealed no significant differences between participants and non-participants neither on sex (p=.314) nor age (p=.714). Likewise, participation rates (p=.279) and reason for missing (p=.438) did not differ between risk groups.

Measures

Beyond the Total score of The Child Behavior Checklist (CBCL), an *emotional/behavioural dysregulation profile* (**CBCL-DP**) can be computed from the CBCL. The CBCL-DP comprises three symptom scales from the CBCL (Aggressive Behavior, Anxious/Depressed, and Attention Problems)(Achenbach & Rescorla, 2001; Althoff, 2010). Two versions of the CBCL-DP are generally used, the stringent **CBCL-DP70** (i.e. T-scores above or equal to 70 on all of the three individual symptom scales) or the broader **CBCL-DP210** (i.e. a sum of the three symptom scale T-scores above or equal to 210) (Aitken, Battaglia, Marino, Mahendran, & Andrade, 2019). A CBCL-DP score above the cut-off, suggestively predicts subsequent psychopathology and poor functioning (Biederman et al., 2012). We computed a normalised CBCL-DP T-score (mean=50 and SD=10) from our study sample's control group for boys and girls separately, with higher scores indicating more problem behaviour. In this study, we utiliszd both the stringent CBCL-DP70 and the broader CBCL-DP210.

An **ADHD-RS composite score (ADHD-RS-comp)** was calculated as the mean from the primary caregiver and teacher-rated ADHD-RS item 1-18, thus excluding conduct disorder item scores (Martel, Schimmack, Nikolas, & Nigg, 2015). A normalizing T-score was calculated by the same method as described for CBCL-DP.

The primary outcome measure of Paper III is **EmReg**; an emotion regulation measure from 'The Tangram Emotion Coding Manual' (TEC-M). The TEC-M was developed as part of, and during the course of this PhD

study and is thus dedicated at chapter of its own. A thorough description of EmReg and TEC-M can hence be found in Chapter 5: The Tangram Emotion Coding Manual (TEC-M).

Analysis

Group differences

Between-group differences in emotion regulation was assessed by ANOVA with post hoc Tukey-Kramer.

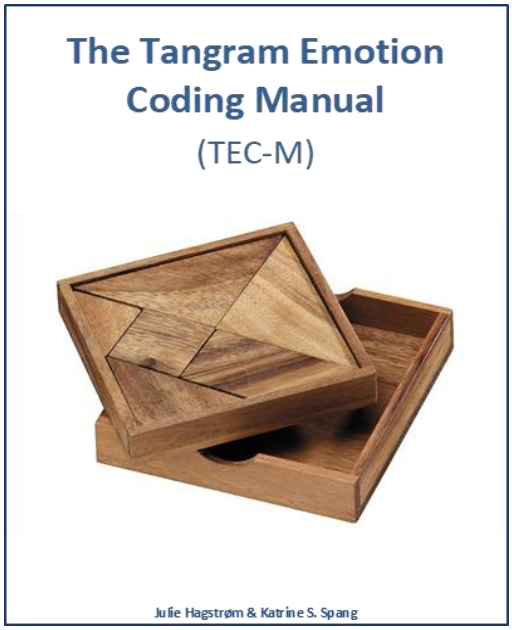
Association analyses

Association between emotion regulation and dimensions of psychopathology and daily life functioning was analysed by Spearman's rank-order correlation for continuous dependent variables and with Pearson correlations for dichotomous dependent variables.

Chapter 5. The Tangram Emotion Coding Manual (TEC-M)

A thorough search of measures on emotion regulation revealed an overwhelming shortage of objective test measures of emotion regulation not relying on self- or parent- reports. To accommodate this shortage and an expressed need for observational ecologically valid methods of assessments of spontaneous emotion regulation (Aldao et al., 2010) we developed the Tangram Emotion Coding Manual (TEC-M) (**Figure 5.1**). The TEC-M is theoretically founded on 'The Process Model of Emotion Regulation' (described page 10) and designed to assess emotion regulation by standardized clinician-ratings in a lab-based setting. The TEC-M utilizes a frustrating dissection puzzle task (The Tangram Construction Task) to elicit emotions and assess behaviour reflecting children's emotion regulation in the context of the social interaction with the primary-caregiver. The primary outcome of the TEC-M is the child's overall ability of emotion regulation; EmReg. Further, the instrument provides scores of behaviours related to emotion regulation. TEC-M was developed through a theoretical-empirical approach in which the items of the manual emerged from going through numerous recordings of participants performing The Tangram Construction Task as well as literature research of emotion assessment and grounding the emerged items in within the theoretic framework of The Process Model of Emotion Regulation.

Figure 5.1 The Tangram Emotion Coding Manual (TEC-M)



The Tangram Puzzle

Tangram is a Chinese dissection puzzle consisting of seven puzzle pieces (Figure 5.2) and can be dated back to the Song Dynasty around year 1000. The Tangram is by some considered to be one of the earliest psychological tests in the world (Sternberg & Baltes, 2004).

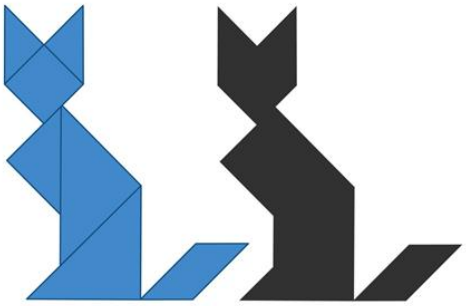
Figure 5.2. Tangram puzzle pieces and figure.

With the Tangram puzzle pieces, it is possible to create an array of figures (**Figure *5.3***).

Figure 5.3. Tangram figure illustrations.

Figures can be created from imagination or by copying a pictured figure. This again can be more or less difficult depending on the shape of the puzzle, the time frame for solving the puzzle, and whether or not puzzle piece outlines are presented on the pictured figures as illustrated in (Figure 5.4).

Figure 5.4. Tangram figure with and without puzzle outlines.



The Tangram Puzzle has previously been used in psychological test settings. In regards to children it has been used for assessing parent-child interactions in the context of child anxiety (Hudson & Rapee, 2001, 2002), and in assessing attachment relations in adopted children (Steele et al., 2007). Most recently it has again been used in the study of child anxiety focusing on the assessment of the parent-child dyad (Esbjørn, Chiristiansen & Steele, unpublished manuscript) and applying a manual with a modified version of the Tangram puzzle; The Tangram Construction Task. The TEC-M utilizes the Tangram Construction Task but applies a new scoring method and enhanced focus specifically on emotion regulation ability of the child and parental behaviour and influence as a secondary measure.

The Tangram Construction Task

The Tangram Construction Task is a five-minute task where the child is presented with the Tangram puzzle pieces and six pictured figures without puzzle piece outlines. The child is instructed to solve as many puzzles as possible within five minutes. The child is accompanied by an adult, in The VIA 7 Study this adult was always the primary caregiver. The adult is handed a solution booklet and instructed (with the child present) that most children can solve the puzzles, but some find it a bit difficult. The adult is asked to sit beside the child to support the child, but only to help if it is truly necessary (with emphasis on the word truly) recorded (Figure 5.5). After instructions the instructor leaves the room and the five minutes are video. Instructions are given verbatim to minimize the influence of having multiple task-administers. The parent and child are left alone and undisturbed during the Tangram Construction Task to increase the ecological validity.

Figure 5.5. Instruction page from the Tangram Emotion Coding Manual (TEC-M) (Hagstrøm & Spang, n.d.)

Procedures

The child and caregiver must sit next to each other at a cleared table. The camera is positioned across the table so that both the table and the faces of the participants are filmed, thereby enabling coding of facial expressions as well as body posture and puzzle solving. The camera should be close enough to capture facial expressions clearly and sound recorder should capture all sounds including whispering. The instructions are given verbatim. Avoid placing the puzzle on the table until the instructions are given in order to keep the child from starting prematurely. As soon as the instructions are given, the test leader leaves the room and returns after five minutes.

Verbal instructions

To the child:

> "*Here is a set of seven funny puzzle pieces* (puzzle is put in front of the child*). When I say "Go" I want you to place the puzzle pieces, so they form the figures shown on this paper* (pictures of the figures are laid on the table). *I would like to see how many correct figures you can do within five minutes".*

To the caregiver:

> *"This is a test of your child's abilities. We want to see how good she/he is at thinking. You shall sit here next to your child to support your child and you are given the answers for your own interest* (answer booklet is handed to the caregiver). *Most children can solve the puzzles, but some find it a bit difficult. You may help if you think he/she TRULY needs it.".*

To both:

> "*When I say 'Go' I will leave the room and be back in five minutes. Do you have any questions?".*

If either the child or the caregiver asks questions, the reply is: "*Just do as you like".* It is important to be as vague as possible in response to additional questions and to avoid further instructions.[2]

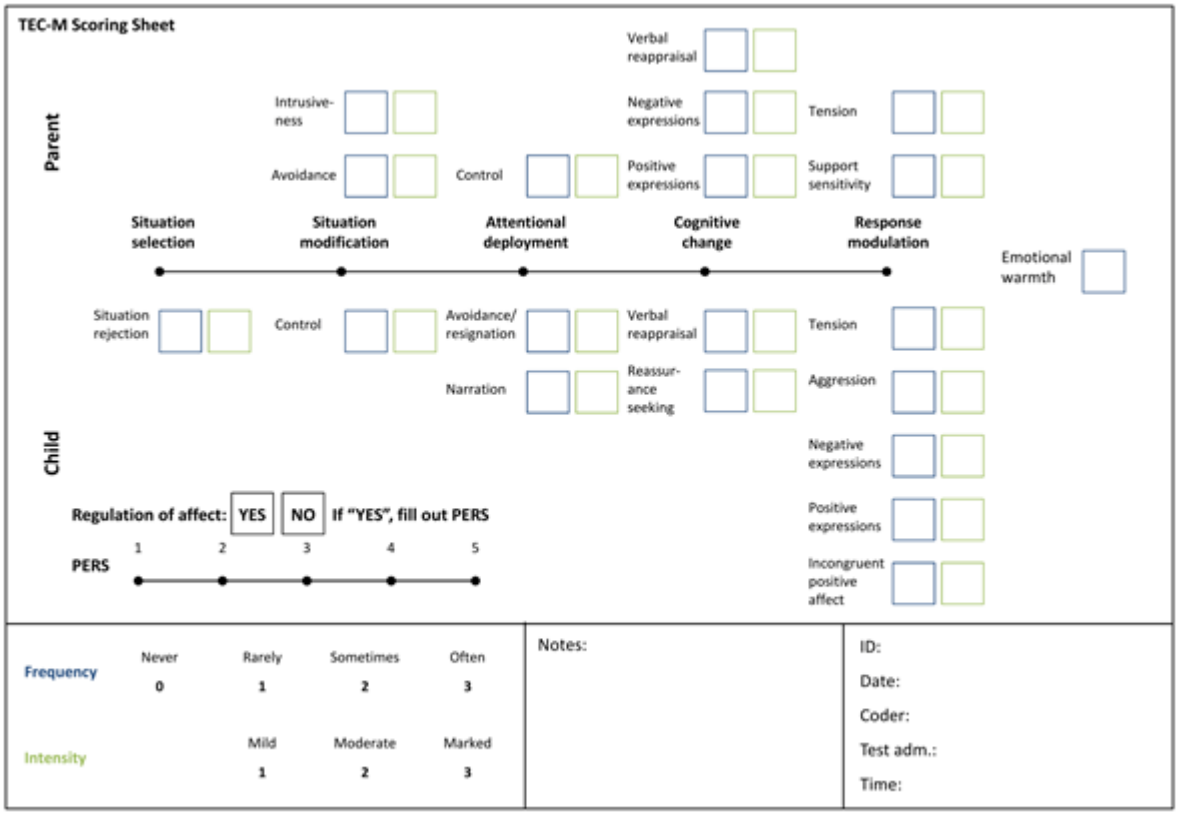
[2] This an unofficial English translation of the Danish TEC-M.

Assessment of emotion regulation with The Tangram Emotion Coding Manual (TEC-M)

The TEC-M manualises coding of behaviour during the Tangram Construction Task. Exactly five minutes of puzzle solving, counting from the last words of instruction, is scored on the TEC-M scoring sheet (Figure ***5.6***). With each five-minute video being scored twice; firstly, observation and subsequently scoring the behaviour of the adult participant, and secondly, the behaviour of the child. Scorings of the adult and child items are exclusively on explicit observed behaviour. That is *what* is seen and heard, not *why*.

Adults are scored on eight items: Intrusiveness, control, Avoidance, Verbal Reappraisal, Support Sensitivity, Positive Expressions, Negative Expressions, and Tension. Children are scored on 11 items: Situation Rejection, Control, Avoidance/Resignation, Narration, Verbal Reappraisal, Reassurance Seeking, Tension, Aggression, Negative Expressions, positive Expressions, and Incongruent Positive Affect. Each item is anchored to one of the five emotion regulation processes of gross' Process Model of Emotion Regulation (Gross, 2014) (Figure ***5.6***).

Figure 5.6. ***TEC-M scoring sheet***



For all items are scored on frequency and intensity of the observed behaviour. Frequency is scored on a Likert scale from 0-3 (0=never, 1= rarely, 2= sometimes, 3= often), and intensity is scored on a Likert scale

from 1-3 (1= mild, 2=moderate, 3=marked). Intensity is only scored when the equivalent frequency score is above 1. Subsequently to the scoring of the adult and child participant, the item 'emotional warmth' is scored as a combined score for the child and parent which indicate the overall impression of the quality of the interaction. This score is qualitatively subjective and scored on a Likert scale from 1-3 (1=poor, 2= intermediate, 3=good). Finally, the child's overall emotion regulation is scored on the Emotion Regulation Scale (EmReg). EmReg is scored based on the scores of the other items while considering all factors of the evaluated test situation, such as the child's level of frustration, parental behaviour, and perceived level of difficulty in the task in combination with the scored behavioural data on the child; e.g. positive and negative expression, reassurance seeking and so forth. The EmReg score is a 5-point Likert scale (1= very poor, 2= poor, 3= moderate, 4= good, 5= excellent).

The TEC-M provides comprehensive information on the content of the individual items as well as a detailed guide to scoring of the single items.

The primary outcome measure of the TEC-M, the EmReg is thus a qualitative score that represents an assessment of the child's overall emotion regulation in a standardized social setting of performing a frustrating and demanding task in the presence of the instructed primary caregiver.

Validation of the Tangram Emotion Coding Manual (TEC-M)

We have performed a valuation study on the TEC-M (Hagstrøm et al., 2019). A brief summary of this study can be found in chapter 7 page 63.

Chapter 6. Results

Firstly, selected participant and background characteristics of the full VIA 7 Study cohort will be presented and then the results of the three papers.

Background characteristics of the VIA 7 Study participants

The children

Age and sex of the children did not differ between groups. Both familial high-risk groups have poorer levels of daily life functioning (CGAS), higher levels of dimensionally measured psychopathology (CBCL) and more frequently fulfil the diagnostic criteria for an Axis I psychiatric diagnosis compared to control children. Familial high-risk children more frequently do not live with both biological parents and also more often with a single parent compared to control children. Approximately one third of familial high-risk children live with the parent diagnosed with schizophrenia or bipolar disorder and roughly 50 percent of the risk families the primary caregiver is the parent with the index diagnosis (

Table 6.1).

Primary caregivers

The primary caregivers are most often female and groups are non-different on this matter. Primary caregivers in the two familial high-risk groups have lower levels of personal and social functioning (PSP) compared to primary caregivers of the control group and related they are less often in employment or studying. Primary caregivers of the familial high-risk schizophrenia group have lower levels of education than both the bipolar group primary caregivers and the control group (

Table 6.1).

Biological parents

The index parents of both familial high-risk groups have lower level of functioning, are less often employed and have lower levels of education. The only exception is parents diagnosed with bipolar disorder who on a group level have equal levels of education as the control parents. Non-index parents of the familial high-risk groups numerically do better than index parents but with exactly the same pattern compared to the control group as seen for index parents (

Table 6.1).

Detailed results regarding child diagnoses, CBCL and TRF are previously published (Ellersgaard, 2018; Ellersgaard et al., 2018) and summarized in chapter 7. Likewise details for child neurocognition (Hemager, 2018; Hemager et al., 2018) and child's home-environment are likewise published (Gantriis et al., 2019)

Table 6.1. Characteristics of children participating in the Danish High Risk and Resilience study, their home environment, biological parents, and primary caregivers.

	FHR-SZ	FHR-BP	Controls	*p*-value	*p*-value FHR-SZ vs. Controls	*p*-value FHR-BP vs. Controls	*p*-value FHR-BP vs. FHR-SZ
Children, N	202	120	200	-	-	-	-
Female, %	46.0	46.7	46.5	.993[C]	-	-	-
Age at inclusion, mean (SD)	7.84 (0.22)	7.86 (0.20)	7.81 (0.20)	.097[A]	-	-	-
CGAS [1] , mean (SD) N= 199, 118, 197	68.1 (15.4)	73.6 (14.9)	77.7 (13.5)	.000[A]	.000[A]	.044[A]	.004[A]
CBCL [2] score, mean (SD) N= 192, 111, 191	27.2 (21.1)	23.4 (19.7)	17.0 (14.7)	.000[A]	.000[A]	.012[A]	.259[A]
TRF [2] score, mean (SD) N=167,103,166	27.2 (26.6)	20.7 (24.0)	15.0 (16.6)	.000[A]	.000[A]	.139[A]	.065[A]
Diagnostic assessment, N	199	118	197				
Any lifetime Axis I diagnosis [3], %	38.7	35.6	15.2	.000[C]	.000[C]	.000[C]	.528[C]
Any lifetime ADHD diagnosis [4]	20.6	9.3	7.1	.000[C]	.000[C]	.481[C]	.009[C]
Any lifetime DBD diagnosis [5]	6.0	3.4	1.0	.025[C]	.007[C]	.136[C]	.299[C]
Child´s home environment							
Living with two biological parents, %	40.6	52.5	84.5	.000[C]	.000[C]	.000[C]	.038[C]
Living with index [8] parent, %	61.4	70.0	-	-	-	-	.118[C]
Living with a single parent, %	37.1	32.5	10.6	.000[C]	.000[C]	.000[C]	.401[C]
Living out of home, %	5.4	0.0	0.5	.001[C]	.004[C]	.438[C]	.009[C]
Primary caregiver [7] is index	43.8	56.7		-	-	-	.025[C]
Primary caregivers [7], N	200	120	200				
Female, %	87.6	92.5	90.0	.373[C]	-	-	-
Age at child´s birth, mean (SD)	30.6 (6.6)	31.8 (5.6)	32.3 (4.2)	.009[A]	.003[A]	.482[A]	.057[A]
PSP [6] primary caregiver [7], mean (SD) N=197, 118, 197	73.1 (14.0)	74.5 (14.1)	84.4 (9.1)	.000[A]	.000[A]	.000[A]	.346[A]
Employed/studying [8], % N=200,119,196	67.0	67.2	91.3	.000[C]	.000[C]	.000[C]	.967[C]
Educational information, N	198	118	197				
Primary/lower secondary, %	18.2	5.9	2.5				
Upper secondary, vocational, short-cycle tertiary, %	44.4	34.7	43.1	.000[L]	.000 [L]	.145 [L]	.000 [L]
Bachelor degree, equivalent or higher, %	37.4	59.3	54.3				
Index [9] Parents , N	200	116	204	-	-	-	-
Female, %	55.5	55.2	56.4	.974[C]	-	-	-
Age at child´s birth, mean (SD)	30.20 (6.07)	33.12 (7.01)	32.83 (4.78)	.000[A]	.000 [A]	1.000 [A]	.000 [A]
PSP [6], mean (SD) N=158, 102, 194	66.1 (15.7)	68.9 (14.1)	84.3 (9.9)	.000[A]	.000 [A]	.000 [A]	.286 [A]
Employed/studying [8], % N= 187, 109, 201	49.7	56.0	92.0	.000[C]	.000[C]	.000[C]	.301[C]
Educational information, N	178	109	197				
Primary/lower secondary, %	30.3	9.2	4.1				
Upper secondary, vocational, short-cycle tertiary, %	42.7	41.3	48.2	.000[L]	.000 [L]	.985 [L]	.000 [L]
Bachelor degree, equivalent or higher, %	27.0	49.5	47.7				

Non-index [10] Parents, N	186	114	192				
Female, %	44.1	44.7	43.2	.966[C]	-	-	-
Age at child´s birth, mean (SD)	30.92 (6.37)	33.10 (5.39)	32.97 (4.28)	.000[A]	.001[A]	1.000[A]	.002[A]
PSP [6], mean (SD) N= 163, 94, 180	76.4 (14.3)	81.8 (13.1)	85.5 (8.4)	.000[A]	.000[A]	.040[A]	.002[A]
Employed/studying [8], % N=177, 109, 188	75.1	85.3	95.2	.000[C]	.000[C]	.003[C]	.040[C]
Educational information, N	176	106	187				
Primary/lower secondary, %	17.6	4.7	5.3				
Upper secondary, vocational, short-cycle tertiary, %	48.9	41.5	47.6	.002[L]	.002 [L]	.276 [L]	.000 [L]
Bachelor degree, equivalent or higher, %	33.5	53.8	47.1				

FHR: Familial High-Risk; BP: Bipolar disorder; SZ: Schizophrenia.
In case information is not available for all participants an N has been added to indicate the number of individuals the result has been calculated from.
In the case of siblings; parent information is only included from the first included sibling in order not to count the same parent twice. This results in a lower number of parent couples than children.
[1] CGAS: Children's Global Assessment Scale (Shaffer et al., 1983).
[2] CBCL: Child Behavior Check List, TRF: Teachers Report Form (Achenbach & Rescorla, 2001).
[3] Any lifetime Axis I diagnosis, [4] Any lifetime Attention Deficit/Hyperactivity Disorder (ADHD) diagnosis, [5] Any lifetime Disruptive Behaviour Disorder (DBD) diagnosis. All diagnosis were assigned using the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL (Kaufman et al., 1997). The DBD diagnosis was constructed by combining the conduct disorder and oppositional defient disorder diagnoses.
[6] PSP: The Personal and Social Performance Scale (Morosini et al., 2000).
[7] Primary caregiver is defined as the parent or foster parent that knows the child best and spends most time with the child
[8] Employed or studying is defined as being under employment (including temporary leave) or adhering to an acknowledged education for a minimum of 15 hours weekly.
[9] Index parent is defined as the parent with a diagnosis of either schizophrenia spectrum disorder or bipolar disorder and their adult matched control.
[10] Non-index parent is defined as the biological parent without a diagnosis of schizophrenia or bipolar disorder.
[A] ANOVA test. Post hoc one-way ANOVA with Least Significant Difference.
[C] Chi square test.
[L] linear by linear association *p* value is used when an ordinal variable has more than two categories.

Results. Paper I – Dimensionally assessed psychopathology

Descriptive SDQ mean values and between-group differences

Primary caregiver ratings

The differences in mean T-scores of parent ratings between the FHR-SZ group and the control group were highly significant on both the Total Difficulties Scale and on all four difficulties scales ($p < 0.001$), but non-significant regarding the Prosocial Behavior scale. The FHR-BP group differed significantly from the control group on the Total Difficulties Scale ($p = .026$), the Emotional Symptoms scale ($p = .025$) and the Conduct Problems scale ($p = .041$). The FHR-BP group scored intermediate of the control group and the FHR-SZ group on all four difficulties scales and were significantly different from the FHR-SZ on all scales ($p = .008$ - $.046$) except the Emotional Symptoms scale (Table 6.2).

Teacher ratings

Rated by teachers, the FHR-SZ group differed from the control group on all scales ($p = <.0001$ - $.003$), including the Prosocial Behavior scale ($p <.001$). The FHR-BP group only differed from the control group on the Total Difficulties Scale ($p = .048$) but did not differ from the FHR-SZ group on any scales of the SDQ-T (Table 6.2).

Table 6.2. The Strengths and Difficulties Questionnaire descriptive mean scores and standard deviations of participating children from the VIA 7 study.

PRIMARY CAREGIVER RATINGS	FHR-SZ		FHR-BP		Controls			FHR-SZ vs. Controls	FHR-BP vs. Controls	FHR-BP vs. FHR-SZ
	Raw score	T-score	Raw score	T-score	Raw score	T-score				
Participants, N	167		103		159					
	Mean (SD)						*p*		*p*-value	
Total Difficulties	9.34 (6.49)	59.6 (16.3)	7.08 (5.66)	54.1 (13.7)	5.45 (4.32)	50.0 (10.0)	<.001	<.001	.026	.008
Emotional Symptoms	2.44 (2.18)	56.8 (14.5)	2.10 (2.35)	54.5 (15.5)	1.43 (1.52)	50.0 (10.0)	<.001	<.001	.025	.454
Conduct Problems	1.69 (1.65)	59.5 (17.0)	1.10 (1.40)	53.9 (14.3)	0.75 (1.15)	50.0 (10.0)	<.001	<.001	.041	.011
Hyperactivity	3.77 (2.89)	55.8 (13.3)	2.97 (2.63)	52.0 (11.9)	2.53 (2.23)	50.0 (10.0)	<.001	<.001	.323	.046
Peer Problems	1.43 (1.85)	56.0 (15.9)	0.91 (1.43)	51.5 (11.9)	0.74 (1.25)	50.0 (10.0)	<.001	<.001	.519	.026
Prosocial Behavior	8.28 (1.86)	52.7 (13.1)	8.73 (1.60)	49.2 (10.7)	8.67 (1.41)	50.0 (10.0)	.039	.093	.810	.045

TEACHER RATINGS	Controls		FHR-BP		FHR-SZ		ANOVA	FHR-SZ vs. Controls	FHR-BP vs. Controls	FHR-BP vs. FHR-SZ
	Raw score	T-score	Raw score	T-score	Raw score	T-score				
Participants, N	134		91		141					
	Mean (SD)						*p*		*p*-value	
Total Difficulties	8.31 (7.02)	57.3 (13.6)	6.75 (7.04)	54.0 (13.9)	4.67 (5.08)	50.0 (10.0)	<.001	<.001	.048	.180
Emotional Symptoms	1.93 (2.07)	54.3 (11.4)	1.78 (2.33)	53.5 (12.7)	1.16 (1.83)	50.0 (10.0)	.003	.003	.072	.885
Conduct Problems	1.37 (2.05)	57.0 (16.5)	.89 (1.66)	53.0 (13.4)	0.51 (1.21)	50.0 (10.0)	<.001	<.001	.156	.123
Hyperactivity	3.50 (3.05)	54.5 (10.7)	2.97 (2.92)	52.2 (10.8)	2.35 (2.87)	50.0 (10.0)	.002	.001	.258	.277
Peer Problems	1.51 (1.93)	57.1 (16.1)	1.11 (2.00)	53.8 (16.7)	0.65 (1.20)	50.0 (10.0)	<.001	<.001	.123	.302
Prosocial Behavior	7.00 (2.54)	55.4 (12.3)	7.52 (2.44)	52.6 (12.0)	8.05 (2.03)	50.0 (10.0)	<.001	<.001	.210	.190

Higher T-scores equal more difficulties and less prosocial behavior. Group differences calculated on T-scores with Welch ANOVA and post hoc Games-Howell. FHR-BP: Familial high-risk bipolar group FHR-SZ: Familial high-risk schizophrenia group

Prevalence of SDQ clinical range scores

Primary caregiver ratings

FHR-SZ children were more likely to have a Total Difficulties Scale score within clinical range compared to control children (28.1% vs 9.4%) (OR = 3.8, CI 2.0 to 7.1, p = <.001). This was also true for FHR-BP children (19.4% vs 9.4%) (OR = 2.3, CI 1.1 to 4.8, p = <.023). FHR-SZ children had higher odds of significant difficulties compared to the control children on all difficulties scales (p = <.001). Odds of FHR-BP children only differed from that of the control children on the Emotional Symptoms scale (p =.010). Neither of the FHR groups differed from the control group regarding Prosocial Behavior (Table 6.3).

Teacher ratings

Teachers rated a lower proportion of FHR children above cut-off than primary caregivers did except regarding peer problems and less prosocial behavior. Further, the OR of conduct problems for FHR-SZ was high (OR = 6.3, CI 2.7-14.7, p =<.001) compared to controls (Table 6.3).

Table 6.3. Proportion of children with familial high-risk of schizophrenia or bipolar disorder scored above cut-off (within clinical range) compared to controls.

PRIMARY CAREGIVER RATINGS	Raw-score cut-off value closest to the 90th (10th)[1] percentile of the PBC		Controls	FHR-SZ			FHR-BP		
	Girls	Boys	Percent in clinical range	Percent in clinical range	OR (CI)	*p*-value	Percent in clinical range	OR (CI)	*p*-value
Total Difficulties	≥ 14	≥11	9.4	28.1	3.8 (2.0-7.1)	<.001*	19.4	2.3 (1.1-4.8)	.023*
Emotional Symptoms	≥ 5	≥4	7.5	24.0	3.9 (1.9-7.7)	<.001*	18.4	2.8 (1.3-6.0)	.010*
Conduct Problems	≥ 2	≥2	13.8	38.3	3.9 (2.2-6.9)	<.001*	23.3	1.9 (1.0-3.6)	.051
Hyperactivity	≥ 7	≥6	7.5	21.6	3.4 (1.7-6.7)	<.001*	14.6	2.1 (0.9-4.7)	.073
Peer Problems	≥ 3	≥3	6.9	20.4	3.4 (1.7-7.1)	<.001*	11.7	1.8 (0.8-4.2)	.191
Prosocial Behavior [1]	≤ 6	≤6	10.7	16.2	1.6 (0.8-3.1)	.151	10.7	1.0 (0.4-2.2)	.998
TEACHER RATINGS	Raw-score cut-off value closest to the 90th (10th)[1] percentile of the PBC		Controls	FHR-SZ			FHR-BP		
	Girls	Boys	Percent in clinical range	Percent in clinical range	OR (CI)	*p*-value	Percent in clinical range	OR (CI)	*p*-value
Total Difficulties	≥12	≥13	8.5	26.1	3.8 (1.9-7.7)	<.001*	15.4	2.0 (0.9-4.4)	.110
Emotional Symptoms	≥5	≥4	10.6	16.4	1.7 (0.8-3.3)	.163	17.6	1.8 (0.8-3.8)	.133
Conduct Problems	≥3	≥3	5.0	24.6	6.3 (2.7-14.7)	<.001*	12.1	2.6 (1.0-7.1)	.055
Hyperactivity	≥5	≥8	9.2	15.7	1.8 (0.9-3.8)	.108	13.2	1.5 (0.7-3.4)	.344
Peer Problems	≥2	≥3	8.5	26.1	3.8 (1.9-7.7)	<.001*	14.3	1.8 (0.8-4.1)	.170
Prosocial Behavior [1]	≤5	≤4	6.4	20.1	3.7 (1.7-8.2)	.001	15.4	2.7 (1.1-6.4)	.031

SDQ clinical cut-off scores (Clinical range= T-score > 65) are calculated from the control group. Odds ratios (OR) and *p*-values are calculated from T-scores
[1]The Prosocial scale is a reversed scale with higher scores equalling better performance.
FHR-BP: Familial high-risk bipolar disorder group; FHR-SZ: Familial high-risk schizophrenia group.
SDQ: The Strengths and Difficulties questionnaire (Goodman, 1997).
*Significant value: For the Total Difficulties Scale a *p*-values of <.05 are considered significant. For the four difficulties scales (Emotional Symptoms, Conduct Problems, Hyperactivity and Peer Problems) and the Prosocial Behavior scale a *p*-value of <.01 is considered significant according to Bonferroni alfa level correction for multiple comparisons (0.05/5=.01)

Differences in prevalence of clinical range Total Difficulties Scale scores depending on sex of the child

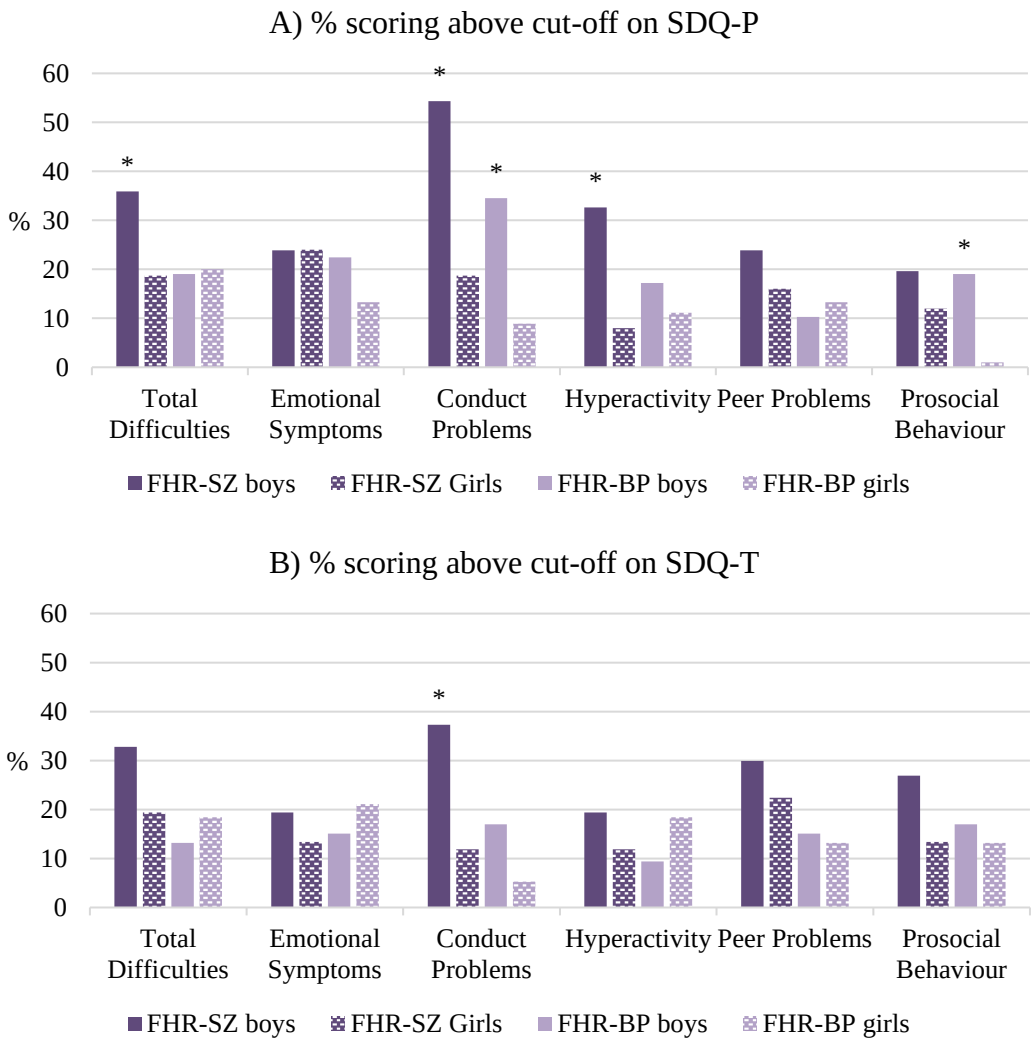
Primary caregiver ratings

Significantly more (p = .011) FHR-SZ boys (35.9%) than FHR-SZ girls (18.7%) scored above cut-off, corresponding to boys accounting for 70.2% of the FHR-SZ above cut-off group. There were no sex differences in the FHR-BP group (Figure 6.1A).

Teacher ratings

Proportion of boys and girls above cut-off differed non-significantly in both FHR groups (FHR-SZ boys=32.8%, FHR-SZ girls=19.4%, p = .077; FHR-BP boys=13.2, FHR-BP girls=18.4%, p = .497) (Figure 6.1B).

Figure 6.1. Proportion of girls and boys above cut-off for significant difficulties



FHR: Familial High-Risk; SZ: Schizophrenia; BP: Bipolar Disorder; SDQ: The Strengths and Difficulties Questionnaire; -P: Parent version filled by primary caregivers; -T: Teacher version
* Significant difference (p<.05) between sexes within FHR group.

Daily life functioning (CGAS) of children scored below and above SDQ Total Difficulties Scale cut-off score

CGAS mean scores were higher for the 'below SDQ-P cut-off groups' (N=347, mean (SD) = 75.8 (13.2)) compared to the 'above SDQ-P cut-off group' (N=82, mean (SD) = 55.9 (12.1)) with a statistically significant difference of 19.9 points, 95% CI [16.8, 23.0], t(427) = 12.446, *p*=.0001 (Table 6.4).
Results of the three individual groups as well as SDQ-T results were very similar to these results (Table 6.4).

Table 6.4. Children's Global Assessment Scale (GAS) mean scores of the SDQ Total Difficulties Scale below and above cut-off groups.

PRIMARY CAREGIVER RATINGS	Below Cut-off group		Above Cut-off group		Mean difference (95% CI)	*p*-value
	N	CGAS mean (SD)	N	CGAS mean (SD)		
Total cohort	347	75.8 (13.2)	82	55.9 (12.1)	19.9 (16.8-23.0)	<.0001
FHR-SZ	120	72.7 (13.5)	47	53.7 (11.7)	19.1 (14.7-23.5)	<.0001
FHR-BP	83	75.5 (13.2)	20	57.6 (12.1)	18.0 (11.6-24.4)	<.0001
Controls	144	78.6 (12.5)	15	60.9 (12.4)	17.7 (11.0-24.3)	<.0001

TEACHER RATINGS	Below Cut-off group		Above Cut-off group		Mean difference (95% CI)	*p*-value
	N	CGAS mean (SD)	N	CGAS mean (SD)		
Total cohort	303	75.3 (13.8)	59	55.6 (12.6)	19.7 (15.9-23.5)	<.0001
FHR-SZ	99	70.5 (15.6)	34	55.2 (12.1)	15.3 (9.5-21.1)	<.0001
FHR-BP	76	75.8 (12.5)	14	52.6 (12.7)	23.2 (15.9-30.5)	<.0001
Controls	128	78.6 (12.0)	11	60.6 (13.5)	18.0 (10.5-25.6)	<.0001

SDQ: The Strengths and Difficulties Questionnaire. CGAS: Children's Global Assessment Scale (Shaffer et al., 1983). FHR-BP: Familial high-risk bipolar group FHR-SZ: Familial high-risk schizophrenia group

The discriminatory ability of the SDQ compared to the CBCL and TRF

Primary caregiver ratings

The ability of the SDQ-P and the CBCL total scores to distinguish between children with and without any Axis I diagnosis was acceptable to excellent and non-different between measures. The ability of the SDQ-P hyperactivity scale to discriminate between children with and without a diagnosis of Attention-Deficit Hyperactivity Disorder (AUC = 92, CI .89 to .95) and the conduct scale in regards to Disruptive Behaviour Disorder (AUC = 93, CI .89 to .98), were both on an outstanding level and non-different from the discriminatory ability of the corresponding CBCL scales. Sensitivity of the SDQ-P and CBCL ranged from 34.2% for any Axis I in the FHR-BP group to 81.3% (SDQ) and 93.8% (CBCL) for any disruptive behaviour disorder, the latter demonstrating the highest discrepancy found between SDQ-P and CBCL. Specificity ranged from 82% to 90.7% (**Table 6.5** A).

Teacher ratings

The discriminatory abilities of SDQ-T and TRF resemble the results of the SDQ-P and CBCL except for the ability to identify the presence of disruptive behaviour disorder where the TRF (AUC = 92, CI .87 to . 97) is significantly better than the SDQ-T (AUC = .82, CI .70 to .94) (**Table 6.5** B).

Table 6.5 A. Ability of SDQ-P and CBCL to discriminate between cases with and without disorders within the FHR groups analysed by ROC curves.

Problem scale SDQ-P/CBCL	Outcome measure (N with/without)	Area under curve (AUC) (95% CI)		AUC SDQ-P vs CBCL	Sensitivity		Specificity	
		SDQ-P	CBCL	*p*-value [a]	SDQ-P	CBCL	SDQ-P	CBCL
Total scale	Any axis I [b] (101/165)	.79 (.73.-84)**	.78 (.72-.83)**	.752	48.5	41.6	89.7	88.5
	FHR-SZ (63/101)	.82 (.75-.89)**	.80 (.72-.87)	.454	57.1	46.0	90.1	88.1
	FHR-BP (38/64)	.75 (.65-.84)	.76 (.67-.86)	.611	34.2	34.2	89.1	90.6
Hyperactivity scale	Any attention-deficit hyperactivity disorder Total cohort (43/226)	.92 (.88-.95)**	.88 (.83-.94)**	.085	69.8	67.4	90.7	88.1
Conduct scale	Any disruptive behaviour disorders Total cohort (16/250)	.91 (.85-.97)**	.88 (.77-.99)**	.511	81.3	93.8	82.0	82.8

Table 6.5 B. Ability of SDQ-T and TRF to discriminate between cases with and without disorders within the FHR groups analysed by ROC curves.

Problem scale SDQ-T/TRF	Outcome measure (N with/without)	Area under curve (AUC) (95% CI)		AUC SDQ-T vs. TRF	Sensitivity		Specificity	
		SDQ-T	TRF	*p*-value [a]	SDQ-T	CBCL	SDQ-T	CBCL
Total scale	Any axis I [bc] (86/136)	.75 (.68-.82)**	.76 (.69-.82)**	.810	37.2	43.0	91.2	89.0
	FHR-SZ (55/77)	.77 (.69-.85)**	.78 (.70-.85)**	.789	43.6	43.6	88.3	87.0
	FHR-BP (31/59)	.72 (.60-.83)*	.71 (.59-.83)*	.764	32.3	41.9	93.2	91.5
Hyperactivity scale	Any attention-deficit hyperactivity disorder [c] Total cohort (36/186)	.85 (.78-.91)**	.86 (.80-.91)**	.685	47.2	47.2	91.4	92.5
Conduct scale	Any disruptive behaviour disorders [c] Total cohort (16/206)	.82 (.70-.94)**	.92 (.87-.97)**	.021	68.8	81.3	84.5	88.8

Only children with both an SDQ-P and an CBCL / SDQ-T and TRF, respectively were included in the analysis. Sensitivity and specificity at cut-off score closest to T-score of 65 according to the ROC curve analyses.

* *p* <.001. ** *p* <.0001. BP: Bipolar disorder; FHR: Familial high-risk; CBCL: Child Behavior Checklist; SDQ: The Strengths and Difficulties Questionnaire; -P: Parent Version; -T: Teacher Version; SZ: Schizophrenia; TRF: Teachers Report Form.

[a] *p*-value of z test for comparing paired area under ROC curves (AUC) of SDQ and CBCL.

[b] Any axis I excluding elimination disorders. [c] Four children who had an SDQ-T/TRF did not have a diagnostic assessment.

Correlation of primary caregiver and teacher rated SDQ scores

Interrater agreement between primary caregiver and teacher on the Total Difficulties Scale was good and regarding the individual SDQ difficulties scales ICC values were primarily in the fair to good range. CBCL and TRF interrater agreement were likewise in the fair to good range (**Table 6.6**).

Table 6.6. Inter-rater agreement

SDQ-P/SDQ-T	ICC (95%CI)			
	Total cohort	FHR-SZ	FHR-BP	Controls
N	347	129	85	133
Total Difficulties Scale	.68 (.60-.74)	.67 (.54-77)	.64 (.44-.77)	.60 (.44-.72)
Emotion scale	.46 (.33-.56)	.36 (.10-.54)	.57 (.34-.72)	.34 (.08-.53)
Conduct scale	.62 (.53-.69)	.64 (.49-.75)	.52 (.26-.69)	.50 (.39-.65)
Hyper scale	.71 (.64-.77)	.77 (.68-.84)	.58 (.36-.73)	.69 (.53-.77)
Peer scale	.56 (.45-.64)	.33 (.05-.53)	.72 (.57-.82)	.64 (.49-.74)
Prosocial scale	.31 (.14-.45)	.40 (.14-.59)	.19 (-.17-.45)	.17 (-.14-.40)
CBCL/TRF	ICC (95%CI)			
	Total cohort	FHR-SZ	FHR-BP	Controls
N	479	160	96	159
Total scale	.63 (.55-.69)	.64 (.51-.74)	.53 (.30-.69)	.58 (.43-.69)
Conduct scale	.68 (.62-.74)	.67 (.55-.76)	.70 (.55-.80)	.53 (.36-.66)
Hyper scale	.60 (.52-.68)	.64 (.51-.73)	.53 (.30-.69)	.58 (.42-.69)

ICC two-way random effects model absolute agreement type. SDQ: The Strengths and Difficulties Questionnaire (Goodman, 1997). The Child Behavior Checklist school-age version (CBCL) (Achenbach & Rescorla, 2001). The Teacher's Report Form (TRF) (Achenbach & Rescorla, 2001).

Results. Paper II Executive functions

Between-group differences of executive functions

Primary caregiver rated

Primary caregivers rated significantly poorer overall executive functions (Global Executive Composite (GEC) scores) of both the FHR-SZ group (mean diff. = 5.4, 95% CI 2.5 to 8.3) and the FHR-BP group (mean diff. = 3.5, 95% CI 0.2 to 6.9) compared with the control group and non-significant functioning between the two high-risk groups. The FHR-SZ group's mean scores were significantly higher than that of the control group on all individual clinical scales, except the Plan/Organize and Organization of Materials scales, whereas, the FHR-BP group scored significantly higher than the control group only on the Emotional Control scale (mean diff. = 4.4, 95% CI 1.1 to 7.7). The two high-risk groups did not differ on any of the clinical scale (Table 6.7).

Teacher rated:

Teachers rated the FHR-SZ group with significantly poorer overall executive functions (GEC score) compared with the control group (mean diff.= 7.1, 95% CI 4.1 to 10.0) whereas the FHR-BP group did not differ significantly from controls (mean diff. = 3.2, 95% CI -0.4 to 6.7). According to teacher ratings the two FHR-groups differed significantly from each other (mean dif. = 3.9, 95% CI 0.04 to 7.7) on overall executive functioning. The FHR-SZ group differed significantly from the control group on all clinical scales, whereas the FHR-BP did not differ significantly from the control group nor the FHR-SZ group on any clinical scale (Table 6.7).

Prevalence of clinical range scores

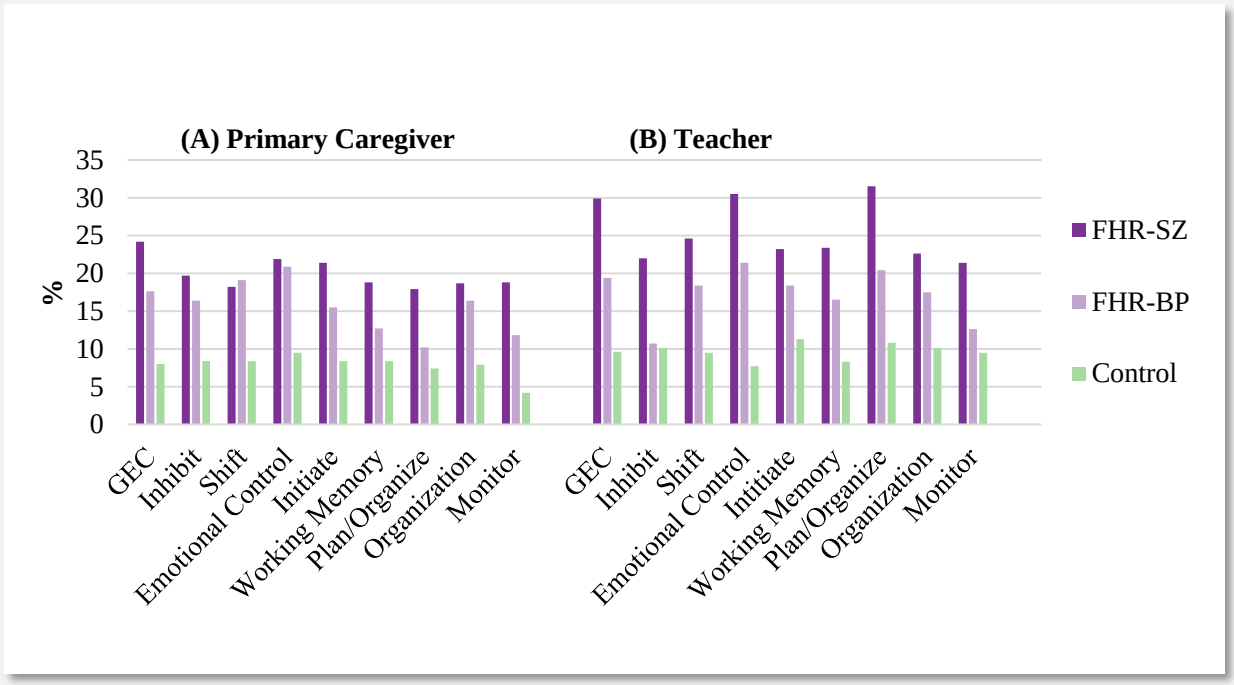
Primary caregiver rated

Significantly more children in both familial high-risk groups (FHR-SZ = 24.2%, FHR-BP = 17.6%) had a GEC score above cut-off compared to the control group (8.0 %) (Figure 6.2A), corresponding to an odds ratio of 3.7 (95% CI 2.0-6.9; p <.0001) for FHR-SZ children and 2.5 (95% CI 1.2-5.1; p = .0146) for FHR-BP children (Table 6.7B). The percentage of children above cut-off was significantly higher in the FHR-SZ group compared to the control group on all eight clinical scales (Table 6.7), but after Bonferroni corrections, the FHR-BP group did not differ significantly from the control group and the FHR-SZ group on any of the clinical scales (Table 6.7 and Figure 6.2).

Teacher rated

The prevalence of a GEC score above cut-off was significantly higher in both FHR-groups (FHR-SZ = 29.9%, FHR-BP = 19.4%) compared to the control group (9.6%) (Figure 6.2B), corresponding to an odds ratio of 4.0 (95% CI 2.2-7.4; p <.0001) for FHR-SZ children and 2.3 (95% CI 1.1-4.6; p = .0233) for FHR-BP children as rated by the teachers. The FHR-SZ group differed from controls on all clinical scales while the FHR-BP group only differed from the controls on the Emotional Control clinical scale with an odds ratio of a score above cut-off of 3.2 (95% CI 1.6-6.8; P= .0018) and the two FHR groups did not differ on any clinical scale (Table 6.7B).

Figure 6.2. Prevalence of children scoring above cut-off (1.5 SD above the mean of the control group) on the BRIEF for each of the three risk groups.



BRIEF: Behavior Rating Inventory of Executive Functions; FHR-BP: Familial High-Risk Bipolar disorder; FHR-SZ: Familial High-Risk schizophrenia; GEC: Global Executive Composite.

Executive functions profiles

The profile shapes of BRIEF clinical scales of the three groups did not differ as analysed by repeated measures ANOVA (F (11.181, 27000.171 Greenhouse-Geisser) = 1.293, p = .221) according to primary caregiver ratings, nor teacher ratings (F (7.482, 1612.326 Greenhouse-Geisser) = 1.548, p = .141.).

Sex differences in executive functions

Primary caregiver ratings revealed no sex differences of executive functions neither for the FHR-SZ group (F (8, 181) = 1.514, p = .155, Pillai's Trace = .063) nor the FHR-BP group (F (8, 99) =.420, p = .907, Pillai's Trace = .033) (Figure 6.3A). The same was true for *Teacher ratings*; FHR-SZ group (F (8, 155) =1.662, p =.112, Pillai's Trace = .079), FHR-BP group (F (8, 94) =.581, p =.792, Pillai's Trace = .047) (Figure 6.3B).

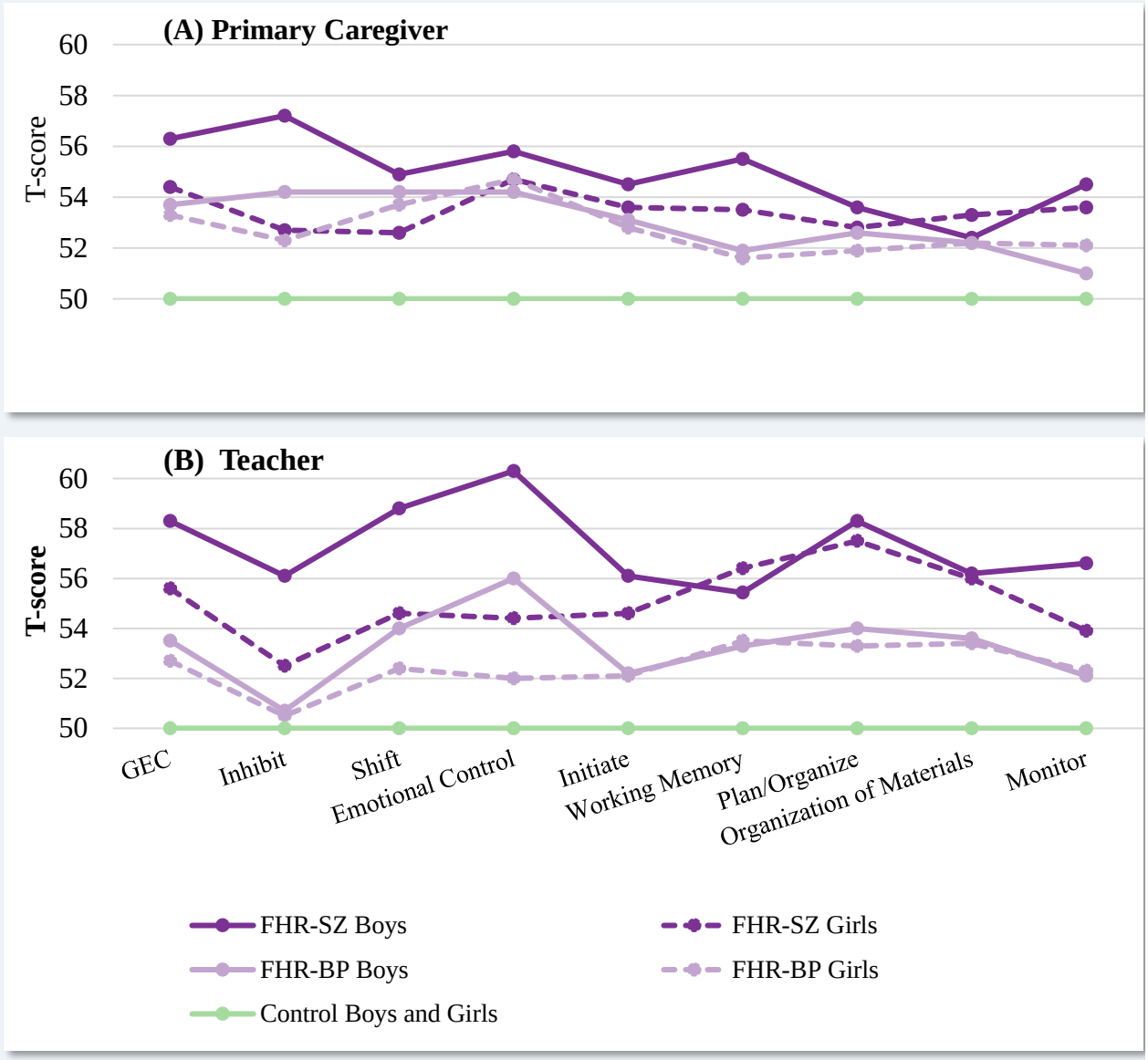
Table 6.7. The Behavior Rating Inventory of Executive Function (BRIEF) Caregiver- and Teacher reports of 515 seven-year-old children.

		Global Executive Composite (GEC)	Clinical scales							
			Inhibit	Shift	Emotional control	Initiate	Working Memory	Plan/ Organize	Organiza-tion of Materials	Monitor
(A) T-score means, standard deviations and statistical significance of the difference in T-scores between groups. T-scores are computed by sex and with the control group as reference group (T-score (SD) = 50 (10.0))										
Primary Caregiver Report										
FHR-SZ N=193	T-score	55.4 (13.7)	55.1 (14.2)	53.8 (12.9)	55.3 (13.1)	54.1 (12.5)	54.6 (12.6)	53.2 (12.5)	52.8 (11.5)	54.1 (12.9)
FHR-BP N=110	(SD)	53.5 (12.6)	53.4 (13.0)	54.0 (13.4)	54.4 (12.4)	53.0 (11.5)	51.8 (11.3)	52.2 (11.7)	52.2 (10.9)	51.5 (11.4)
FHR-SZ vs. Control[a]		<.001*	.001*	.004*	<.001*	.001*	<.001*	.017	.028	.002*
		(0.45)	(0.41)	(0.33)	(0.45)	(0.35)	(0.40)	(0.28)	(0.26)	(.35)
FHR-BP vs. Control[a]	*p*-value *	.036*	.053	.020	.005*	.068	.348	.221	.184	.499
	(Cohen d)	(0.32)	(0.30)	(0.35)	(0.41)	(0.28)	(0.17)	(0.21)	(0.22)	(0.14)
FHR-SZ vs. FHR-BP		.451	.524	.995	.831	.702	.121	.785	.896	.172
		(0.14)	(0.13)	(0.01)	(0.07)	(0.09)	(0.23)	(0.08)	(0.05)	(0.21)
Teacher Report										
FHR-SZ N=168	T-score	57.1 (12.6)	54.4 (12.0)	56.8 (13.9)	57.6 (15.0)	55.4 (11.2)	55.9 (11.9)	58.0 (13.7)	56.1 (14.5)	55.3 (11.5)
FHR-BP N=103	(SD)	53.2 (13.1)	50.6 (10.7)	53.3 (14.3)	54.2 (15.6)	52.1 (12.8)	52.8 (12.7)	53.7 (13.9)	53.5 (13.0)	52.2 (11.1)
FHR-SZ vs. Control[b]		<.001*	<.001*	<.001*	<.001*	<.001*	<.001*	<.001*	<.001*	<.001*
		(0.62)	(0.40)	(0.57)	(0.59)	(0.51)	(0.54)	(0.66)	(0.49)	(0.50)
FHR-BP vs. Control[b]	*p*-value *	.091	.882	.103	.039	.323	.139	.053	.054	.240
	(Cohen d)	(0.28)	(0.06)	(0.28)	(0.34)	(0.19)	(0.25)	(0.32)	(0.31)	(0.21)
FHR-SZ vs. FHR-BP		.047*	.019	.116	.197	.089	.118	.043	.270	.065
		(0.30)	(0.33)	(0.25)	(0.22)	(0.27)	(0.25)	(0.31)	(0.19)	(0.28)

(B) Odds ratio (OR) and statistical significance that an FHR child will be classified as 1.5 SD above the mean of the control group compared to an individual from the control group, and for FHR-SZ vs. FHR-BP										
Primary Caregiver Report										
FHR-SZ vs. Control	OR (CI)	3.7 (2.0-6.9)	2.7 (1.4-5.0)	2.4 (1.3-4.6)	2.7 (1.5-4.8)	3.0 (1.6-5.5)	2.5 (1.3-4.7)	2.7(1.4-5.2)	2.7 (1.4-5.1)	5.3 (2.4-11.6)
	p-value	<.0001*	.0020*	.0058*	.0012*	.0005*	.0038*	.0030*	.0026*	<.0001*
FHR-BP vs. Control	OR (CI)	2.5 (1.2-5.1)	2.1 (1.0-4.4)	2.6 (1.3-5.2)	2.5 (1.3-4.9)	2.0 (1.0-4.1)	1.6 (.74-3.4)	1.4 (.6-3.2)	2.3 (1.1-4.7)	3.0 (1.2-7.6)
	p-value	.0146*	.0396	.0082	.0065	.0642	.2339	.4165	.0267	.0168
FHR-SZ vs. FHR-BP	OR (CI)	1.5 (0.8-2.7)	1.3 (0.7-2.3)	0.9 (0.5-1.7)	1.1 (.6-1.9)	1.5 (0.8-2.8)	1.6 (0.8-3.1)	1.9 (0.9-4.0)	1.2 (0.6-2.2)	1.7 (0.9-3.4)
	p-value	.185	.473	.853	.844	.212	.172	.078	.617	.119
Teacher Report										
FHR-SZ vs. Control	OR (CI)	4.0 (2.2-7.4)	2.5 (1.4-4.7)	3.1 (1.7-5.8)	5.2 (2.7-10.1)	2.4 (1.3-4.3)	3.4 (1.7-6.5)	3.8 (2.1-6.9)	2.6 (1.4-4.8)	2.6 (1.4-4.9)
	p-value	<.0001*	.0036*	.0004*	<.0001*	.0046*	.0003*	<.0001*	.0025*	.0032*
FHR-BP vs. Control	OR (CI)	2.3 (1.1-4.6)	1.1 (.5-2.4)	2.1 (1.1-4.4)	3.2 (1.6-6.8)	1.8 (.9-3.5)	2.2 (1.0-4.6)	2.1 (1.1-4.2)	1.9(.9-3.8)	1.4(.6-3.0)
	p-value	.0233*	.8830	.0364	.0018*	.1034	.0437	.0315	.0829	.4247
FHR-SZ vs. FHR-BP	OR (CI)	1.8 (1.0-3.2)	2.4 (1.1-4.9)	1.4 (0.8-2.6)	1.6 (0.9-2.9)	1.3 (0.7-2.5)	1.5 (0.8-2.9)	1.8 (1.0-3.2)	1.4 (0.7-2.6)	1.9 (0.9-3.8)
	p-value	.059	.020	.243	.101	.354	.180	.048	.311	.070

(A) GEC analysed with Welch's ANOVA and post hoc Games-Howell. Clinical scales analysed by MANOVA and post hoc Games-Howell.
(B) Odds ratios analysed by logistic regression.
FHR-BP: familial high-risk of bipolar disorder; FHR-SZ: familial high-risk of schizophrenia spectrum disorder.
[a] Controls N=190. [b] Controls N= 168.
* Significant *p*-value. Fore GEC an alfa level below .05 is considered significant. For clinical scale scores an alfa level below .00625 are considered significant after Bonferroni adjustment for multiple comparisons.
7 primary caregiver and 5 teacher BRIEF reports had missing items that prohibited calculation of 1 or more scales.

Figure 6.3. BRIEF T-scores of female and male participating children as rated by their primary caregiver (A) and teacher (B)



BRIEF: Behavior Rating Inventory of Executive Functions; FHR-BP: Familial High-Risk Bipolar disorder; FHR-SZ: Familial High-Risk schizophrenia; GEC: Global Executive Composite.
Control group standardized as reference group with T-score mean=50 and SD=10 on boys and girls separately.

Results. Paper III – Emotion regulation

We found no significant differences in emotion regulation between the three groups as measured by EmReg, (F (2,462) = 1.155, *p* = .316) (Table 6.8).

Table 6.8. Emotion Regulation (EmReg) as measured with the Tangram Emotion Coding Manual (TEC-M)

	Study Group			*p*-value	*p*-value Pairwise comparison		
	FHR-SZ	FHR-BP	Controls		FHR-SZ vs. Controls	FHR-BP vs. Controls	FHR-BP vs. FHR-SZ
Children, N	179	103	183				
EmReg, mean [95% CI]	3.21 [3.06-3.36]	3.39 [3.21-3.56]	3.25 [3.11-3.40]	.316 [A]	-	-	-

EmReg: Emotion Regulation ability, higher scores represent better emotion regulation; FHR: Familial High-Risk; SZ: Schizophrenia spectrum disorder; BP: Bipolar disorder. [A] ANOVA.

Correlation analyses on the total cohort revealed a statistically significant, weak and inverse correlation between the EmReg score and ADHD-RS-comp; (r_s(460) = -.170, *p* = < .001) and CBCL-Total; (r_s (445) = -.132, *p* = .005). Correlation between EmReg and the broader CBCL-DP210 dysregulation profile were significant, weak and negative; *r*(444) = -.177, *p* = <.001. The stringent CBCL-DP70 dysregulation profile was non-significantly correlated with the EmReg score (Table 6.9). Daily life functioning (CGAS) was significantly, weak and positively correlated with EmReg (r_s (462) = .150, *p* = .001) (Table 6.9). All within-group associations were likewise weak. Associations between EmReg and ADHD-RS were only significant in the FHR-SZ group (r_s (177) = -.273, *p* = < .001). CBCL-DP210 was significantly associated with EmReg in both the FHR-SZ and the control group, and in the control group associations between EmReg and the CBCL-Total and the CGAS were likewise significant. The only significant association in the FHR-BP group was between EmReg and CGAS (Table 6.9).

Table 6.9. Correlation between emotion regulation (EmReg) and measures of psychopathology, symptom severity and daily life functioning.

	Total Cohort		FHR-SZ		FHR-BP		Controls	
	Correlation coefficient (df)	*p*	Correlation coefficient (df)	*p*	Correlation coefficient (df)	*p*	Correlation coefficient (df)	*P*
ADHD-RS-comp	-.170 (460) [S]	<.001	-.273 (177) [S]	<.001	-.107 (100) [S]	.284	-.130 (179) [S]	.082
CBCL-Total	-.132 (445) [S]	.005	-.111 (171) [S]	.147	-.177 (95) [S]	.082	-.173 (175) [S]	.021
CBCL-DP210	-.177 (444) [P]	<.001	-.199 (171) [P]	.009	-.194 (94) [P]	.058	-.156 (175) [P]	.039
CBCL-DP70	-.087 (444) [P]	.065	-.140 (171) [P]	.068	-	-	-	-
CGAS	.150 (462) [S]	.001	.137 ((177) [S]	.068	.201 (101) [S]	.042	.173 (180) [S]	.020

ADHD-RS-Comp: The modified version of the ADHD-Rating Scale parent-teacher composite score.
EmReg: Overall Emotion Regulation Scale. Higher scores equal better emotion regulation.
CBCL: Child Behavior Checklist. Higher scores equal more symptomatology.
CBCL-DP: Child Behavior Checklist Dysregulation Profile. DP70 and DP210 are dichotomous outcome measure of whether the child fulfils criteria for the profile. CBCL-DP70: t-score above 70 on the three CBCL-DP subscales; CBCL-DP210: t-score above 210 on the combined CBCL-DP subscales.
CGAS: Children's Global Assessment Scale. Higher scores equal better performance.
[S] Spearman's rank-order correlation.
[P] Pearson correlation.

Supplementary results

Table 6.10. BRIEF Primary caregiver and Teacher inter-rater agreement

	ICC (95%CI)			
	Total cohort	FHR-SZ	FHR-BP	Controls
N	406	154	94	158
GEF	.62 (.54-.69)	.63 (.50-.74)	.58 (.36-.72)	.52 (.35-.65)
Inhibit	.52 (.54-.69)	.64 (.51-.74)	.56 (.34-.71)	.58 (.43-.69)
Shift	.55 (.45-.63)	.60 (.45-.71)	.54 (.32-.70)	.37 (.14-.54)
Emotional control	.50 (.39-.59)	.50 (.31-.63)	.45 (.17-.63)	.39 (.16-.55)
Initiate	.53 (.43-.61)	.54 (.37-.66)	.53 (.30-.69)	.42 (.21-.58)
Working Memory	.66 (.59-.72)	.63 (.49-.73)	.65 (. 47-.77)	.66 (.53-.75)
Plan/Organize	.53 (.43-.62)	.58 (.43-.70)	.47 (.21-.65)	.41 (.19-.57)
Organization of Materials	.31 (.17-.43)	.38 (.16-.55)	.16 (-.26-.44)	.17 (-.14-.39)
Monitor	.53 (.42-.61)	.50 (.32-.64)	.55 (.32-.70)	.47 (.28-.61)

ICC two-way random effects model absolute agreement type.
GEF: Global Executive Functions Scale.

Chapter 7. Results from relevant or related papers and dissertations

Chapter 7 provide short summaries and results of two papers related to the results of Paper III as well as a short overview of two other PhD theses from the VIA 7 Study, all relevant for framing the discussion of the present thesis.

Results of papers related to Paper III

The Puzzle of Emotion Regulation – Development and evaluation of the Tangram Emotion Coding Manual for Children **(Hagstrøm et al., 2019)**

The aim of this study was to describe the development of the Tangram Emotion Coding manual and to examine its psychometric properties, comprising inter- and intra-rater reliability, convergent validity, discriminant validity, content validity, and the instrument's ability to delineate a group of children aged 7-12 years with ADHD (N=23) from a group of typically developing controls (n=62). We found high levels of inter- and intra-rater reliability. Evidence for convergent and discriminant validity were mixed as was expected due to the novelty and experimental nature of the measure, making it difficult to compare with questionnaire-based measures. Content validity analysis was satisfactory, and the primary outcome measure differentiated the groups well. The conclusion wat that, overall the instrument demonstrated high feasibility and satisfactory psychometric properties. The generic nature of the test makes it suitable for use across psychiatric disorders and age groups with potential relevance in both research and clinical settings.

Emotion Regulation in Children with Tourette Syndrome – Associations with ADHD and Tic severity by Julie Hagstrøm, Katrine S. Spang, Signe Vangkilde, Katrine Maigaard, Liselotte Skov, Anne Katrine Pagsberg, Jens Richardt Møllegaard Jepsen, Kerstin Jessica Plessen **(in review)**

The aim of this study was to investigate emotion regulation in medication-naïve children aged 7-12 years, with either Tourette's syndrome (N=49), ADHD (N=23), or Tourette's syndrome combined with ADHD (N=16) and typically developing control children (N=62). Emotion regulation and parent and child behaviours were assessed with the Tangram Emotion Coding Manual. Group differences in emotion regulation, as well as potential associations between emotion regulation and symptoms pertaining to Tourette's syndrome and ADHD were examined. Children with ADHD and children with Tourette's syndrome combined with ADHD had significantly poorer emotion regulation than children with Tourette's syndrome only and control children. Emotion regulation correlated inversely with ADHD symptom severity (inattention and hyperactivity/impulsivity).

Presentation of previous studies of The Danish High Risk and Resilience study

The Danish High Risk and Resilience study has to date formed the basis for 6 PhD theses and xx published papers other than the present theses and papers printed within. To put the findings of this thesis in context selected results relevant for these theses will briefly be addressed here.

"Neurocognitive Function in 7-year-old Children at Familial High Risk of Schizophrenia or Bipolar Disorder – The Danish high Risk and Resilience Study VIA 7" Ph.D. thesis written by Nicoline Hemager (2018) *(Hemager, 2018)*

This thesis investigated cognitive abilities of the participating children by means of a comprehensive cognitive test battery of validated tests of intelligence, processing speed, memory, attention, executive functions, and decision making. Intelligence was assessed by the Reynold's Intellectual Screening test (RIST) (C. Reynolds & Kamphaus, 2003). The RIST Index was used as an IQ estimate. The control group of The VIA 7 Study was utilized as reference group to construct RIST Index reference norms. The FHR-SZ group had a significantly lower RIST Index compared to control children, whereas the FHR-BP performed equal to the control group. Widespread cognitive impairments were found in the FHR-SZ group. No cognitive impairments were found in the FHR-BP group compared to the control group. Impairments in aspects of decision making was not found in neither familial high-risk group, but suboptimal decision making, however, was associated with poorer verbal working memory, spatial recognition and more affective problems in both familial high-risk groups.

"Psychopathology, psychotic-like experiences, quality of life and self-perception in seven-year-old children with familial high risk of schizophrenia or bipolar disorder: The Danish High Risk and Resilience Study – VIA 7; a population-based cohort study" Ph.D. thesis written by Ditte Ellersgaard (2018) *(Ellersgaard, 2018)*

This thesis investigated psychopathology by means of both diagnostic interviews of both the child and the child's primary caregiver as well as validated questionnaires of psychopathology. Lifetime DSM-IV disorders was found more frequently in the FHR-SZ group (38.7%) and FHR-BP group (35.6%) compared with the control group (15.2%). Dimensionally assessed psychopathology was likewise found with higher levels in the FHR-SZ group compared with the control group and FHR-BP children ranging intermediate. Regarding level of daily life functioning, again a gradient was found, with the FHR-SZ group rated most poorly followed by the FHR-BP group compared to the control group. Further both FHR-groups reported more psychotic like experiences, more bullying victimization compared to controls. Only the FHR-SZ children reported lower quality of life as well as lower self-perception compared to the control group.

Chapter 8. Discussion

The purpose of this work was to investigate behaviour-based executive functions, emotion regulation, and dimensionally measured psychopathology in children of parents diagnosed with schizophrenia spectrum psychosis or bipolar disorder compared with matched register-based controls. We applied a multi-informant approach using both primary caregiver and teacher assessments. We assessed psychopathology dimensionally with the 'Strengths and Difficulties Questionnaire'; SDQ, and executive functions with the 'Behavior Rating Inventory of Executive Functions'; BRIEF, questionnaire. We assessed emotion regulation with a direct researcher rated, standardized observational measure, the Tangram Emotion Coding Manual; TEC-M, as well as emotion regulation related subscales of BRIEF and SDQ. Additionally, we aimed to assess if the SDQ, as a short dimensional assessment measure of psychopathology, could function as a screening instrument of clinically relevant behavioural problems in children with familial high-risk for schizophrenia or bipolar disorder.

In this chapter, I first briefly present the main findings and then discuss the methodology of the study to provide a frame for the successive discussion of the results. Strengths and limitations of the overall study are discussed in the 'methodological considerations' section, and strengths and limitations related to specific themes are discussed in the according sections.

Summary of main findings

We found a significantly higher occurrence of behavioural difficulties and more frequently at a level indicative of mental illness and significant global behaviour-based executive function difficulties in children with a familial predisposition for schizophrenia and children with a familial predisposition for bipolar disorder compared with matched register-based control children. This, according to both primary caregiver and teacher assessments, though teacher ratings were more ambiguous regarding children with a familial high-risk of bipolar disorder.

According to daily life behavioural assessments, both high-risk groups displayed emotional regulation related difficulties. However, we did not find emotion regulation difficulties according to an applied clinician-rated observational test-measure of emotion regulation, the TEC-M. Again, teacher-rated behavioural assessments were less clear regarding children with familial high-risk of bipolar disorder.

The investigated short dimensional measure of psychopathology, the SDQ, displayed sound discriminatory abilities.

Methodological considerations

Representativity

Representativity analyses of the VIA 7 Study cohort are currently ensuing, and we do not yet have all the results. Thus, until we know for sure, several actualities concerning representativity of the study cohort must be recognized.

Firstly, regarding the register extract: The central registries do not include individual diagnosed and treated by general practitioners and private practising specialists in psychiatry, and thus, this group is not represented in this familial high-risk study. We theorize that individuals with schizophrenia or bipolar disorder who have not been in contact with secondary sector services most likely represent a milder affected and better performing group, but also a small group. So, if they were included, this would not significantly alter the results of the study. Supportive of this notion is that the Danish National Registers are documented to be almost complete for the registration of severe mental illness (Mors et al., 2011). This, probably due to the non-existence of private psychiatric hospitals in Denmark and the fact that general practitioners and private practising specialists in psychiatry mainly treat mild to moderate mental illnesses (Mors et al., 2011) as well as patients who are discharged from hospital treatment and are in the stabilizing or remission phases.

Secondly, regarding the recruitment procedure: We recruited more families from the area of greater Copenhagen. Due to the matching procedure, this should not affect the results regarding differences between risk groups, but it could affect the generalizability of the study as the cohort might not be entirely representable of the full national population. This is indicated by one of the results, that we do already have regarding urbanization, where we find that the cohort includes significantly more children from densely populated areas (46.6%) than non-participating children (29.3%) of the register extract. However, as expected, the difference in population density living was equal across all three included risk groups.

Thirdly, regarding the families who declined participation. We speculate that the very ill and poor performing families and likewise families where the index parent only had few or miner episodes, and potentially decades before we contacted them, might be more inclined to decline participation. However, we know from the families that did participate, which includes both very severely ill and as described those with passing illness years before, that they shared motivations for participation. These motivations included, amongst others, concern for their children's wellbeing and desire to contribute to research that might help others. Also, we encountered that some had not told their families, not even their spouse of their illness, and this included both formerly and presently ill individuals. Further, the cohort does include children who are in out of home care because of the parent's illness as well as children of admitted parents. In all, this indicates that we succeeded in including a broad, potentially representative, spectrum of affected families.

Lastly, strengthening the representativity is the method of matching of the families: We did not match families on socioeconomic variables, only municipality. This was a deliberate choice as low socioeconomic

status is often directly related to more illness (Agerbo, Byrne, Eaton, & Mortensen, 2004; Hakulinen et al., 2019) and by matching for socioeconomic status, we would risk that the control group would be less representative of the background population.
reflect

Analytic strategy

Because of the low number of double high-risk children i.e. children where both parents are diagnosed with either schizophrenia or bipolar disorder, these children were analysed together with the single high-risk children. We theorize that double high-risk children could perform more poorly than single high-risk children due to both their double genetic risk status and environmental effects (Gottesman et al., 2010) , but because of the low number of double high-risk children, we do not suspect that this has affected the results of the study. However, we cannot rule out the possibility as the analysis has not been performed without inclusion of these children.
We made a decision not to adjust for socio-economic status (e.g. level of education, income, employment status, living conditions) as socio-economic status is in many cases closely linked to severe mental disorders. Adjusting for these factors we would risk over-adjustment and likely blur true results and thus introduce the risk of failing to identify key components of being a high-risk family. A further aspect of adjustment is multiple comparisons. In all analysis we considered thoroughly how, when, and how much we should adjust for multiple comparisons in order not to commit a type I error of acknowledging a finding as true when it was not or a type II error of ruling out a true finding by over-adjusting for multiple comparisons.

Validity of parent and teacher reports

It is generally acknowledged that primary caregiver ratings can be affected by the presence of mental illness in the caregiver, him or herself and that agreement between parent and teacher reports regarding child psychopathology symptoms is generally low (Achenbach, McConaughy, & Howell, 1987; Cheng et al., 2018; De Los Reyes et al., 2015; Madsen, Rask, Olsen, Niclasen, & Obel, 2020). Studies of rater bias mainly focus on parental depression and child psychopathology and show mixed results. One study (Maoz et al., 2014) found that the mood state of parents with bipolar disorder, especially if manic, significantly affected questionnaire reports regarding their offspring's psychopathology. The study showed that parents with a current mood episode rated higher levels of psychopathology (currently depressed rated more externalizing and currently manic or hypomanic rated more externalizing and internalizing) in their children and this was not reflected in teacher or self-reports. However, a higher rate of depressive disorders was found in children of parents with a current mania or hypomania episode compared to offspring of parents in remission implying that the parents reported valid information that teacher reports did not reflect. At the same time, studies report that teachers are generally good at recognizing the existence and severity of problem behaviours related to mental health, but are often less accurate than caregivers in relation to detecting and reporting internalizing (emotional) problems (Loades & Mastroyannopoulou, 2010; Vaz et al.,

2016). Collectively investigations of bias and validity of parental and teachers differentiate in their results and interpretations, but there is an overall agreement that both types of reports contribute with valuable information regarding the child's mental health. This by presenting unique information resulting from different settings (Cheng et al., 2018).

The severity of illness as well as current illness status amongst the participating index parents in the VIA 7 Study varied greatly, however the primary caregivers who were also index parents were most often partly or completely in remission or euthymic and only relatively few were severely ill (NB. This is the immediate impression of the research team. We have collected data to investigate this claim, but this has not yet been processed) and we thus do not expect severe bias on account of current primary caregiver illness. Further, in 43.3 percent of the families the index parent was not the primary caregiver. Supporting that illness of the index did not severely affect their ratings is that the SDQ results of our study are in accordance with other studies, with primary caregivers generally rating problems more severely than teachers, but also with teachers being more prone to rate externalizing problems, like hyperactivity and problems with social interaction with peers, than primary caregivers are (Vaz et al., 2016). Also, interrater agreement of the primary caregiver and the teacher-rated SDQ fell in line with (or were better than) results of other studies which in general have found reliable agreement on all difficulties scales and best agreement on the total scale and the hyperactivity scale (R. Goodman, 1997; Mieloo et al., 2012; Stone et al., 2010). Likewise, primary caregiver and teacher ratings of the BRIEF had primarily fair to good interrater agreement. Collectively this implies that parent and teacher reports of this study are reliable and represent important information regarding the children.

Multi-method and multi-informant assessments

Utilizing and incorporating information results from both primary caregivers and teacher ratings allows us to investigate whether the same patterns emerge in children with familial high-risk of schizophrenia as for children with familial high-risk of bipolar disorder, compared with population-based controls. And this in two different environments that pose different requirements and from informants with different perspectives and relations to the child. We found that teacher ratings both supported and complemented the primary caregiver ratings. Regarding behaviours potentially related to mental illness, on the SDQ teachers generally rated less difficulties than primary caregivers except regarding behaviours related to hyperactivity and peer problems. Likewise, regarding the BRIEF ratings, teachers tended to rate more difficulties on the two scales Plan/Organize, and Organizations of Materials than primary caregivers which may indicate higher demands on these aspects of executive functions in a school setting.

The multiple-informant assessment contributed with valuable information that would not have been recognized if only a single informant was used. Further, as will be discussed we found group differences in executive function as assessed with behaviour-based assessments which were not found with lab-based measures. Likewise, we found differentiating results of emotion regulation depending on the assessment method applied. This highlights the clinical utility of behaviour-based measures as demands can vary across

settings and the necessity of assessing functioning and behaviour in diverse environments to obtain an ample evaluation as well as the advantage of applying multi-method assessments.

Constructing reference scores from the control group

For both the SDQ and the BRIEF we utilized our control group as reference group for calculating both Z-scores and cut off-scores. With the reservations of representativeness of the control group in mind this has the advantage of not only the control group being matched to the familial high-risk children, thus ensuring resemblance on age and municipality, but also being population/register based. In many cases, the construction of the control group from registers, renders our reference group larger and more representative than that of the reference groups used in original manuals e.g. the BRIEF. This, due to the elution of problems of referral bias, as well as the considerable sample size and very narrow age interval of the control children.

A cross-sectional study

Even though the Danish High Risk and Resilience study is a prospective cohort study, the present study represent results from cross-sectional data. It is important to recognize that the presented results are from an early time point in the children's lives where neither of the children have yet developed a severe mental illness. However, some children do already have other psychiatric disorders and many familial high-risk children have lower levels of daily life functioning than control children (Ellersgaard et al., 2018) as well as affected neurocognition (Hemager et al., 2018). When considering the presented results, it is crucial to remember that they are from a cross-sectional study and thus represent a snapshot of the current status at age seven. We do not know if the identified differences or lack of differences are transitory, will persevere or increase and we can likewise not conclude on the predictive value of the results. However regarding psychopathology, previous studies indicate a predictive value of SDQ scores at age 5-7 and the presence of mental illness at age 11-12 (Nielsen et al., 2019; Rimvall et al., 2014) and likewise emotion regulation and executive functions ability at a young age has been implied to correlate with later life functioning and outcome (Graziano, Reavis, Keane, & Calkins, 2007; Moffitt et al., 2011; Mulder, Hoofs, Verhagen, van der Veen, & Leseman, 2014).

Dimensionally assessed psychopathology

We assessed child psychopathology dimensionally with the Strengths and Difficulties Questionnaire, SDQ, and found that a substantially larger proportion of seven-year-old children with a familial high-risk of schizophrenia or bipolar disorder had significant everyday life emotional and behavioural difficulties compared to matched control children. This, as evaluated both by primary caregivers and schoolteachers. Children with familial high-risk of schizophrenia, particularly boys of this group, were at especially high risk of having difficulties at a level indicative of emerging or existing mental illness. Further, children who were found above cut-off for significant difficulties had a markedly lower level of daily life functioning, as measured with the Children's Global Assessment Scale, compared to children below cut-off for significant

difficulties. These results are in line with previous findings from the same cohort, which by using CBCL data, found significantly more dimensionally assessed psychopathology in both groups, and children from the familial high-risk schizophrenia group being generally more affected than the children from the bipolar disorder group. Conversely, categorically assessed psychopathology revealed equally high occurrence of mental disorder in the two high risk groups, though with diverse disorders between groups (Ellersgaard et al., 2018). This could suggest that behavioural assessments are not as sensitive in detecting disorder in children with familial high-risk for bipolar disorder compared to children with familial high-risk for schizophrenia. An indication of this could be found in the screening abilities of the both the SDQ and the CBCL, where sensitivity characteristics are notably poorer for children at familial high-risk of bipolar disorder as opposed to schizophrenia. The study however did not compare the discriminatory abilities between high risk groups, but this could be a future goal.

Cut-off scores constructed from our control group tend to be lower for boys than previous findings both in Danish and in other Scandinavian settings with caregiver ratings showing the most considerable discrepancy. For girls however, they are in line with previous investigations of the general Danish population (Arnfred et al., 2019; Niclasen, 2013) and other Scandinavian countries (Niclasen, 2013) as well as in line with cut-off scores determined from ROC analysis and 90th percentiles in a Swedish sample (Malmberg, Rydell, & Smedje, 2003). Also, a significantly larger proportion of FHR-SZ boys are above cut-off, but only according to caregiver ratings. However, we find that an equal proportion of boys and girls score above cut-off in the FHR-BP group both according to caregiver ratings and teacher ratings. If boys from the control group should somehow be "better" functioning than average, we would have expected that a substantially larger proportion of boys than girls in both of the two FHR groups would score above cut-off for significant difficulties and this by both teachers and caregivers, which is not the case. Further strengthening the validity of our results is, that the above cut-off group has a markedly lower level of daily life functioning than the below cut-off group with a discrepancy of approximately 20 points. Even if one standard deviation is added in the two familial high-risk groups, they do not achieve normal range which is considered to be above 70 (Shaffer et al., 1983). It is important to note that this study was based on a subpopulation of the VIA 7 study cohort as the SDQ questionnaire was introduced a while into the inclusion process. However, we know that more children from area of greater Copenhagen were included in the beginning of the study, rendering the full study cohort unrepresentative of the full national cohort. Due to the late introduction of the SDQ it is these families who are not included, and it could be speculated that the SDQ sub-cohort could potentially be more representative demographically.

Screening for mental illness

We assessed the abilities of the Strengths and Difficulties Questionnaire (SDQ) to differentiate between familial high-risk children with and without a psychiatric diagnosis and found that the discriminatory abilities of the SDQ were good, with high area under the curve (AUC) values and moderate to high sensitivity and high specificity values determined from Receiver Operating Characteristic (ROC) curves.

Moreover, the SDQ was compellingly equating to the well-recognized and validated, but more time-consuming Child Behavior Checklist (CBCL) and the corresponding Teachers Report Form (TRF). These results and the noticeable equality between discriminatory abilities of the SDQ and the CBCL resemble previous findings (Goodman & Scott, 1999; Hysing, Elgen, Gillberg, Lie, & Lundervold, 2007; Klasen et al., 2000; Malmberg et al., 2003; Nielsen et al., 2019) supporting the reliability of the present findings.
We performed this analysis to investigate if reportings from caregivers and teachers on a short behavioural assessment measure could adequately identify children with mental illness and thus possibly be used for timely screening of at-risk children. The results strongly indicate that the SDQ can be used in a high-risk population like this. However, results regarding the SDQ and the comparisons to the abilities of the CBCL and TRF, are necessarily preliminary as the study is limited to a very narrow age group. Supportive of the utility of the SDQ is that several previous studies with other study groups and age ranges have arrived at similar conclusions (Goodman & Scott, 1999; Klasen et al., 2000; Koskelainen, Sourander, & Kaljonen, 2000; Malmberg et al., 2003; Nielsen et al., 2019; Sveen et al., 2013; Ullebø et al., 2011). In this study we focused on the ability of the SDQ to adequately recognize the presence of mental illness. However, the aspiration is to identify children in the premorbid phase before mental illness occurs. Thus, it could be considered to use less stringent cut-off scores thus slacking on specificity in order to 'catch' more children with behavioural difficulties and investigate if they could benefit from early intervention. On the other hand, we did not seek to identify the two disorders of focus, namely schizophrenia and bipolar disorder, and several studies have shown that other mental disorders often precede severe mental disorders as part of the developmental trajectory of the disorders (Duffy et al., 2018; Rapoport et al., 2012). In this study we constructed cut-off points from our study cohort's control group. Another approach could be to construct cut-off points by means of ROC curve analysis and thus base cut-off values on the instrument's ability to correctly identify specific disorders and in specific risk groups, e.g. children at familial high-risk of severe mental illness. This would allow more accurate cut-off scores for particular children and hereof higher diagnostic potential, and also allow a choice of sensitivity over specificity and vice versa according to the specific aim of the screening (Silva, Osório, & Loureiro, 2015).

Executive functions

We assessed executive functions with the Behavior Rating Inventory of Executive Functions (BRIEF) rated by both primary caregivers and teachers. Already at age seven, children with a parental history of schizophrenia or bipolar disorder displayed significant impairments of executive functions in everyday life situations. Children with familial high-risk of schizophrenia displayed widespread impairments whereas children with familial high-risk of bipolar disorder were especially impaired on the emotional control scale. This is in line with previous studies that report behaviour-based (Li et al., 2014) and performance-based (Bora, 2017; Hemager et al., 2018) executive functions in children with familial high-risk of schizophrenia. However, a previous study of performance-based assessments of executive functions on the same cohort of children as in the present study, found the group of children with familial high-risk of bipolar disorder non-

different from control children (Hemager et al., 2018). This suggests that parental behaviour ratings are a more sensitive measure of executive functions impairments (not including executive functions related to emotional or motivational processes as this was not included in the performance-based assessment) in a familial high-risk bipolar population of this young age (Cohens D effect sizes below 0.15 for performance-based assessments vs. 0.14-0.35 for behaviour-based assessment by primary caregiver rated BRIEF), whereas subtle executive functions deficits may not be detected in a highly structured neuropsychological test setting. Our findings could also indicate that behaviour- and performance-based measures assess different aspects of executive functions. This is in line with a previous finding of few or no significant associations between performance-based measures and the BRIEF, in a population of children with acquired or developmental neurological disorders as well as controls (G. A. Gioia, Isquith, Kenworthy, & Barton, 2002). Furthermore, evidence from the present study on familial high-risk bipolar children and from previous studies of individuals with bipolar disorder and their relatives (K. W. Miskowiak et al., 2017), indicate that executive functions impairments most severely pertain to aspects of executive functions related to emotional and motivational processing which are often not included in performance-based assessments of executive functions. The executive functions performance tasks of the previously published VIA 7 study also did not include such measures (Hemager et al., 2018).

Studies of cognitive functioning in offspring of parents with bipolar disorder before 10 years of age are limited (Bora & Özerdem, 2017; Burton et al., 2018; Hemager et al., 2018; Klimes-Dougan, Jeong, Kennedy, & Allen, 2017), and to our knowledge no studies of behaviour-based executive function assessments exist involving 7-year-old children of parents with bipolar disorder. Thus, these results are novel and should be sought replicated. Further this is the result of cross-sectional data and as executive functions mature rapidly throughout childhood with large inter-individual differences (Brocki & Bohlin, 2004; Brydges, Fox, Reid, & Anderson, 2014; Friedman et al., 2008), and potentially augmented in familial high-risk children, the results should be interpreted with caution. However, the narrow age group should be upheld as a wide age range will further obscure acknowledgement of group differences and in longitudinal studies obscure differential developmental trajectories.

Emotion regulation

We did not find a difference across groups on our primary measure of emotion regulation, EmReg, derived from the Tangram Emotion Coding Manual. This is in contrast to the emotion regulation related scales of the two applied daily life behavioural assessments BRIEF and SDQ, where both high-risk groups displayed emotion regulation related difficulties compared to the control group.

Though we strived to make a naturalistic set up of the child caregiver interaction, TEC-M is a lab-based assessment and it has repeatedly been shown for other types of lab-based assessments, e.g. cognitive, including executive functions assessment, that they only correlate poorly to every-day-life behaviour-based assessments (Toplak et al., 2013). It is argued that emotion regulation like other types of regulation require internal resource capacity and that this capacity differs between individuals (Urry & Gross, 2010).

Potentially the Tangram construction Task was not demanding or lengthy enough to elucidate emotion regulation difficulties in these high-risk groups at this age. Added, it is important to consider that emotion regulation is at this age still under development and that the children are at an age where caregivers still provide some level of external regulation (Plessen & Kabicheva, 2010; Schweizer et al., 2020). This thought entails another consideration, that regulation provided by the caregiver may be so subtle that it is not recognized adequately by the TEC-M rater. However, EmReg was found to inversely correlate, though modestly, with ADHD symptom load which support the validity of ratings. Further supporting the validity of the instrument is the high interrater reliability found in both the present study as well as the initial validation study (Hagstrøm et al., 2019). The significant correlations between EmReg and ADHD symptom load cohere with previous findings from a related study (Hagstrøm, 2019) which likewise found significant differences in emotion regulation, measured with the EmReg, between children diagnosed with ADHD and typically developing controls. Collectively the results of non-difference between the three groups and the correlation between EmReg and ADHD could indicate that emotion regulation is more related to the child's psychopathology than familial high-risk status. This could carry back to the thought of emotion regulation being a depletable resource capacity and that the EmReg is only able to elicit emotion regulation difficulties in children, of this cohort and at this age, with inherent low capacity due to, e.g. ADHD. This presumption of inherent low capacity in children with ADHD can be argued supported by another dimension of the resource capacity theory. This dimension of the resource capacity theory entails that different forms of regulation draw on different forms of cognitive capacities and abilities (Urry & Gross, 2010). Individuals with ADHD are documented to have cognitive impairments, and ADHD is defined based on dysfunctional regulation of, e.g. attention (Petrovic & Castellanos, 2016). Further supporting the validity of the results is that better emotion regulation was positively related to higher levels of daily life functioning which corresponds well with findings of associations between emotion regulation and overall wellbeing and life outcome (Graziano et al., 2007; National Scientific Council on the Developing Child, 2015).

The results of the TEC-M contrast with the results of the BRIEF and SDQ scales described assessing emotion regulation behaviour. The BRIEF scale 'Emotional Control' is described as capturing behaviour of appropriate emotional response modulation (G. A. Gioia et al., 2002) where the SDQ scale 'Emotional Symptoms' comprise five quite diverse questions: "Often complains of headaches, stomach-ache or sickness"; "Many worries, often seem worried"; "Often unhappy, down-hearted or tearful"; "Nervous or clingy in new situations, easily loses confidence"; and "Many fears, easily scared" (Goodman, 1997). Both instruments identify behaviours related to emotion regulation difficulties in a higher proportion of familial high-risk children compared with control children. As discussed, discrepancies between methods are well-known. Further, as noted, different settings present different demands to both cognitive ability, cognitive resources and also emotion regulation abilities and resources (Gross, 2014). Lab-based behavioural assessments reflect a snapshot of behaviour and does thus neither necessarily capture the child at a point where his or her resources are low or depleted nor reflect the individual child's resource capacity. Questionnaires of daily performance has the advantage of assessment in diverse situations and

during a longer temporal period. Thus, the discrepancies do not necessarily reflect poor performance of the used measure but could reflect the differential methodology. Collectively the results indicate that the TEC-M may not be sensitive enough in this specific population at this age. Even though the measure is designed to resemble a naturalistic situation, it is a lab-setting and thus does not entail all the demands of everyday life. Evaluation of real-life emotion regulation may be more valid in this population at this age.

Additions to strengths and limitations

Recruitment of the cohort of uniform age through use of the Danish national registers is if not the most important strength of the study, then certainly one of the most important strengths.

The Danish national registers enabled inclusion of a large sample of both high-risk children and controls with a uniform age from a full national cohort and independent of admissions to hospitals and time of diagnosis. This recruitment method was expected to result in a heterogenous high-risk sample but of uniform age. Moreover, controls were recruited as a population-based control group instead of a healthy control group. Collectively this eludes referral bias and hopefully produces more generalizable results. Furthermore, including two different familial high-risk groups and a large control group allows for assessment of shared as well as distinct features of two potentially related disorders.

Regarding assessments, the study has several strengths: Blinding of the assessors regarding the risk status of the child thus preventing rater bias; Consolidating parental diagnosis with a thorough diagnostic interview; Including assessments of both parents and children as well as information on multiple domains (cognitive, motor, emotional, home environment and so forth); and lastly, the application of a multimethod (questionnaires, interviews, performance based tests, observational tests) multi-informant (self-, primary caregiver- teacher, professional reports) assessment.

An additional and important strength lies in the Danish national Registers which will allow us to follow the life course of these children (if they allow it) even in the absence of future direct participation in The Danish High Risk and Resilience Study.

The study also has some important limitations that needs to be addressed. Firstly, there is the already discussed issue of representativity; Representativity analysis are currently being undertaken but until we have the results, we do not know for sure how well we succeeded in recruiting a representative sample. Also as discussed, this is a cross-sectional study and we cannot predict future development.

Moreover, the included familial high-risk bipolar group was smaller than the two other groups and therefore the study had less power to detect differences between the familial high-risk bipolar group and the two other study groups. As the familial high-risk bipolar group overall performed intermediate to the two other groups, this potential underpowering was especially problematic and could have led to a type 2 error of not detecting true differences. It is also important to keep in mind that even though familial predisposition is the single most influential risk factor for schizophrenia and bipolar disorder (Mortensen et al., 1999) most cases of illness occur in individuals without familial disposition. Therefore, translation of results from familial high-risk studies to the specific disorders in general is cautioned.

Chapter 9. Conclusions and perspectives

"A man who is master of himself can end a sorrow as easily as he can invent a pleasure.
I don't want to be at the mercy of my emotions. I want to use them, to enjoy them, and to dominate them."

— Oscar Wilde (1854-1900), The Picture of Dorian Gray (Wilde, 1998)

Within these lines, Oscar Wilde captures some of the essence of self-regulation, specifically emotion regulation, and the immense power of regulation. At the same time, it gives an unspoken hint of the potentially detrimental consequences of failure to regulate appropriately.

Research indicates that cognitive functions such as executive functions as well as aspects of self-regulation potentially underly the development of schizophrenia and bipolar disorder. With this in mind, we aimed to investigate aspects of these functions in children of parents diagnosed with either of these illnesses compared with control children.

The Danish High Risk and Resilience Study VIA 7, a prospective cohort study of children, established by utilizing Danish national registers, provided the basis for empirical evidence of severe and widespread impairments in children with familial high-risk of schizophrenia and bipolar disorder. We identified widespread executive function difficulties, problems with emotion regulation and that one-third of seven-year-old children with familial high-risk of schizophrenia and one-fifth of children with familial high-risk of bipolar disorder, have behavioural difficulties indicative of mental illness. Whether these findings are antecedents for later severe mental illness or not; a significant proportion of these familial high-risk children have current difficulties that warrant attention. Both executive functions and emotion regulation difficulties are indicated to predict later-life adversities, and the application of interventions should be considered. The objective of this thesis was to further knowledge with the goal of reducing adverse consequences of being a child with a familial high-risk predisposition. With the presented studies, we have sought to increase knowledge and hopefully brought the collective research community a step closer to this goal. It will be of great value to follow this cohort prospectively to identify and investigate the developmental trajectories of these children and with this the changes in and effects on emotion regulation and executive functions as well as psychopathological and overall future life outcomes. Of further value could be to investigate the effects of interventions in randomized controlled trials of familial high-risk children.

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List of figures and tables

List of abbreviations

ADHD	Attention-deficit/hyperactivity disorder
ADHD-RS	ADHD-Rating Scale
ANOVA	Analysis of Variance
BP	Bipolar disorder
BRIEF	Behavior Rating Inventory of Executive Function
CBCL	The Child Behavior Checklist
CBCL-DP	CBCL Dysregulation Profile
CGAS	Children's Global Assessment Scale
CI	Confidence Interval
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
EF	Executive Functions
EmReg	Overall Emotion Regulation ability measure of the TEC-M
FHR	Familial High-Risk
GEC	Global Executive Composite Scale – from BRIEF
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
K-SADS	Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version
LSD	Least Significant Difference
MD	Mean difference
OR	Odds ratio
p	*p*-value of significance level
PSP	Personal and Social Performance Scale
ROC	receiver operating characteristics
SD	Standard deviation
SDQ	Strengths and Difficulties Questionnaire
SPSS	Statistical Package for the Social Sciences
SZ	Schizophrenia
TEC-M	Tangram Emotion Coding Manual
TRF	Teachers Report Form
The VIA Study	The Danish High Risk and Resilience Study

Attachments

The SDQ Questionnare

Strengths and Difficulties Questionnaire

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of the child's behaviour over the last six months or this school year.

Child's Name ..... Male/Female

Date of Birth.....

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot stay still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children (treats, toys, pencils etc.)	☐	☐	☐
Often has temper tantrums or hot tempers	☐	☐	☐
Rather solitary, tends to play alone	☐	☐	☐
Generally obedient, usually does what adults request	☐	☐	☐
Many worries, often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐
Often fights with other children or bullies them	☐	☐	☐
Often unhappy, down-hearted or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often lies or cheats	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
Thinks things out before acting	☐	☐	☐
Steals from home, school or elsewhere	☐	☐	☐
Gets on better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Sees tasks through to the end, good attention span	☐	☐	☐

Signature ..... Date .....

Parent/Teacher/Other (please specify:)

Thank you very much for your help

Paper I.

The Strengths and Difficulties Questionnaire; Seven-year-old children with familial high risk of schizophrenia or bipolar disorder and controls - The Danish High Risk and Resilience Study - VIA 7; a population-based cohort study (Manuscript)

The Strengths and Difficulties Questionnaire; seven-year-old children with familial risk of schizophrenia or bipolar disorder and population-based controls.

The Danish High Risk and Resilience Study –VIA 7; a population-based cohort study

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Abstract

Background: Children born to parents with severe mental illness are at increased risk of experiencing mental and behavioural difficulties during childhood. We aimed to investigate the occurrence of behavioural difficulties at a clinically significant level in seven-year old children of parents diagnosed with schizophrenia or bipolar disorder compared with controls by using the Strengths and Difficulties Questionnaire (SDQ). Further, we aimed to determine if the SDQ could function as a screening instrument for clinically relevant behavioural problems of familial high-risk children.

Methods: By means of the Danish National Registers, we established a cohort of 522 seven-year old children stratified by familial high risk for schizophrenia spectrum disorder (N= 202), bipolar disorder (N=120), and controls (N= 200). The child's primary caregiver completed the SDQ parent version and the Child Behavior Checlist (CBCL) while the schoolteacher completed the SDQ teacher version and the CBCL teacher equivalent; the Teachers Report Form (TRF).

Results: Children with familial high risk of schizophrenia spectrum disorder or bipolar disorder have an increased risk (OR = 3.8 and 2.3) of suffering clinically significant behavioural difficulties at age seven-years according to SDQ parent ratings. The SDQ discriminates with moderate to high sensitivity and high specificity between familial high-risk children with and without a psychiatric diagnosis and has overall compelling discriminatory abilities in line with the more time consuming CBCL/TRF.

Conclusions Familial high-risk children had more behavioural difficulties and more frequently at a level indicative of mental illness compared to control children as measured by the SDQ. The SDQ works well as a screening instrument for clinically relevant behavioural problems in high-risk children.

Abbreviations:

ADHD: Attention-Deficit/Hyperactivity Disorder. CBCL: The Child Behavior Checklist school-age version. CGAS: The Children's Global Assessment Scale. DBD: Disruptive Behaviour Disorder. FHR: Familial High Risk. FHR-BP: Familial high risk for Bipolar disorder. FHR-SZ: Familial High Risk for Schizophrenia. ICC: Intra-class Correlation Coefficient. K-SADS-PL: The Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version. ROC: Receiver Operating Characteristics. SDQ: The Strengths and Difficulties Questionnaire. The VIA 7 Study: The Danish High Risk and Resilience Study – VIA 7. TRF: The Teacher's Report Form.

Introduction

The single strongest risk factor for developing schizophrenia or bipolar disorder is to have a parent with the concordant illness (Gottesman, Laursen, Bertelsen, & Mortensen, 2010). Further, the risk of developing other mental illnesses than the parental, is also markedly increased in children of parents with severe mental illness compared with children of unaffected parents (Dean et al., 2010; Ellersgaard et al., 2018; Rasic, Hajek, Alda, & Uher, 2014; Uher & Zwicker, 2017). Considering this, children with familial high risk of severe mental illness require attention and care. Detection of early signs and symptoms of psychiatric illness in childhood is increasingly advocated, as well as the crucial importance of appropriate pre-emptive measures before illness specific symptoms emerge, and importantly, before the onset of distress or impairment (McGorry & Nelson, 2016; Uher & Zwicker, 2017). Nevertheless, sensitive and specific means to identify which children who will develop a mental illness are still lacking.

One first step towards early identification of the individual child who has or are at risk of developing mental illness, could be to identify signs of daily life behavioural difficulties indicative of mental health problems. This, preferably at an early age and in an easily accessible and user-friendly way and utilizing multiple informants, especially schools, to complement and take part in the important work of early detection. If a broad band dimensional measure of psychopathology identifies the presence of mental illness with satisfactory accuracy, regular and early age assessments applying less strict cut-offs, could potentially be used to detect children before manifest disorder and thus render the possibility of intervention. By utilizing a familial high-risk study design, in which some children already have a mental illness, it is possible to assess if a dimensional assessment measure of psychopathology can identify children with a diagnosis with satisfactory accuracy, potentially rendering it an applicable screening tool.

The repeatedly validated (Goodman, 2001; van den Heuvel et al., 2017; Mieloo et al., 2012; Niclasen et al., 2012; Stone, Otten, Engels, Vermulst, & Janssens, 2010) and highly used ‘Strength and Difficulties Questionnaire’ (SDQ) (Goodman, 2001; Obel, Dalsgaard, Stax, & Bilenberg, 2003), has the quality of being brief, free to use for non-commercial purposes and widely accepted by responders (‘http://www.sdqinfo.org’, n.d.). The SDQ can be used to approximately determine the probability of mental illness in a population with 80 percent of a population-based sample classified as ‘unlikely’ to have a mental illness, 10 percent as ‘possibly’ and lastly the 10th percentile poorest scoring classified as ‘probably’ having a mental illness. Utilizing these classifications the SDQ has repeatedly been found to discriminate well between clinical and non-clinical populations as well as having satisfactory predictive values in population studies (Nielsen et al., 2019; Rimvall et al., 2014; Stone et al., 2010; Sveen, Berg-Nielsen, Lydersen, & Wichstrøm, 2013; Ullebø, Posserud, Heiervang, Gillberg, & Obel, 2011). The SDQ could thus potentially serve

as a dimensional screening tool of psychopathology and act as the first step to identify developing mental illness in children with a familial predisposition for severe mental illness.

The aim of this study was twofold. Firstly, we aimed to compare behavioural difficulties assessed with the SDQ in young children with a familial high-risk of schizophrenia or bipolar disorder compared to matched population-based controls and to investigate if a higher proportion of children from the two high-risk groups would have behavioural difficulties at a level indicative of mental illness compared to controls. To qualify an assumption of an association between an SDQ score indicative of mental illness and poorer general functioning, we sequentially aimed to assess difference in general functioning assessed by the 'Children's Global Assessment Scale' (CGAS, (Shaffer et al., 1983)) between children with and without potential mental illness as identified by the SDQ. Secondly, we aimed to investigate the potential of the SDQ as a short and accessible measure that could be easily used in primary health care services by assessing if it can adequately identify children with mental illness opposed to children without mental illness in this risk population, and in line with this, compare the discriminatory qualities of the SDQ with another highly used and validated but more time-consuming assessment measure of psychopathology; the Child Behavior Checklist (CBCL) (Achenbach & Edelbrock, 1983). Our main focus was reports from the child's primary caregiver and, secondly we investigated teacher SDQ reports against the CBCL teacher-rated equivalent; the Teachers Report Form (TRF) (Achenbach & Rescorla, 2001).

Method:

Participants

Four hundred forty-eight children were assessed with the SDQ; 429 children were rated by their primary caregiver; 366 children were rated by their schoolteacher and 347 were rated by both their primary caregiver and their schoolteacher (Figure 1). The primary caregiver of the child was defined as the parent or legal guardian who, at the time of the study, knew the child the best. The participating children were all part of The Danish High Risk and Resilience Study – VIA 7, hereafter referred to as the VIA 7 Study. We identified participants for the VIA 7 Study by combining information from the Danish Civil Registration System (Pedersen, 2011) and the Danish Psychiatric Central Research Register (Mors, Perto, & Mortensen, 2011). The Danish National Registries allowed for identification of all 7-year-old children born and living in Denmark during the study period, while also fulfilling the VIA 7 Study inclusion criteria. The VIA 7 cohort was stratified into three groups; 1) children with familial high-risk of schizophrenia spectrum psychosis (FHR-SZ) which included children who had at least one parent diagnosed and registered with schizophrenia spectrum psychosis defined as schizophrenia, delusional disorder or schizoaffective disorder (ICD 10-codes F20, F22 and F25 or ICD 8-codes 295, 297, 298.29, 298.29, 298.89, 298.99 (Sundhedsstyrelsen, 1971; World Health Organization Collaborating Centre for Research and

Training in Mental Health, 1994); 2) children with familial high-risk of bipolar disorder (FHR-BP) which included children who had at least one parent diagnosed and registered with bipolar disorder (ICD 10-code F30 or F31 or ICD 8-codes 296.19, 296.39 (Sundhedsstyrelsen, 1971; World Health Organization Collaborating Centre for Research and Training in Mental Health, 1994); and lastly 3) a population-based control group of children with neither parents registered with any of the diagnoses mentioned above. We matched control children to FHR-SZ children on municipality, sex and age. We included FHR-BP children as a non-matched group. We designated children where one parent was diagnosed with bipolar disorder and the other diagnosed with schizophrenia to the FHR-SZ group as per the hierarchal principles of ICD-10. The VIA 7 Study was conducted between year 2013 and 2016, and the final prospective VIA 7 Study cohort consisted of 522 children; 202 FHR-SZ children, 120 FHR-BP children and 200 control children. Parents with a diagnosis of BP or SZ as specified above were classified as index-parents and the other biological parent without these diagnoses was classified as the biological non-index parent. Index parents in the FHR-SZ groups were matched with the parent of the same sex in the matched control family. (Thorup et al., 2015). The primary outcome measure of the current study; the SDQ, was unfortunately not included from the beginning of the data collection but was introduced six months into the study. This resulted in a smaller total number of potential SDQ participants.

Measures:

The Strengths and Difficulties Questionnaire (SDQ) was developed as a brief behavioural screening tool to help assess child and adolescent behaviours, emotions and relationships (Goodman, 1997). The SDQ consists of 25 questions selected on the basis of contemporary diagnostic criteria and factor analysis. The 25 items comprise five scales; four difficulties scales (Emotional Symptoms, Conduct Problems, Hyperactivity, Peer Problems) and one scale on Prosocial Behaviour, and each scale consisting of five items each. A Total Difficulties Scale score is generated by summing the four difficulties scales. All questions are identical for the parent- and teacher-version and have the following response options; *"Not true"*, *"Somewhat true"* or *"Certainly true"* corresponding to a score of 0, 1 and 2 or reversed scores of 2, 1 and 0 for some items. For each scale, a score between zero and ten can be obtained. For the four difficulties scales, higher scores indicate more problem behaviour, whereas, for the prosocial scale, a higher score indicates better performance. The respondent is asked to consider the behaviour of the child during the previous six-month period when rating the SDQ. The SDQ is widely used internationally, and satisfactory psychometric properties as well as the clinical utility of the questionnaire, have been repeatedly confirmed (Goodman, 2001; van den Heuvel et al., 2017; Mieloo et al., 2012; Niclasen et al., 2012).

Best estimate lifetime DSM-IV children's psychiatric research diagnoses were ascertained through combining information from all available data on the child obtained during the test period with the

semi-structured diagnostic interview; The Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). The K-SADS-PL interview was performed firstly with the primary caregiver and then with the child. For the present study, we utilised the attention-deficit/hyperactivity disorder (ADHD) diagnosis and any Axis I diagnosis of the K-SADS-PL. We further utilized the conduct disorder diagnosis and oppositional defiant disorder diagnoses to construct a disruptive behaviour disorder (DBD) diagnosis category. We included both definite and probable research diagnoses in the analysis. We excluded elimination disorders diagnoses entirely.

The current level of daily life functioning of the child was evaluated with the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983) as part of the K-SADS-PL interview. CGAS is clinician rated and constitute a single score on a numeric scale that ranges from 1 to 100 with higher scores reflecting higher levels of functioning. Scores are defined within ten increment point intervals with a score that range from 1-10 classified as 'extremely impaired' and scores above 70 indicating normal functioning. CGAS is rated independent of specific mental health diagnoses and is scored on basis of the level of functioning within the last four weeks.

The Child Behavior Checklist school-age version (CBCL) (Achenbach & Rescorla, 2001) includes 118 questions on problem behaviour that are rated on a Likert scale from zero (not true) to two (very true/often true). The CBCL total score is summed from the 118 problem behaviour items. Further an Internalizing and an Externalizing broad-band subscale can be computed, as well as six DSM-IV oriented subscales of which we utilize the Attention-Deficit/Hyperactivity Problems scale and the Conduct Problems scale. The CBCL was completed by the primary caregiver. The Teacher's Report Form (TRF) (Achenbach & Rescorla, 2001) corresponds to the CBCL with minor differences and was completed by the child's schoolteacher. Detailed results on diagnoses, CBCL, and TRF results are published elsewhere (Ellersgaard et al., 2018).

Procedures:

The Danish Data Protection Agency has approved the VIA 7 Study (RHP-2012-06). The study was evaluated by The Danish National Committee on Health Research Ethics. Due to the observational nature of the study, approval was not deemed necessary by the authority. We obtained informed written consent from all adult participants and custody holder(s) of the children, including a separate written consent to contact the child's schoolteacher. We asked the child's primary caregiver and the child's schoolteacher to complete the SDQ – Danish parent (SDQ-P) and teacher (SDQ-T) versions respectively. The primary caregiver was also the main informant on all other measures concerning the child. The primary caregiver most often was a biological parent but could be a stepparent or foster parent. Trained psychologists, medical doctors and nurses performed all

assessments under the supervision of a senior specialist in child neuropsychology (JRMJ) and a specialist in child and adolescent psychiatry (AAET). Child assessors were kept blinded to the risk status of the child. The study design of the VIA 7 Study has been described in detail elsewhere (Thorup et al., 2015).

Statistical analyses

Participants' characteristics

Demographic and clinical characteristics were analysed by one-way analysis of variance (ANOVA), chi-square test or the Mantel-Haenszel linear-by-linear test of association, as appropriate. (Table 1).

Descriptive SDQ mean values and between-group differences

SDQ scores were converted to Z-scores for boys and girls separately using the control group as the reference group. Hereafter Z-scores were computed into T-scores (mean=50 and SD=10) with higher T-scores indicating more problem behaviour on the four difficulties scales and less prosocial behaviour on the prosocial scale.

The SDQ generally has highly skewed distribution of scores (Obel et al., 2004). In recognition of this, we present mean raw and T-scores and comparisons of group differences analysed on T-scores by Welch ANOVA followed by Games-Howell post hoc tests solely as descriptive illustrations of the data (Table 2).

Prevalence of SDQ clinical range scores

To quantify the clinical significance of between-group differences, we applied logistic regression analyses to compare the proportion of children from each risk group that were rated within the 10 percent (90^{th} percentile) poorest performing, calculated from the control group, on all subscales and the Total Difficulties Scale. The 90^{th} percentile from the control group was chosen as an illustrative cut-off because it approximates cut-off for significant problems in a normal population, as previously shown in other studies (Goodman, 1997; Mieloo et al., 2012; Niclasen et al., 2012). This method was selected as although Danish norms have recently been published (Arnfred et al., 2019), we do not have national cut-off scores for this particular, narrow age group. As the individual scales are within a narrow range (1-10), producing exact 90^{th} percentile cut-offs are not feasible nor clinically relevant. We thus chose the cut-off score that encompasses the 90^{th} percentile with the closest proximity and indicated the exact percentage of children in the control group (Table 3). We report the main results of group differences as the proportion of children above cut-off and odds ratios (OR) between groups because of the skewed distribution of scores (Table 3). We analysed differences in the proportion of boys and girls scoring above cut-off in the individual high-risk groups with chi-square tests.

Difference in general functioning (CGAS) between children scored below and above SDQ Total Difficulties Scale cut-off

We assessed differences in CGAS mean scores between the above and below cut-off groups by independent samples t-test, to qualify the assumption of an association between an SDQ Total Difficulties scale score above cut-off and poorer general functioning.

The discriminatory ability of the SDQ compared to the CBCL and TRF

We applied receiver operating characteristics (ROC) curves to determine the ability of SDQ and the CBCL total scores to distinguish between FHR children with any lifetime Axis I diagnosis versus non-diagnosed children. ROC curve analysis was further used to determine the ability of the SDQ and CBCL hyperactivity and conduct scales to distinguish between FHR children with and without a lifetime ADHD and DBD diagnosis, respectively. Comparisons of the areas under the ROC curves for SDQ and CBCL respectively were performed using paired sample statistics (Table 4). All ROC analyses were performed on outcome T-scores.

Results on the discriminatory abilities of the SDQ, CBCL and TRF analysed with ROC curves are expressed by sensitivity, specificity and area under the curve (AUC) where an AUC of 1.0 reflects perfect discrimination, and 0.5 reflects no better than chance accuracy. To aid interpretation of the results, we applied the following distinction: 0.5-0.7 = poor discrimination (coin toss), 0.7-0.8 = Acceptable discrimination, 0.8-0.9 = Excellent discrimination, >0.9 = outstanding discrimination (Hosmer, Lemeshow, & Sturdivant, 2013). Sensitivity and specificity values closest to the T-score =65 cut-off value is reported.

Teachers' SDQ ratings were examined by the same methods as described above. SDQ-T ROC curves were compared to the TRF, the teacher-rated equivalent to the CBCL.

Correlation of primary caregiver and teacher rated SDQ scores

Interrater agreement between the primary caregiver and teacher SDQ ratings and between primary caregiver and teacher rated CBCL/TRF were performed by intra-class correlation coefficient (ICC) with two-way random effect model on absolute agreement (Liu et al., 2016; Shrout & Fleiss, 1979). To guide interpretation the following classifications will be used: ICC values < 0.40 are considered poor agreement, values from 0.40-0.59 are fair, values between 0.60-0.74 are good, and ICC values > 0.75 are considered excellent (Cicchetti, 1994).

Handling of missing:

According to the SDQ scoring manual, subscale scores can be scaled up pro-rata, if at least three of five items are rated ('SDQ_English(UK)_4-17scoring.pdf', n.d.). If a subscale had more than two missing items, the subscale for that respondent was censured. To ensure that data was not affected by this procedure, all missing values were assessed, and found to be missing at random and to represent a minute fraction of the data.

We used IBM SPSS Statistics, version 26 for ROC comparisons. All other analyses were conducted using IBM SPSS Statistics, version 25.

Results (875 words)

Participants' characteristics

The three groups did not differ regarding age or sex of the children. FHR children less often lived with both biological parents, and their primary caregiver had a lower level of functioning than control primary caregivers (Table 1). Distribution of sex did not differ between children participating with SDQ data and non-participants in any of the three groups. Daily life functioning (CGAS) differed significantly between FHR-BP participants (mean (SD) = 72.1 (14.8)) and non-participants (N=15 with a CGAS, mean (SD) = 83.9 (11.3)) (p = .004) but only on the SDQ-P.

Descriptive SDQ mean values and between-group differences

The difference in SDQ-P mean T-scores between the FHR-SZ group and the control group was highly significant on both the Total Difficulties Scale and on all four difficulties scales ($p < 0.001$), but non-significant regarding the Prosocial Behaviour scale. The FHR-BP group differed significantly from the controls on the SDQ-P Total Difficulties Scale (p =.026), the Emotional Symptoms scale (p =.025) and the Conduct Problems scale (p =.041), but not on the remaining scales. The two FHR groups were significantly different from each other on all SDQ-P scales (p = .011-.046) except the Emotional Symptoms scale. The FHR-BP group scored intermediate of the control group and the FHR-SZ group on all four SDQ-P difficulties scales (Table 2).

Regarding SDQ-T ratings, the FHR-SZ group differed significantly from the control group on all scales (p = <.0001 - .003), including the Prosocial Behaviour scale (p <.001), whereas the FHR-BP group only differed significantly from the control group on the Total Difficulties Scale (p =.048). However, the two FHR groups did not differ significantly from each other on any scales of the SDQ-T (Table 2).

Prevalence of SDQ clinical range scores

FHR-SZ children were more likely to have an SDQ-P Total difficulties Scale score within clinical range compared to control children (28.1% vs 9.4%) (OR = 3.8, CI 2.0 to 7.1, p = <.001). This was also true for FHR-BP children (19.4% vs 9.4%) (OR = 2.3, CI 1.1 to 4.8, p = <.023). On all SDQ-P difficulties scales, FHR-SZ children had higher odds of significant difficulties compared to the control children (p = <.001). Odds of FHR-BP children only differed significantly from that of the control children on the SDQ-P Emotional Symptoms scale (p =.010). Neither of the FHR groups differed significantly from the control group regarding the SDQ-P Prosocial Behavior scores (Table 3).

Proportion of boys and girls above cut-off on the SDQ-P Total Difficulties Scale differed significantly in the FHR-SZ group (p = .011) with 18.7% of FHR-SZ girls scoring above cut-off and 35.9% of FHR-SZ boys above cut-off, corresponding to boys accounting for 70.2% of the

FHR-SZ above cut-off group. The were no sex differences in the FHR-BP group regarding the SDQ-P Total Difficulties Scale scores (Figure 2a).

SDQ-T identified a lower proportion of FHR children above cut-off than the SDQ-P except regarding peer problems and less prosocial behaviour. Further, the OR of conduct problems for FHR-SZ was high (OR = 6.3, CI 2.7-14.7, *p* =<.001) compared to controls according to the SDQ-T. Proportion of boys and girls above cut-off on the SDQ-T Total Difficulties Scale differed non-significantly in the FHR groups with 19.4% of FHR-SZ girls above cut-off and 32.8% of FHR-SZ boys above cut-off (*p* = .077) and 18.4% of FHR-BP girls above cut-off and 13.2% of FHR-BP boys above cut-off (*p* = .497) (Table 3, Figure 2b).

Difference in general functioning (CGAS) between children scored below and above SDQ Total Difficulties Scale cut-off

CGAS mean scores were significantly higher for the 'below SDQ-P cut-off groups' (N=347, mean (SD) = 75.8 (13.2)) compared to the 'above SDQ-P cut-off group' (N=82, mean (SD) = 55.9 (12.1)) with a statistically significant difference of 19.9 points, 95% CI [16.8, 23.0], t(427) = 12.446, *p*=.0001. Results for the individual high-risk groups as well as all SDQ-T results were very similar to these results (Table S1).

The discriminatory ability of the SDQ compared to the CBCL and TRF

The ability of the SDQ-P and the CBCL total scores to distinguish between children with and without any Axis I diagnosis was acceptable to excellent and non-different between measures. The ability of the SDQ-P hyperactivity scale to discriminate between children with and without a diagnosis of Attention-Deficit Hyperactivity Disorder (AUC = 92, CI .89 to .95) and the conduct scale in regards to Disruptive Behaviour Disorder (AUC = 93, CI .89 to .98), were both on an outstanding level and non-different from the discriminatory ability of the corresponding CBCL scales (Table 4a). Sensitivity of the SDQ-P and CBCL ranged from 34.2% for any Axis I in the FHR-BP group to 81.3% and 93.8% for SDQ-P and CBCL respectively for any disruptive behaviour disorder, the latter demonstrating the highest discrepancy found between SDQ-P and CBCL. Specificity ranged from 82% to 90.6%.

The discriminatory abilities of SDQ-T and TRF resemble the results of the SDQ-P and CBCL (Table 4b) except for the ability to identify the presence of disruptive behaviour disorder where the TRF (AUC = 92, CI .87 to . 97) is significantly better than the SDQ-T (AUC = .82, CI .70 to .94) (Table 6.5 B)..

Correlation of primary caregiver and teacher rated SDQ scores

Interrater agreement between primary caregiver and teacher on the Total Difficulties Scale was good and regarding the individual SDQ difficulties scales ICC values were primarily in the fair to good range. CBCL and TRF interrater agreement were likewise in the fair to good range (Table S2).

Discussion (1613 words)

A substantially larger proportion of seven-year-old children with a familial high risk of schizophrenia or bipolar disorder had significant everyday life behavioural difficulties compared to matched control children as evaluated both by their primary caregivers and their schoolteachers on the Strengths and Difficulties Questionnaire. FHR-SZ children and particularly FHR-SZ boys were especially at risk of having difficulties at a level indicative of emerging or existing mental illness. Further, children who were found above cut-off for significant difficulties had a markedly lower level of daily life functioning measured with CGAS compared to children below cut-off. Teachers identified less prosocial behaviour in both FHR groups. The discriminatory abilities of the SDQ were good, with high AUC values and moderate to high sensitivity and high specificity values. Moreover, the SDQ was compellingly equating to the well-recognized, but more time-consuming CBCL and TRF. These results were found in a uniquely constructed cohort drawn from the Danish National Registries. Interrater agreement of the caregiver and the teacher-rated SDQ fell in line with results of other studies which in general have found reliable agreement on all difficulties scales and best agreement on the total scale and the hyperactivity scale (R. Goodman, 1997; Mieloo et al., 2012; Stone et al., 2010).

Identifying that between one fifth and one third of seven-year-old FHR-BP and FHR-SZ children respectively scored above threshold for emotional and behaviour problems indicative of mental illness is a prominent finding that deserves attention. Mean scores and the cut-off scores based on our cohorts' control group are somewhat lower than reported from other European countries (Niclasen, 2013). Nevertheless, for girls, they are in line with previous investigations of the general Danish population (Arnfred et al., 2019; Niclasen, 2013) and other Scandinavian countries (Niclasen, 2013) as well as in line with cut-off scores determined from ROC analysis and 90th percentiles in a Swedish sample (Malmberg, Rydell, & Smedje, 2003), thus supporting the validity of our findings. However, our cut-off scores for boys tend to be lower than previous findings both in Danish and in other Scandinavian settings with caregiver ratings having the most considerable discrepancy. Nonetheless, we find that an equal proportion of boys and girls are scored above cut-off in the FHR-BP group both according to caregiver ratings and teacher ratings. Only a significantly larger proportion of FHR-SZ boys are above cut-off, and this is only according to caregiver ratings. If boys from the control group should somehow be "better" functioning than average, we would have expected that a substantially larger proportion of boys than girls in both the two FHR groups would be scored above cut-off for significant difficulties by both teachers and

caregivers. We thus believe that the finding of a relatively high proportion of children in the two high-risk groups with significant difficulties suggestive of mental illness is a true finding that warrants pre-emptive measures early in life for these at-risk children. Further strengthening the validity of our results is that the above cut-off group has a markedly lower level of functioning than the below cut-off group.

Our secondary aim was to investigate whether a short and accessible measure of children's behavioural difficulties could distinguish between children with and without a psychiatric diagnosis determined by a thorough diagnostic interview, the K-SADS. The results from ROC analysis indicate that the SDQ has a compelling ability to discriminate between children with and without a psychiatric diagnosis with moderate to high sensitivity and high specificity. These results and the noticeable equality between discriminatory abilities of the SDQ and the CBCL resemble previous findings (Goodman & Scott, 1999; Hysing, Elgen, Gillberg, Lie, & Lundervold, 2007; Klasen et al., 2000; Malmberg et al., 2003; Nielsen et al., 2019) supporting the reliability of the present findings.

Collectively, these results indicate that the SDQ could function well as a screening tool for the identification of children at FHR for SZ and BP in need of aid. These results are from a time point in the FHR children’s lives were they have not yet developed any severe mental illness, but some do already have other psychiatric disorders and many have lower levels of functioning than controls (Ellersgaard et al., 2018) as well as affected cognition (Hemager et al., 2018). It is, however, essential to remember that this is a cross sectional study and that the results are a snapshot of current status at age seven. We do not yet know the future development of these children or if the current identified problems are transitory although other studies indicate a predictive value of SDQ scored at age 5-7 and the presence of mental illness at age 11-12 (Nielsen et al., 2019; Rimvall et al., 2014).

Our focus was on the primary caregiver rated SDQ, but analyses of the teacher rated SDQ revealed very similar results. This, together with good correlation between primary caregiver and teacher SDQ ratings, and also notably higher than what has been found in other studies (Achenbach, McConaughy, & Howell, 1987; Mieloo et al., 2012), strengthens the robustness of the study results. Teachers generally rated less difficulties than primary caregivers except for on the Hyperactivity scale and the Peer Problem scale, where teachers rated both high-risk groups as having more problems. When comparing results of SDQ teacher and primary caregiver ratings, it is important to note that the teacher and primary caregiver rated SDQ cohorts are not entirely overlapping. Further, it has to be acknowledged that primary caregiver ratings could be affected by the presence of mental illness in the caregiver, him- or herself, as this is a factor known to potentially distort reporting’s (Achenbach et al., 1987; Cheng et al., 2018). However, the results of the present study are in

accordance with other studies where primary caregivers also rated problems more severely than teachers and teachers also were more prone to rate externalising problems like hyperactivity and problems regarding social interaction with peers (Vaz et al., 2016).

Strengths and limitations

A significant strength of this study is that we applied a multi-informant method in a register-based sample of 522 same age children. Assessing children in different social settings gives valuable information of behaviours potentially related to mental illness. We explored emotional and behavioural problems both by multi-informant and by a multimethodological (questionnaires, interviews, lab-tests, etc.) approach, thus giving us a unique opportunity to compare instruments. Importantly SDQ and CBCL were not calculated previous to or used explicitly in connection to evaluation of child diagnosis, but single items of both the SDQ, CBCL and TRF could potentially in some cases have been consulted in relations to the diagnostic process thus rendering the diagnosis not completely independent of the questionnaires.

Further, we estimated cut-off points indicative of significant difficulties constructed from our control group, which had the qualities of not only being matched to the FHR-SZ children but also being population based. Further strengthening the present study is that all children were within a narrow age range and drawn and matched through registers from a national cohort of eligible children. We thus did not have a problem of referral bias and the children were included regardless of their parent's current stage of illness and potential contact to the psychiatric system. Also strengthening the study is the high participation and completion rate of families in both the VIA 7 Study as a whole and in the present study. The group of participating FHR-BP families in the VIA 7 Study was from the outset planned to be smaller than the two other groups partly due to economic and practical issues. With more participants in the FHR-BP group, we might have found significant results on more scales, and it would undoubtedly have strengthened the study. Replication of the study in a larger scale could thus be of value. Because of the low number of siblings and double high-risk children (i.e. children with two parents with severe mental illness), we did not include the effects of siblings or double high-risk children in the analyses. The influence of genetic similarity and genetic load respectively was thus not included in the statistical model and we cannot rule out a possible effect.

The results regarding the discriminatory and predictive abilities of the SDQ and comparisons to the abilities of the CBCL and TRF, are necessarily preliminary as the study is limited to a very narrow age group. However, previous studies with other study groups and age ranges have arrived at similar conclusions (Goodman & Scott, 1999; Klasen et al., 2000; Koskelainen, Sourander, & Kaljonen, 2000; Malmberg et al., 2003; Nielsen et al., 2019; Sveen et al., 2013; Ullebø et al., 2011).

Conclusion

We aimed to assess whether children at familial high risk of schizophrenia or bipolar disorder had more everyday life difficulties indicative of mental illness compared to control children. We found that the SDQ not only identified a significant proportion of familial high-risk children with substantial everyday life difficulties indicative of mental illness, but also that these children had markedly affected daily life functioning. Further, the SDQ was able to discriminate between FHR children with and without a diagnosis with compelling accuracy and undistinguishable from the lengthier CBCL. The SDQ is a short and accessible measure assessing both strengths and difficulties of children, rendering it highly acceptable for both parents and teachers. The discriminatory abilities of the SDQ found in the present study, along with its general acceptability to respondents, it's brevity as well as low costs of administration and evaluation, renders the SDQ a compelling screening instrument for the identification of children with potential mental illness. This, both in research, clinical and importantly, in pre-clinical settings were the SDQ could serve as an epidemiological screening tool of large groups of FHR children.

Collaboration between child and adolescent psychiatry and adult psychiatry as well as schools, could allow early identification and interventions targeting FHR children who are exhibiting problematic behaviour indicative of mental illness. Early identification could give these at-risk children a chance to turn their development in a more positive direction and as a result of this alleviate adverse consequences.

Declarations

The study was approved by the Danish Data Protection Agency (J.nr.:2012-58-0004) and follows all present laws concerning personal data. The Danish Ministry of Health granted the permission to draw data from Danish national Registers. The Danish National Committee on Health Research Ethics evaluated the study and concluded that further approval was not required due to the observational nature of the study. Verbal and written informed consent were obtained for all participants or custody holders, including a separate written consent to contact the child's teacher. The study was funded by TrygFonden, the Mental Health Services of the Capital Region of Denmark, The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Aarhus University, and the Beatrice Surovell Haskell Fund for Child Mental Health Research of Copenhagen.

Funding: This work was supported by TrygFonden, the Mental Health Services of the Capital Region of Denmark, The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Aarhus University, and the Beatrice Surovell Haskell Fund for Child Mental Health Research of Copenhagen.

Conflicts of interest: The authors have no conflicts of interest to disclose.

Ethics approval: The Danish High Risk and Resilience Study - VIA 7 was approved by the Danish Data Protection Agency (J.nr.:2012-58-0004). The Danish National Committee on Health Research Ethics evaluated the study and concluded that further approval was not required due to the observational nature of the study.

Consent to participate: Verbal and written informed consent was obtained for all participants or custody holders, including a separate written consent to contact the child's teacher.

Availability of data and material: access can be granted upon request

Code availability: Access can be granted upon request

Author contributions: All authors contributed to the study conception and design. KSS wrote the manuscript and performed data analysis with input from all authors. KSS, DE, NH, CC, BKB, ANG, DG, MG collected the data. All co-authors critically revised the manuscript and approved the final version.

Acknowledgements:

The authors extend their gratitude to all the families and teachers for their will to participate and to generously lent us their time and effort. The authors would also like to express their gratitude to M. Skjærbæk, A. Søndergaard, A. Ranning, H. Jensen, C. Gregersen, D-M. Henriksen, H. Stadsgaard, K. Zahle and M. Melau for contributing to data collection; to C. Bøcker Pedersen for assistance in retrieving the register extract; to M. Chaine for help with data management; to P.B. Mortensen T. Werge, D. Hougaard, M. G. Pedersen and, A. Børglum for collaboration in iPSYCH. The authors have no conflict of interest.

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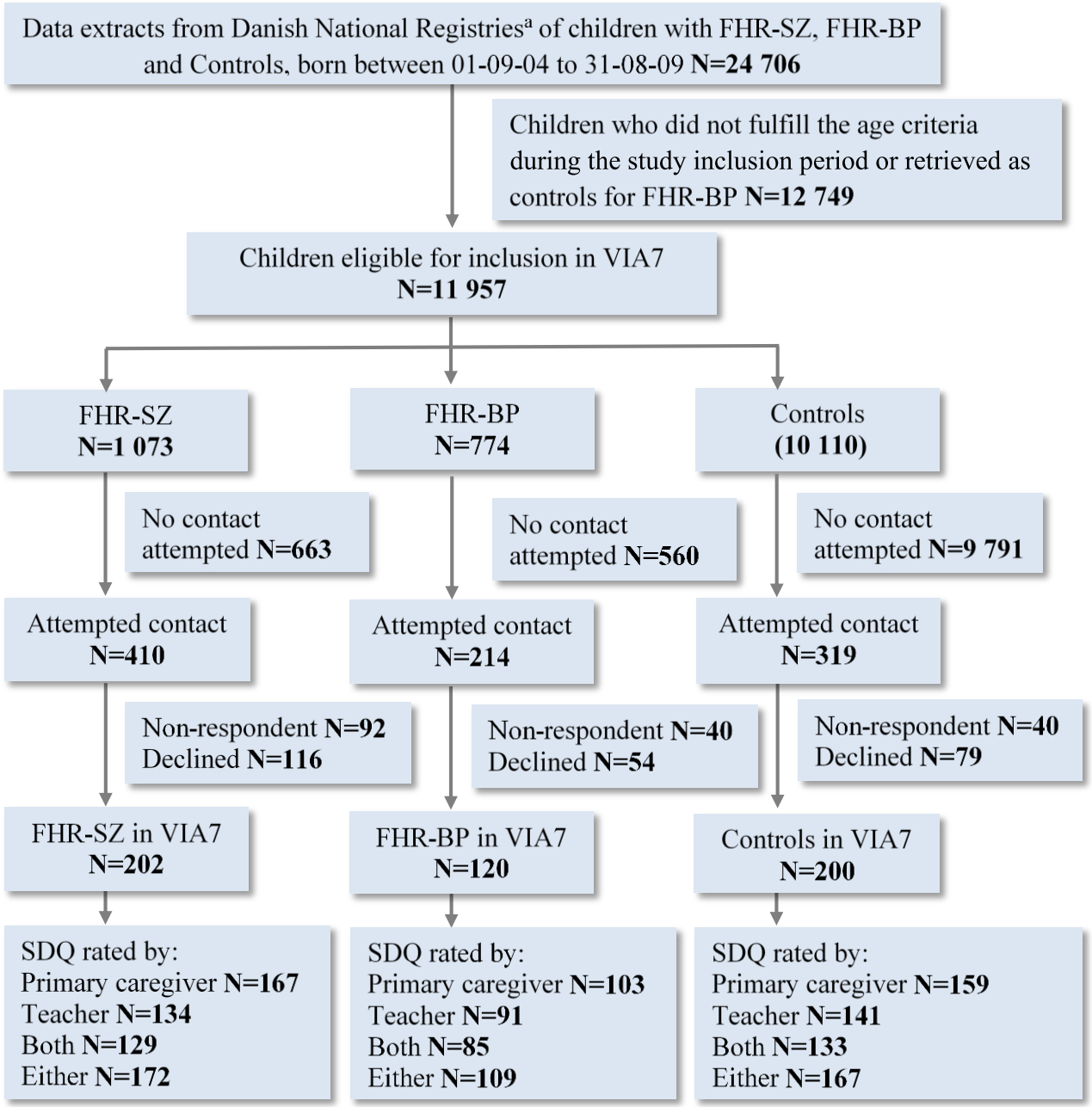
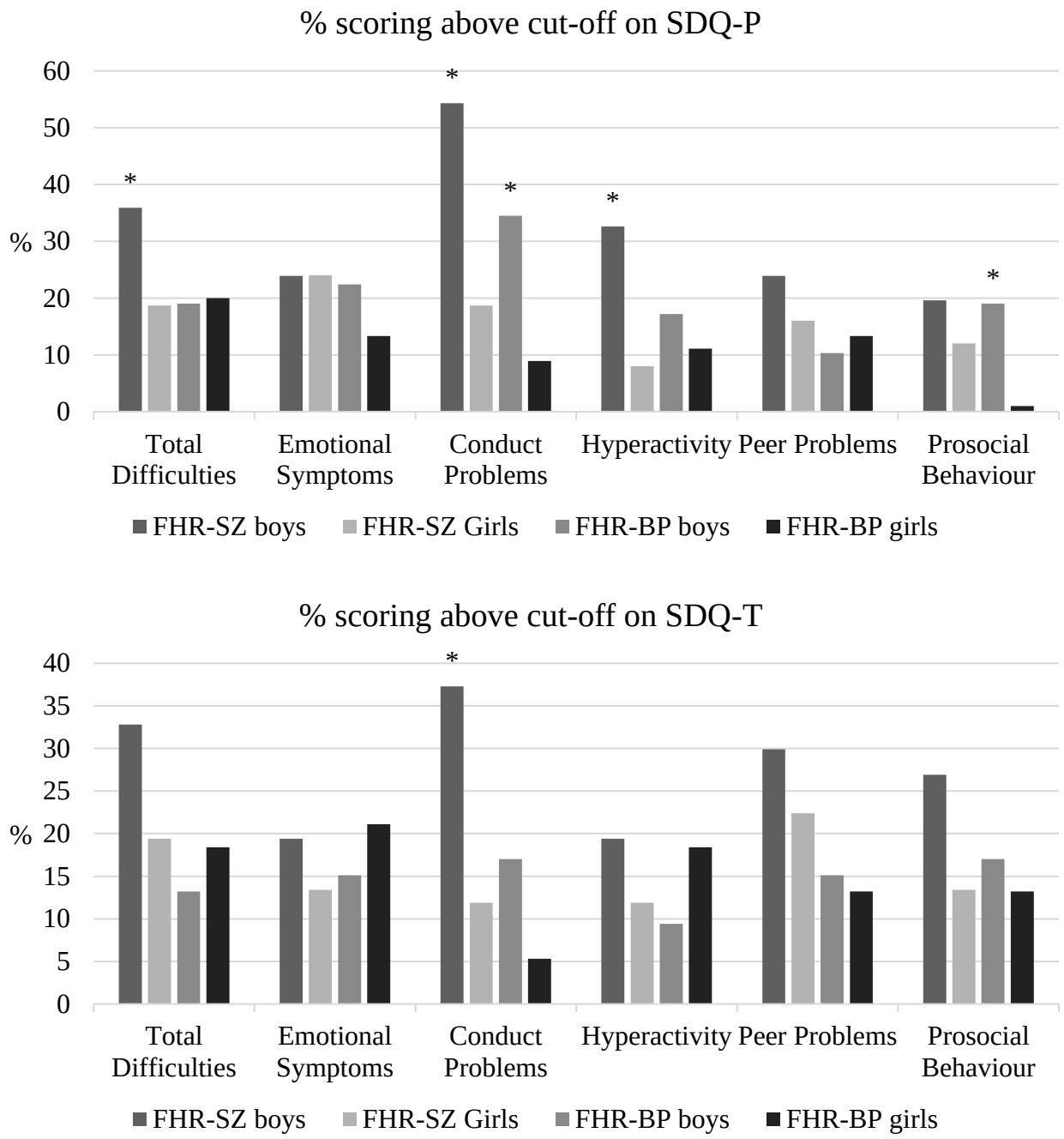
Figure 1. Flowchart of the inclusion of children in the Danish High Risk and Resilience Study – VIA 7 and children contributing with SDQ data.



SDQ: Strengths and Difficulties questionnaire. FHR-SZ: Children of parents with schizophrenia spectrum disorders. FHR-BP: Children of parents with bipolar disorder. PBC: Population-based control children of parents with no diagnoses of schizophrenia spectrum disorders or bipolar disorder.

[a] Danish Civil Registration System and Danish Psychiatric Central Research Register.

Figure 2. Proportion of girls and boys above cut-off for significant difficulties



FHR: Familial High Risk; SZ: Schizophrenia; BP: Bipolar Disorder; SDQ: The Strengths and Difficulties Questionnaire; -P: Parent version; -T: Teacher version

* Significant difference ($p<.05$) between sexes within FHR group.

Table 1 Characteristics of children in the Danish High Risk and Resilience study with an SDQ-P, their home environment and their biological parents.

	FHR-SZ	FHR-BP	Controls	*p*-value	*p*-value		
					FHR-SZ vs. Controls	FHR-BP vs. Controls	FHR-BP vs. FHR-SZ
Children (N=429), N	167	103	159				
% of full cohort	82.7	85.8	79.5	.348[C]	-	-	-
Female, %	44.9	43.7	44.0	.977[C]	-	-	-
Age at inclusion, mean (SD)	7.87 (.20)	7.87 (.20)	7.84 (.19)	.255[A]	-	-	-
CGAS [1], mean (SD)	67.4 (15.6)	72.1 (14.8)	76.9 (13.4)	<.0001[A]	<.0001[A]	.026[A]	.033[A]
CBCL [2] score, (N=164, 102,158), N, mean (SD)	28.4 (20.9)	23.5 (19.8)	16.8 (14.4)	.000[A]	.000[A]	.013[A]	.101[A]
TRF [2] score, (N=141, 88,134), N, mean (SD)	28.5 (27.0)	22.3 (25.3)	14.7 (16.7)	.000[A]	.000[A]	.054[A]	.154[A]
Any lifetime Axis I diagnosis [3]	38.3	36.9	17.6	<.0001[C]	<.0001[C]	<.0001[C]	.814 [C]
Any lifetime ADHD diagnosis [4]	19.2	10.7	8.2	.009 [C]	.004 [C]	.493 [C]	.064 [C]
Any lifetime DBD diagnosis [5]	7.2	3.9	1.3	.028 [C]	.008 [C]	.165 [C]	.264 [C]
Child´s home environment							
Living with both biological parents, %	38.3	53.4	85.5	<.0001[C]	<.0001[C]	<.0001[C]	.015[C]
Living with index [8] parent, %	61.1	68.9	93.7	-	-	-	.191[C]
Living with a single parent, %	35.9	31.1	9.4	<.0001[C]	<.0001[C]	<.0001[C]	.413[C]
PSP [6] primary caregiver [7] (N=165, 103,159), mean (SD)	72.7 (14.2)	74.5 (14.0)	83.6 (9.4)	<.0001[A]	<.0001[A]	<.0001[A]	.740[A]
Primary caregiver is index	45.5	53.4	-	-	-	-	.208
Index [9] Parents , N	167	102	163	-	-	-	-
Female, %	55.7	53.9	55.8	.948[C]	-	-	-
Age at child´s birth, mean (SD)	29.66 (5.85)	33.27 (7.14)	32.79 (4.66)	<.0001[A]	<.0001[A]	1.000[A]	<.0001[A]

PSP [6] (N=133, 91, 156), mean (SD)	65.3 (15.7)	69.5 (13.4)	83.4 (10.3)	<.0001[A]	<.0001[A]	<.0001[A]	.055[A]
Employed/studying [8] (N=156, 96, 161), %	47.4	56.3	92.5	<.0001[C]	<.0001[C]	<.0001[C]	.174 [C]
Educational information, N	145	96	158				
Primary/lower secondary, %	32.4	8.3	3.2				
Upper secondary, vocational, short-cycle tertiary, %	43.4	41.7	50.0	<.0001[L]	<.0001[L]	.831[L]	<.0001[L]
Bachelor degree, equivalent or higher, %	24.1	50.0	46.8				
Non-index [10] Parents, N	155	100	151	-	-	-	-
Female, %	43.9	46.0	43.7	.928[C]	-	-	-
Age at child´s birth, mean (SD)	30.47 (6.29)	33.11 (5.46)	33.07 (4.23)	<.0001[A]	<.0001[A]	1.000[A]	<.0001[A]
PSP [6] (N=138, 86, 146), mean (SD)	75.6 (14.5)	81.5 (13.0)	85.0 (8.9)	<.0001[A]	<.0001[A]	.097[A]	.001[A]
Employed/studying [8] (N= 147, 96, 148), %	74,1	88.5	95.3	<.0001[C]	<.0001[C]	.0495[C]	.006[C]
Educational information, N	146	93	149				
Primary/lower secondary, %	18.1	5.5	3.4				
Upper secondary, vocational, short-cycle tertiary, %	50.7	42.9	50.3	.001[L]	.001[L]	.405[L]	<.001[L]
Bachelor degree, equivalent or higher, %	31.3	51.6	46.3				

FHR: Familial High-Risk; BP: Bipolar disorder; SZ: Schizophrenia.
In case information is not available for all participants an N has been added to indicate the number of individuals the result has been calculated from.
In the case of siblings; parent information is only included from the first included sibling in order not to count the same parent twice. This results in a lower number of parent couples than children.
[1] CGAS: Children's Global Assessment Scale. (Shaffer D. A Children's Global Assessment Scale (CGAS). Arch Gen Psychiatry. 1983 Nov 1;40(11):1228.)
[2] CBCL: Child Behavior Check List, TRF: Teachers Report Form (Achenbach, T. M., & Rescorla, L. A. (2001). Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.)
[3] Any lifetime Axis I diagnosis, [4] Any lifetime Attention Deficit/Hyperactivity Disorder (ADHD) diagnosis, [5] Any lifetime Disruptive Behaviour Disorder (DBD) diagnosis. All diagnosis were assigned using the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL (Kaufman et al., 1997). The DBD diagnosis was constructed by combining the conduct disorder and oppositional defient disorder diagnoses.
[6] PSP: The Personal and Social Performance Scale. (P.L. Morosini, L. Magliano, L. Brambilla, S. Ugolini, R. Pioli Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning Acta Psychiatrica Scandinavica, 1001 (2000), pp. 323–329)

[7] Primary caregiver is defined as the parent or foster parent that knows the child best and spends most time with the child

[8] Employed or studying is defined as being under employment (including temporary leave) or adhering to an acknowledged education for a minimum of 15 hours weekly.

[9] Index parent is defined as the parent with a diagnosis of either schizophrenia spectrum disorder or bipolar disorder and their adult matched control.

[10] Non-index parent is defined as the biological parent without a diagnosis of schizophrenia or bipolar disorder.

[A] ANOVA test. Post hoc one-way ANOVA with Least Significant Difference..

[C] Chi square test.

[L] linear by linear association p value is used when an ordinal variable has more than two categories.

Table 2. The Strengths and Difficulties Questionnaire descriptive mean scores and standard deviations of participating children from the VIA 7 study.

PRIMARY CAREGIVER RATINGS	FHR-SZ		FHR-BP		Controls		ANOVA	FHR-SZ vs. Controls	FHR-BP vs. Controls	FHR-BP vs. FHR-SZ
	Raw score	T-score	Raw score	T-score	Raw score	T-score				
Participants, N	167		103		159					
	Mean (SD)						*p*-value	*p*-value		
Total Difficulties	9.34 (6.49)	59.6 (16.3)	7.08 (5.66)	54.1 (13.7)	5.45 (4.32)	50.0 (10.0)	<.001	<.001	.026	.008
Emotional Symptoms	2.44 (2.18)	56.8 (14.5)	2.10 (2.35)	54.5 (15.5)	1.43 (1.52)	50.0 (10.0)	<.001	<.001	.025	.454
Conduct Problems	1.69 (1.65)	59.5 (17.0)	1.10 (1.40)	53.9 (14.3)	0.75 (1.15)	50.0 (10.0)	<.001	<.001	.041	.011
Hyperactivity	3.77 (2.89)	55.8 (13.3)	2.97 (2.63)	52.0 (11.9)	2.53 (2.23)	50.0 (10.0)	<.001	<.001	.323	.046
Peer Problems	1.43 (1.85)	56.0 (15.9)	0.91 (1.43)	51.5 (11.9)	0.74 (1.25)	50.0 (10.0)	<.001	<.001	.519	.026
Prosocial Behaviour	8.28 (1.86)	52.7 (13.1)	8.73 (1.60)	49.2 (10.7)	8.67 (1.41)	50.0 (10.0)	.039	.093	.810	.045

TEACHER RATINGS	FHR-SZ		FHR-BP		Controls		ANOVA	FHR-SZ vs. Controls	FHR-BP vs. Controls	FHR-BP vs. FHR-SZ
	Raw score	T-score	Raw score	T-score	Raw score	T-score				
Participants, N	134		91		141					
	Mean (SD)						*p*-value	*p*-value		
Total Difficulties	8.31 (7.02)	57.3 (13.6)	6.75 (7.04)	54.0 (13.9)	4.67 (5.08)	50.0 (10.0)	<.001	<.001	.048	.180
Emotional Symptoms	1.93 (2.07)	54.3 (11.4)	1.78 (2.33)	53.5 (12.7)	1.16 (1.83)	50.0 (10.0)	.003	.003	.072	.885
Conduct Problems	1.37 (2.05)	57.0 (16.5)	.89 (1.66)	53.0 (13.4)	0.51 (1.21)	50.0 (10.0)	<.001	<.001	.156	.123
Hyperactivity	3.50 (3.05)	54.5 (10.7)	2.97 (2.92)	52.2 (10.8)	2.35 (2.87)	50.0 (10.0)	.002	.001	.258	.277
Peer Problems	1.51 (1.93)	57.1 (16.1)	1.11 (2.00)	53.8 (16.7)	0.65 (1.20)	50.0 (10.0)	<.001	<.001	.123	.302
Prosocial Behaviour	7.00 (2.54)	55.4 (12.3)	7.52 (2.44)	52.6 (12.0)	8.05 (2.03)	50.0 (10.0)	<.001	<.001	.210	.190

Higher T-scores equal more difficulties and less prosocial behaviour. Group differences calculated on T-scores with Welch ANOVA and post hoc Games-Howell. FHR-BP: Familial high-risk bipolar group FHR-SZ: Familial high-risk schizophrenia group

Table 3. Proportion of children with familial high risk of schizophrenia or bipolar disorder scored above cut-off (within clinical range) compared to controls.

PRIMARY CAREGIVER RATINGS	Raw-score cut-off value closest to the 90th (10th)[1] percentile of the PBC		Controls	FHR-SZ			FHR-BP		
	Girls	Boys	Percent in clinical range	Percent in clinical range	OR (CI)	*p*-value	Percent in clinical range	OR (CI)	*p*-value
Total Difficulties	≥ 14	≥11	9.4	28.1	3.8 (2.0-7.1)	<.001*	19.4	2.3 (1.1-4.8)	.023*
Emotional Symptoms	≥ 5	≥4	7.5	24.0	3.9 (1.9-7.7)	<.001*	18.4	2.8 (1.3-6.0)	.010*
Conduct Problems	≥ 2	≥2	13.8	38.3	3.9 (2.2-6.9)	<.001*	23.3	1.9 (1.0-3.6)	.051
Hyperactivity	≥ 7	≥6	7.5	21.6	3.4 (1.7-6.7)	<.001*	14.6	2.1 (0.9-4.7)	.073
Peer Problems	≥ 3	≥3	6.9	20.4	3.4 (1.7-7.1)	<.001*	11.7	1.8 (0.8-4.2)	.191
Prosocial Behaviour [1]	≤ 6	≤6	10.7	16.2	1.6 (0.8-3.1)	.151	10.7	1.0 (0.4-2.2)	.998
TEACHER RATINGS	Raw-score cut-off value closest to the 90th (10th)[1] percentile of the PBC		Controls	FHR-SZ			FHR-BP		
	Girls	Boys	Percent in clinical range	Percent in clinical range	OR (CI)	*p*-value	Percent in clinical range	OR (CI)	*p*-value
Total Difficulties	≥12	≥13	8.5	26.1	3.8 (1.9-7.7)	<.001*	15.4	2.0 (0.9-4.4)	.110
Emotional Symptoms	≥5	≥4	10.6	16.4	1.7 (0.8-3.3)	.163	17.6	1.8 (0.8-3.8)	.133
Conduct Problems	≥3	≥3	5.0	24.6	6.3 (2.7-14.7)	<.001*	12.1	2.6 (1.0-7.1)	.055
Hyperactivity	≥5	≥8	9.2	15.7	1.8 (0.9-3.8)	.108	13.2	1.5 (0.7-3.4)	.344
Peer Problems	≥2	≥3	8.5	26.1	3.8 (1.9-7.7)	<.001*	14.3	1.8 (0.8-4.1)	.170
Prosocial Behaviour [1]	≤5	≤4	6.4	20.1	3.7 (1.7-8.2)	.001	15.4	2.7 (1.1-6.4)	.031

SDQ clinical cut-off scores (Clinical range= T-score > 65) are calculated from the control group. Odds ratios (OR) and *p*-values are calculated from T-scores

[1]The Prosocial scale is a reversed scale with higher scores equalling better performance.

FHR-BP: Familial high-risk bipolar disorder group; FHR-SZ: Familial high-risk schizophrenia group.

SDQ: The Strengths and Difficulties questionnaire (Goodman, 1997).

*Significant value: For the Total Difficulties Scale a *p*-values of <.05 are considered significant. For the four difficulties scales (Emotional Symptoms, Conduct Problems, Hyperactivity and Peer Problems) and the Prosocial Behaviour scale a *p*-value of <.01 is considered significant according to Bonferroni alfa level correction for multiple comparisons (0.05/5=.01)

Table 4a. Ability of SDQ-P and CBCL to discriminate between cases with and without disorders within the FHR groups analysed by ROC curves.

Problem scale SDQ-P/CBCL	Outcome measure (N with/without)	Area under curve (AUC) (95% CI)		AUC SDQ-P vs CBCL	Sensitivity		Specificity	
		SDQ-P	CBCL	*p*-value [a]	SDQ-P	CBCL	SDQ-P	CBCL
Total scale	Any axis I [b] (101/165)	.79 (.73.-84)**	.78 (.72-.83)**	.752	48.5	41.6	89.7	88.5
	FHR-SZ (63/101)	.82 (.75-.89)**	.80 (.72-.87)	.454	57.1	46.0	90.1	88.1
	FHR-BP (38/64)	.75 (.65-.84)	.76 (.67-.86)	.611	34.2	34.2	89.1	90.6
Hyperactivity scale	Any attention-deficit hyperactivity disorder Total cohort (43/226)	.92 (.88-.95)**	.88 (.83-.94)**	.085	69.8	67.4	90.7	88.1
Conduct scale	Any disruptive behaviour disorders Total cohort (16/250)	.91 (.85-.97)**	.88 (.77-.99)**	.511	81.3	93.8	82.0	82.8

Table 4b. Ability of SDQ-T and TRF to discriminate between cases with and without disorders within the FHR groups analysed by ROC curves.

Problem scale SDQ-T/TRF	Outcome measure (N with/without)	Area under curve (AUC) (95% CI)		AUC SDQ-T vs. TRF	Sensitivity		Specificity	
		SDQ-T	TRF	*p*-value [a]	SDQ-T	CBCL	SDQ-T	CBCL
Total scale	Any axis I [bc] (86/136)	.75 (.68-.82)**	.76 (.69-.82)**	.810	37.2	43.0	91.2	89.0
	FHR-SZ (55/77)	.77 (.69-.85)**	.78 (.70-.85)**	.789	43.6	43.6	88.3	87.0
	FHR-BP (31/59)	.72 (.60-.83)*	.71 (.59-.83)*	.764	32.3	41.9	93.2	91.5
Hyperactivity scale	Any attention-deficit hyperactivity disorder [c] Total cohort (36/186)	.85 (.78-.91)**	.86 (.80-.91)**	.685	47.2	47.2	91.4	92.5
Conduct scale	Any disruptive behaviour disorders [c] Total cohort (16/206)	.82 (.70-.94)**	.92 (.87-.97)**	.021	68.8	81.3	84.5	88.8

Only children with both an SDQ-P and an CBCL / SDQ-T and TRF, respectively were included in the analysis. Sensitivity and specificity at cut-off score closest to T-score of 65 according to the ROC curve analyses.

* p <.001. ** p <.0001. BP: Bipolar disorder; FHR: Familial high risk; CBCL: Child Behavior Checklist; SDQ: The Strengths and Difficulties Questionnaire; -P: Parent Version; -T: Teacher Version; SZ: Schizophrenia; TRF: Teachers Report Form.

[a] P-value of z test for comparing paired area under ROC curves (AUC) of SDQ and CBCL.

[b] Any axis I excluding elimination disorders. [c] Four children who had an SDQ-T/TRF did not have a diagnostic assessment.

Table S1. CGAS mean scores of the SDQ Total Difficulties Scale below and above cut-off groups.

PRIMARY CAREGIVER RATINGS	Below Cut-off group		Above Cut-off group			*p*-value
	N	CGAS mean (SD)	N	CGAS mean (SD)	Mean difference (95% CI)	
Total cohort	347	75.8 (13.2)	82	55.9 (12.1)	19.9 (16.8-23.0)	<.0001
FHR-SZ	120	72.7 (13.5)	47	53.7 (11.7)	19.1 (14.7-23.5)	<.0001
FHR-BP	83	75.5 (13.2)	20	57.6 (12.1)	18.0 (11.6-24.4)	<.0001
Controls	144	78.6 (12.5)	15	60.9 (12.4)	17.7 (11.0-24.3)	<.0001

TEACHER RATINGS	Below Cut-off group		Above Cut-off group			*p*-value
	N	CGAS mean (SD)	N	CGAS mean (SD)	Mean difference (95% CI)	
Total cohort	303	75.3 (13.8)	59	55.6 (12.6)	19.7 (15.9-23.5)	<.0001
FHR-SZ	99	70.5 (15.6)	34	55.2 (12.1)	15.3 (9.5-21.1)	<.0001
FHR-BP	76	75.8 (12.5)	14	52.6 (12.7)	23.2 (15.9-3054)	<.0001
Controls	128	78.6 (12.0)	11	60.6 (13.5)	18.0 (10.5-25.6)	<.0001

SDQ: The Strengths and Difficulties Questionnaire. CGAS: Children's Global Assessment Scale.

FHR-BP: Familial high-risk bipolar group FHR-SZ: Familial high-risk schizophrenia group

Table S2. Inter-rater agreement between.

SDQ-P/SDQ-T	ICC (95%CI)			
	Total cohort	FHR-SZ	FHR-BP	Controls
N	347	129	85	133
Total Difficulties scale	.68 (.60-.74)**	.67 (.54-77)**	.64 (.44-.77)**	.60 (.44-.72)**
Emotion scale	.46 (.33-.56)**	.36 (.10-.54)*	.57 (.34-.72)**	.34 (.08-.53)*
Conduct scale	.62 (.53-.69)**	.64 (.49-.75)**	.52 (.26-.69)**	.50 (.39-.65)**
Hyper scale	.71 (.64-.77)**	.77 (.68-.84)**	.58 (.36-.73)**	.69 (.53-.77)**
Peer scale	.56 (.45-.64)**	.33 (.05-.53)*	.72 (.57-.82)**	.64 (.49-.74)**
Prosocial scale	.31 (.14-.45)**	.40 (.14-.59)**	.19 (-.17-.45)^{NS}	.17 (-.14-.40)^{NS}

CBCL/TRF	ICC (95%CI)			
	Total cohort	FHR-SZ	FHR-BP	Controls
N	479	160	96	159
Total scale	.63 (.55-.69)**	.64 (.51-.74)**	.53 (.30-.69)**	.58 (.43-.69)**
Conduct scale	.68 (.62-.74)**	.67 (.55-.76)**	.70 (.55-.80)**	.53 (.36-.66)**
Hyper scale	.60 (.52-.68)**	.64 (.51-.73)**	.53 (.30-.69)**	.58 (.42-.69)**

ICC two-way random effects model absolute agreement type *p-value <.05. **p-value <.001
ns = not significant. SDQ: The Strengths and Difficulties Questionnaire (Goodman, 2001)

Paper II.

Executive functions in seven-year-old children of parents with schizophrenia or bipolar disorder compared with controls compared with controls - The Danish High Risk and Resilience Study - VIA 7, a register-based cohort study (In Review)

Executive functions in seven-year-old children of parents with schizophrenia or bipolar disorder compared with controls – The Danish High Risk and Resilience Study – VIA 7, a population-based cohort study

Abbreviated title: Executive functions in familial high-risk children

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Acknowledgements

This work was supported by TrygFonden, the Mental Health Services of the Capital Region of Denmark, The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Aarhus University, and the Beatrice Surovell Haskell Fund for Child Mental Health Research of

Copenhagen.The authors extend their gratitude to all the families for their will to participate and to generously lent us their time and effort. The authors would also like to express their gratitude to M. Skjærbæk, A. Søndergaard, M. Gregersen, A. Ranning, H. Jensen, C. Gregersen, D-M. Henriksen, H. Stadsgaard, K. Zahle and M. Melau for contributing to data collection; to C. Bøcker Pedersen for assistance in retrieving the register extract; to M. Chaine for help with data management; to P.B. Mortensen T. Werge, D. Hougaard and A. Børglum for collaboration in *i*PSYCH. The authors have no conflict of interest.

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Word count:
Abstract, key words, abbreviations = 289
Article text = 3513

Abstract:

Background *Cognitive impairments are well-established in schizophrenia (SZ) and bipolar disorder (BP) and executive functions (EF) impairments are likely a key feature. Studies of behavior rated EF in young children at familial high risk of SZ (FHR-SZ) are scarce and to our knowledge non-existent in young children at familial high risk of BP (FHR-BP).*

Aims: *We aimed to compare behaviour rated EF of FHR-SZ, FHR-BP and control children.*

Methods*: A nationwide population-based cohort of 522 seven-year-old children with parents diagnosed with either SZ (N=202) or BP (N=120) and matched controls (N=200) were recruited using the Danish national registries. Children were assessed with the Behavior Rating Inventory of Executive Functions rated by primary caregivers and teachers.*

Results: *According to primary caregiver assessments, FHR-SZ children displayed widespread EF impairments and had an odds ratio of 3.7 (2.0-6.9) of having clinically significant global EF impairments compared to controls. FHR-BP children were most severely impaired regarding EF related to emotional control and had an odds ratio of 2.5 (1.2-5.1) of clinically significant global EF impairments compared to controls. Teacher assessments were overall comparable to primary caregiver assessments.*

Conclusions: *Already at age seven, children with a parental history of SZ or BP displayed significant impairments of EF in everyday life situations. FHR-SZ children displayed widespread impairments of EF whereas FHR-BP children were specifically impaired on emotional control. Thus, emotional control appears to be a shared deficit between the two FHR groups and may reflect shared risk factors. Clinicians should be aware of potential EF impairments in children with FHR children.*

Keywords:

Schizophrenia. Bipolar disorder. Familial high risk. Executive function.

Abbreviations:

BP: Bipolar disorder

BRIEF: Behavior Rating Inventory of Executive Function

EF: Executive Functions

FHR: Familial High Risk

GEC: Global Executive Composite

SZ: Schizophrenia

Introduction:

Cognitive impairments are well-established in schizophrenia (SZ) and bipolar disorder (BP) (Emre Bora, Yucel, & Pantelis, 2009; Reichenberg & Harvey, 2007b) and a significant overlap of cognitive impairments is suggested but with less severe impairments in individuals with BP [3]. Robust evidence points towards executive functions (EF) as a key feature of cognitive impairments in SZ (Li, Cao, Shao, & Xue, 2014b; Raffard & Bayard, 2012). EF deficits are detectable early in life in individuals who later develop SZ (Reichenberg et al., 2010a) and in first degree relatives, including offspring of parents diagnosed with SZ (E. Bora, 2017b; Burton et al., 2018b; Christiani et al., 2019b; Hemager et al., 2018b). EF of individuals who later develop BP are less examined, and results are conflicting (Emre Bora & Pantelis, 2015; Meyer et al., 2004b) as are results regarding offspring of parents diagnosed with BP with findings of significantly impaired as well as intact EF (E. Bora, 2017b; Burton et al., 2018b; Hemager et al., 2018b; Kamilla W. Miskowiak et al., 2017). These discrepancies may be explained by methodological and/or age differences in the included offspring (Klimes-Dougan, Jeong, Kennedy, & Allen, 2017b; de la Serna et al., 2016).

The most convincing differences of cognition between unaffected first-degree relatives of individuals with BP and controls are related to emotional or motivational processes (Kamilla W. Miskowiak et al., 2017).

EF are most commonly assessed by neuropsychological tasks in experimental conditions (Performance-based) or by questionnaires assessing complex real-world behaviour (Behaviour-based), both designed to measure one or more components of EF [16]. Consistently small and mostly non-significant correlations between performance-based and ecologically valid, behaviour-based EF measures suggest that both types of measures contribute independently with valuable information by assessing different aspects of EF (Toplak et al., 2013).

Studies of cognitive functioning in offspring of parents with BP before 10 years of age are limited (E. Bora & Özerdem, 2017b; Burton et al., 2018b; Hemager et al., 2018b; Klimes-Dougan et al., 2017b), and to our knowledge no studies of behaviour-based EF assessment exist involving 7-year-old children of parents with BP. Investigating EF and EF profiles in young children at familial high risk of BP and SZ will potentially elucidate specific deficits related to familial risk-status. Further, including two disorders with shared genetic risk factors [19] in the same study allows identification of shared and nonshared EF deficits as well as potentially separate endophenotypes [20] .

In the present study, we examined EF in seven-year-old offspring at familial high risk (FHR) for SZ or BP, by means of behaviour ratings. We hypothesised that children of parents diagnosed with either bipolar disorder (FHR-BP) or schizophrenia (FHR-SZ) would have EF impairments and more often clinically significant impairments compared to control children. We expected the FHR-BP group to perform intermediate between the FHR-SZ group and the controls. Finally, we expected that FHR-SZ children would show impairments across all EF but with a jagged pattern of impairment,

whereas FHR-BP children would primarily display impairment of EF specifically related to emotional processing.

Methods:

Participants:

The Danish Psychiatric Central Research Register (Mors et al., 2011a) and the Danish Civil Registration System (Pedersen, 2011a) were used to form The Danish High Risk and Resilience Study – VIA 7 (the VIA 7 study), a nationwide population-based cohort study of 522 seven-year-old children, born and living in Denmark with one, two or neither of their parents diagnosed with bipolar disorder (ICD-10 code: F30 and F31 or ICD-8 codes 296.19 or 296.39) or schizophrenia spectrum psychosis (ICD-10 codes F20, F22 or F25 or ICD-8 codes 295, 297, 298.29, 298.39, 298.89 or 298.99). Control children were matched via register data to FHR-SZ children on age, sex and municipality prior to inclusion. The primary caregiver was the key informant concerning the child and defined as the adult that spent the most time with and knew the child best at time of the study. The VIA 7 study design has been described in detail elsewhere (Thorup et al., 2015a).

Measures:

We measured EF with the Behavior Rating Inventory of Executive Function (BRIEF (G. A. Gioia et al., 2000)); Danish parent (rated by the primary caregiver) and teacher version (G. Gioia et al., 2005). The BRIEF consists of 86 statements about EF problem behaviours. Higher scores indicate worse functioning. Aspects of EF are reflected in eight non-overlapping clinical scales; Inhibit, Shift, Emotional Control, Initiation, Working Memory, Planning, Organization of Materials, and Monitoring. The eight clinical scales are summed into a Global Executive Composite (GEC) score. Cronbach's alpha on GEC for caregiver and teacher-rated BRIEF was calculated to be 0.97 and 0.98 respectively in the VIA 7 study cohort. We utilized the large population-based control group (N=190) to construct T-score reference group values adjusted for sex of the child. Effect of age was non-significant in all groups. Clinical cut-off scores were defined as 1.5 standard deviations above the mean (T-score>65) (G. Gioia et al., 2005).

Procedures:

The VIA 7 study was approved by the Danish Data Protection Agency (J.nr.:2012-58-0004). The Danish National Committee on Health Research Ethics evaluated the study and concluded that further approval was not required due to the observational nature of the study. Informed written consent was obtained for all participants or custody holders, including a separate written consent to contact the child's teacher.

Statistical analysis:

Between-group differences on demographic and clinical characteristics were analysed by ANOVA, chi-square test or the Mantel-Haenszel linear-by-linear test of association, as appropriate.

Between group differences of BRIEF GEC scores were analysed by Welch ANOVA followed by Games-Howell post hoc test. The eight clinical scales were analysed jointly by MANOVA reporting Wilks' lambda statistics. In case of a significant result, Welch ANOVA was performed on each of the eight individual clinical scales with Games-Howell post hoc test .

Exploratory analysis by one-way MANOVA with the child's sex as fixed factor and the eight clinical scales as dependent variables was performed to identify potential sex differences in EF associated with FHR-SZ and FHR-BP status. Pillai's trace results are reported.

We performed one-way repeated-measures ANOVA to detect potential differences in EF profile shapes between the three groups. Group was set as between-subject factor, and the eight clinical scales were set as within-subject repeated measures. Greenhouse-Geisser corrections are reported. If deviations from flatness (in the BRIEF-clinical scales profiles of the FHR-SZ/FHR-BP group compared to the control group) was suggested by a significant group by BRIEF-clinical scale profile interaction, the individual clinical scales were assessed using paired-samples t-test to identify which EF-functions were relatively differently impaired within each of the two high risk groups.

Between-group differences in the proportion of children scoring above clinical cut-off were analysed by logistic regression with odds ratios reported as effect size measures. This analysis was performed to quantify the clinical significance of group differences by assessing the prevalence of potentially clinially relavent impairment in each of the three groups.

An alpha level of 0.05 was set for analyses on GEC. The alpha level was adjusted to 0.00625 (Bonferroni adjustment) for the eight clinical scales to counter the risk of type I errors when performing multiple comparisons. All analyses were performed on BRIEF T-scores.
IBM SPSS Statistics, version 25.0 was used for all statistical analyses.

Results

515 children were assessed with BRIEF by either a primary caregiver (N=493), teacher (N=417) or both (N=/439). There were no significant differences between groups regarding age or sex of the children. In FHR-BP families the primary caregiver was more often also the parent with the indicator diagnosis than in FHR-SZ families (57.3% vs 44.0%, P =.023) (Table 1).

Primary caregiver ratings: The GEC mean score differed significantly between the three groups (Welch's F (2, 265.360) = 10.332 P < .0001) according to Welch ANOVA. Post hoc Games-Howell analyses exposed that GEC mean scores of both the FHR-SZ group (mean difference = 5.4, 95% CI 2.5 to 8.3) and the FHR-BP group (mean difference = 3.5, 95% CI 0.2 to 6.9) were significantly

higher than that of the control group. GEC mean scores did not differ significantly between the FHR-SZ and the FHR-BP group (Table 2A).

The eight clinical scales differed across groups as analysed by MANOVA (F (16,952) = 2.061; Wilks' Λ = .934; partial $\eta 2$ = .033; P = .0082). Games-Howell analyses revealed the FHR-SZ group mean scores significantly higher than control group mean scores on all clinical scales, except the Plan/Organize and Organization of Materials scales which were non-significant after Bonferroni correction. After Bonferroni corrections, the FHR-BP group scored significantly higher than the control group on the Emotional Control scale only (mean difference = 4.4, 95% CI 1.1 to 7.7). The FHR-SZ and FHR-BP groups were non-significantly different on all clinical scales (Table 2A).

The percentage of children with a GEC score above cut-off was significantly higher for both FHR-groups compared to the control group (Table 2B) as analysed by logistic regression. 24.2% of the FHR-SZ and 17.6% of the FHR-BP children scored above cut-off versus 8% of the population-based controls (Figure 1A). This corresponds to an odds ratio of 3.7 (95% CI 2.0-6.9; P <.0001) for FHR-SZ children and 2.5 (95% CI 1.2-5.1; P = .0146) for FHR-BP children. The percentage of children above cut-off was also significantly higher in the FHR-SZ group compared to the control group on all eight clinical scales (Table 2B). In the FHR-BP group the percentage of children above cut-off was higher compared to the controls on all clinical scales, but the difference was statistically non-significant after Bonferroni corrections. There were no significant differences in odds ratios between the two FHR-groups on any of the clinical scales (Table 2B and Figure 1A).

The profile shapes of BRIEF clinical scales of the three groups did not differ as analysed by repeated measures ANOVA (F (11.181, 27000.171 Greenhouse-Geisser) = 1.293, P = .221).

One-way MANOVA on stratified T-scores revealed no sex differences of EF neither for the FHR-SZ group (F (8, 181) = 1.514, P = .155, Pillai's Trace = .063) nor the FHR-BP group (F (8, 99) =.420, P = .907, Pillai's Trace = .033) (Figure 2A).

Teacher ratings: Analyses revealed significant differences between groups on GEC mean scores (Welch's F (2, 243.648) = 15.887, P <.0001). Both FHR groups scored higher than the controls, but only the FHR-SZ group (mean difference = 7.1, 95% CI 4.1 to 10.0) differed significantly from the control group in the post hoc Games-Howell analyses (FHR-BP group (mean difference = 3.2, 95% CI -0.4 to 6.7)). The two FHR-groups differed significantly from each other (mean difference = 3.9, 95% CI 0.04 to 7.7) (Table 2A).

MANOVA on clinical scales revealed significant differences across groups, (F (16,848) = 3.238; Wilks' Λ = .888; partial $\eta 2$ = .058, P = <.0001). Mean scores of both FHR groups were higher than the control group on all clinical scales but only the FHR-SZ group and the control group differed significantly from each other according to post hoc Games-Howell analyses with Bonferroni correction. (Table 2A).

The prevalence of a GEC score above cut-off was significantly higher for both FHR-groups compared to the control group (Table 2B), with 29.9% of the FHR-SZ and 19.4% of the FHR-BP children versus 9.6% of the population-based controls. FHR-BP children had an odds ratio of a score above cut-off on the Emotional Control clinical scale of 3.2 (95% CI 1.6-6.8; *P*= .0018) compared to controls.

The profile shapes of BRIEF clinical scales did not differ between the three groups as analysed by repeated measures ANOVA on BRIEF teacher ratings (*F* (7.482, 1612.326 Greenhouse-Geisser) = 1.548, *P* = .141.).

One-way MANOVA revealed no sex differences of EF neither for the FHR-SZ group (*F* (8, 155) =1.662, *P* =.112, Pillai's Trace = .079) nor the FHR-BP group (*F* (8, 94) =.581, *P* =.792, Pillai's Trace = .047) (Figure 2B).

Discussion

In this large, nationwide, and population-based cohort study, seven-year-old children with a parental history of schizophrenia or bipolar disorder demonstrated significant global behaviour-based EF impairments compared with a population-based control group. FHR-SZ children displayed widespread EF deficits whereas FHR-BP children were specifically impaired on emotional control.

The widespread EF deficits in FHR-SZ offspring are in agreement with several other studies that report behaviour-based [4] and performance-based [7, 10] EF deficits in FHR-SZ offspring. The FHR-BP group differed from the population-based control group on the Emotional Control scale only, supporting our hypothesis of specific impairments of EF related to emotional processing in FHR-BP children. However, the EF profiles of the FHR-BP and the FHR-SZ groups did not differ from that of the population-based controls. This finding of a flat deficit profile, may support the notion that EF deficits in FHR-SZ reflect a generalised cognitive common factor impairment [26, 27]. On the other hand, the non-jagged EF profile may also be due to the young age of the participants. It has been argued that EF in childhood are largely undifferentiated, and with maturation will become more differentiated with more distinct functioning [28]. Consequently, specific deficits may become apparent with maturation. The latter is supported by several studies that find differential impairments of EF in individuals with SZ together with seemingly preserved overall neuropsychological functioning [5, 26]. This pattern is also present in this cohort regarding the FHR-BP children, as we in the current study find behaviour-based EF impairments, whereas we found intact abilities across numerous cognitive functions in a previous study on performance-based cognitive functions (including EF) [10].

In alignment with previous findings the FHR-BP group was, by both their primary caregivers and teachers, consistently rated intermediate between the FHR-SZ group and the population-based

controls on both the GEC and the eight clinical scales [7]. Furthermore, the FHR-BP offspring did not differ from the FHR-SZ group on any of the clinical scales. These findings support the notion that already at a young age, FHR-BP children have reduced behaviour-based EF abilities compared with population-based controls.

In the aforementioned study of cognitive data from the VIA 7 study cohort, performance-based measures of EF (including EF domains; working memory and aspects of flexibility and verbal fluency) revealed similar results to those of the present study of behaviour-based assessment of EF with regards to the FHR-SZ group. The FHR-BP group however, performed comparable to controls on all performance-based measures of EF and different from the FHR-SZ group on several aspects of the performance-based measures of EF [10]. In the present analyses however, FHR-SZ and FHR-BP groups were non-significantly different on behaviour-based assessment of EFacording to primary-caregiver ratings. This suggests that parental behaviour ratings are a more sensitive measure of EF's impairments (not including EF related to emotional or motivational processes as this was not included in the performance-based assessment) in a FHR-BP population of this young age (Cohens D effect sizes below 0.15 for performance-based assessments vs. 0.14-0.35 for behaviour-based assessment by primary caregiver rated BRIEF), whereas subtle EF deficits may not be detected in a highly structured neuropsychological test setting. Our findings could also indicate that behaviour- and performance-based measures assess different aspects of EF. This is in line with a previous finding of few or no significant associations between performance-based measures and the BRIEF, in a population of children with acquired or developmental neurological disorders as well as controls (G. A. Gioia et al., 2002). Furthermore, evidence from the present study on FHR-BP children and from previous studies of individuals with BP and their relatives [13], indicates that EF impairments most severely pertain to aspects of EF related to emotional and motivational processing which are often not included in performance-based assessments of EF. The EF performance tasks of the previously published VIA 7 study also did not include such measures [10].

The lack of between sex differences of EF within groups indicate that apparent EF differences between male and female FHR children are reflective of sex differences also present in the population-based controls.

The finding that the FHR-SZ and FHR-BP groups are not equally affected on their EF abilities suggests that despite partially shared risk factors the two risk groups have distinct neurodevelopmental pathophysiology and trajectories. Emotional Control may represent a partially shared endophenotype of schizophrenia and bipolar disorder whereas the widespread and more severe EF deficits found in FHR-SZ children compared to FHR-BP children may reflect non-shared risk factors of schizophrenia.

Large interindividual differences in maturation of EF exist (Brocki & Bohlin, 2004b; Brydges, Fox, Reid, & Anderson, 2014b; Friedman et al., 2008) as well as differential developmental

trajectories of different EF components [33]. Thus, between-group differences in the present study may represent differences in maturational pace and pathways specific for each FHR group. A longitudinal follow-up study of a birth cohort where some individuals eventually developed SZ found both static cognitive deficits and an increasing developmental lag as well as differences in developmental pathways compared to non-SZ subjects (Reichenberg et al., 2010a). As EF develop from infancy and through young adulthood (Anderson, 2002b; Best & Miller, 2010b), with rapid developmental spurts before the age of five, around age seven, and again in adolescence (Brocki & Bohlin, 2004b), a wide age range will obscure acknowledgement of a possible developmental lag. Previous high-risk studies have been relatively small and often included children within a wide age range and children into the age of puberty or older [7, 18, 36]. Including a large sample within a very narrow age range, as is in the VIA 7 study, contributes to a higher degree of homogeneity. Thus, the longitudinal VIA 7 study design enables us to determine if the between group EF differences found at age seven are stable effects or will diminish or increase over time.

Incorporating results from both primary caregivers and teacher ratings allows us to investigate whether the same patterns emerge in FHR-SZ and FHR-BP children, compared with population-based controls in two different environments that pose different requirements and from informants with different perspectives and relations to the child. Analyses of teacher ratings indicate that teachers assess FHR-SZ offspring to have widespread EF impairments with significant differences in EF, compared to the population-based controls on all clinical scales. Contrary to this, the two scales Plan/Organize, and Organizations of Materials were non-significantly different from population-based controls when assessed by primary caregivers, which may indicate higher demands on these aspects of EF in a school setting. This also highlights the clinical usability of behaviour-based measures of EF as demands can vary across settings and highlights the necessity of assessing functioning in diverse environments to obtain an ample evaluation.

The VIA 7 study is unique, as it is the largest and to date the only population-based familial high-risk study of children born to parents with SZ or BP, and matched controls. This is the first study to assess behaviour-rated EF in everyday life in FHR-BP children at the young age of seven-years.

The inclusion of children based on national register data, and the use of a population-based control group instead of a healthy control group, eludes referral bias and generates more generalisable results. However, it is important to keep in mind that even though familial predisposition is the single most influential risk factor of SZ and BP [37], most cases occur in individuals without close family disposition. Therefore, translation of results from familial high-risk studies to the specific disorders in general is cautioned. There are several limitations to the present study. We cannot be sure that we recruited the most severely affected families, or oppositely, if participation was motivated by specific concerns for the child’s wellbeing and that we hereby

included children with more difficulties. The latter was reported as a reason for participation for some at risk families but could be true also for population-based control families.

Potential associations between primary caregiver-reported impaired EF in the children and the severity of primary caregiver's illness is important to consider. Studies of rater bias on account of the rater's own mental illness; mainly focused on parental depression and child psychopathology, show mixed results [38]. One recent study found that BP parents' mood state, especially if manic, significantly affected questionnaire reports regarding their offspring's psychopathology. The study showed that parents with a current mood episode rated a higher level of psychopathology in their children and this was not reflected in teacher or self-reports (Maoz et al., 2014). Thus, including information from other sources e.g. the children themselves or teachers is valuable. In our study, we found that teacher ratings both supported and complemented the primary caregiver ratings. Cognitive abilities, including EF, have a high degree of heritability [32]. Nevertheless, home environment and socioeconomic status of the family can potentially influence the EF of children [4, 39]. This is an important factor to consider as we know that especially FHR-SZ children more often live in insufficient home environments (Gantriis et al., 2019) and have parents with lower educational levels, whereas parents in both high risk groups have lower rates of employment (Ellersgaard et al., 2018). However, we did not correct for these factors as this could remove key effects of being an FHR-child, and we were interested in the overall genetic and environmental effects. A future study goal could be the effect of social factors as well as identification of subgroups within and across the high-risk groups to address heterogeneity within the disorders.

Conclusion

At this early stage of life, a relatively large proportion of both FHR groups had EF impairments in everyday-life situations that exceeded clinical threshold. These EF impairments pose a genuine risk of affecting these FHR children's ability to engage in practical, social and academic activities (Castellanos, Kronenberger, & Pisoni, 2018b). Both pre-clinically and in clinical settings a heightened awareness of possible EF impairments in FHR children is warranted, as EF's are crucial for overall functioning and could represent a key target for intervention. The BRIEF questionnaire could function as a low cost and accessible measure to identify children in need of intervention. Adequate and appropriate support e.g.in their educational setting and in their home environment could hopefully improve well-being and support a positive development and potentially prevent transition to mental illness.

- Executive functions (EF) deficits are detectable early in life in individuals who later develop schizophrenia (SZ) and also in their offspring. EFs deficits are also present in bipolar disorder (BP) but are less established premorbid and sparsely investigated in young offspring.
- To our knowledge, we are the first to investigate and demonstrate behaviour rated EFs impairments in young BP offspring also found in SZ offspring. In both groups, a relatively large proportion demonstrates EF impairments above clinical threshold.
- Awareness of possible EFs deficits in high-risk offspring is warranted both preclinically and in a clinical setting. EFs impairments affect both social and academic functioning and may be a key target for intervention.

Declarations

Funding: This work was supported by TrygFonden, the Mental Health Services of the Capital Region of Denmark, The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Aarhus University, and the Beatrice Surovell Haskell Fund for Child Mental Health Research of Copenhagen.

Conflicts of interest: The authors have no conflicts of interest to disclose.

Ethics approval: The VIA 7 study was approved by the Danish Data Protection Agency (J.nr.:2012-58-0004). The Danish National Committee on Health Research Ethics evaluated the study and concluded that further approval was not required due to the observational nature of the study.

Consent to participate: Verbal and written informed consent was obtained for all participants or custody holders, including a separate written consent to contact the child's teacher.

Availability of data and material: access can be granted upon request

Code availability: Acces can be granted upon request

Author contributions: All authors contributed to the study conception and design. KSS wrote the manuscript and performed data analysis with input from all authors and especially JRMJ and NH. MGP, OM, MN, KJP, JRMJ,AAET, DE contributed to planning of the study and drafting the cohort. KSS,DE, NH, CC, BKB, ANG, DG collected the data. All co-authors critically revised the manuscript and approved the final version.

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Table 1. Demographic and clinical characteristics of participants contributing with behaviour rated executive functions data.

					P-value Pairwise comparison		
	FHR-SZ group	**FHR-BP group**	**Control group**	***P*-value**	**FHR-SZ vs. Control**	**FHR-BP vs. Control**	**FHR-BP vs. FHR-SZ**
Children (N=515), N	200	117	198				
Female, %	46.0	46.2	46.0	.999[C]	-	-	-
Age at inclusion, mean (SD)	7.84 (.22)	7.87 (.20)	7.82 (.20)	.111[A]	-	-	-
CGAS, mean (SD)	68.1 (15.4)	73.6 (15.0)	77.6 (13.5)	<.0001[A]	<.0001[A]	.019[A]	<.001[A]
CBCL, mean (SD)	27.2 (21.1)	23.4 (19.8)	17.0 (14.7)	<.0001[A]	<.0001[A]	.004[A]	.084[A]
Primary Caregivers[a] (N=515), N	200	117	198				
Female, %	87.5	92.3	89.9	.393[C]	-	-	-
Age at child´s birth in years, mean (SD)	30.59 (6.62)	31.83 (5.64)	32.26 (4.24)	.009[A]	.003[A]	.511[A]	.056[A]
Primary Caregiver is index[b], %	44.0	57.3	59.1	-	-	-	.023[C]
PSP, mean (SD)	73.2 (14.1)	74.2 (14.1)	84.4 (9.1)	<.0001[A]	<.0001[A]	<.0001[A]	.489[A]
Employed or studying[c], %	67.2	66.4	91.3	<.0001[C]	<.0001[C]	<.0001[C]	.886[C]
Education,							
Primary/lower secondary, %	17.3	6.1	2.6				
Upper secondary, vocational, short-cycle tertiary, %	44.9	34.8	43.4	<.0001[L]	<.0001[L]	.135[L]	<.0001[L]
Bachelor degree, equivalent or higher, %	37.8	59.1	54.1				

FHR: Familial high risk; BP: Bipolar disorder SZ: schizophrenia; CGAS: Children's Global Assessment Scale (D. Shaffer et al., 1983); CBCL: Child Behavior Checklist school-age version (Achenbach & Edelbrock, 1983b; Henriksen, Nielsen, & Bilenberg, 2012); PSP: The Personal and Social Performance Scale (Morosini, Magliano, Brambilla, Ugolini, & Pioli, 2000b). [A] One-way ANOVA; [C] Chi square test.; [L] linear by linear association.

[a]Primary caregiver is defined as the parent or foster parent that knows the child best and spends most time with the child.

[b]Index is defined as the parent with a diagnosis of either schizophrenia spectrum disorder or bipolar disorder and their adult matched control.

[c]Employed or studying is defined as being either in employment (including temporary leave e.g. maternity leave) or adhering to an acknowledged education for a minimum of 15 hours weekly.

Table 2. The Behavior Rating Inventory of Executive Function (BRIEF) Caregiver- and Teacher reports of 515 seven-year-old children.

		Global Executive Composite (GEC)	Clinical scales							
			Inhibit	Shift	Emotional control	Initiate	Working Memory	Plan/ Organize	Organiza-tion of Materials	Monitor
A) T-score means, standard deviations and statistical significance of the difference in T-scores between groups. T-scores are computed by gender and with the control group as reference group (T-score (SD) = 50 (10.0))										
Primary Caregiver Report										
FHR-SZ N=193	T-score	55.4 (13.7)	55.1 (14.2)	53.8 (12.9)	55.3 (13.1)	54.1 (12.5)	54.6 (12.6)	53.2 (12.5)	52.8 (11.5)	54.1 (12.9)
FHR-BP N=110	(SD)	53.5 (12.6)	53.4 (13.0)	54.0 (13.4)	54.4 (12.4)	53.0 (11.5)	51.8 (11.3)	52.2 (11.7)	52.2 (10.9)	51.5 (11.4)
FHR-SZ vs.		<.001*	.001*	.004*	<.001*	.001*	<.001*	.017	.028	.002*
Control[a]		(0.45)	(0.41)	(0.33)	(0.45)	(0.35)	(0.40)	(0.28)	(0.26)	(.35)
FHR-BP	*P*-value*	.036*	.053	.020	.005*	.068	.348	.221	.184	.499
vs. Control[a]	(Cohen d)	(0.32)	(0.30)	(0.35)	(0.41)	(0.28)	(0.17)	(0.21)	(0.22)	(0.14)
FHR-SZ		.451	.524	.995	.831	.702	.121	.785	.896	.172
vs. FHR-BP		(0.14)	(0.13)	(0.01)	(0.07)	(0.09)	(0.23)	(0.08)	(0.05)	(0.21)
Teacher Report										
FHR-SZ N=168	T-score	57.1 (12.6)	54.4 (12.0)	56.8 (13.9)	57.6 (15.0)	55.4 (11.2)	55.9 (11.9)	58.0 (13.7)	56.1 (14.5)	55.3 (11.5)
FHR-BP N=103	(SD)	53.2 (13.1)	50.6 (10.7)	53.3 (14.3)	54.2 (15.6)	52.1 (12.8)	52.8 (12.7)	53.7 (13.9)	53.5 (13.0)	52.2 (11.1)
FHR-SZ vs.		<.001*	<.001*	<.001*	<.001*	<.001*	<.001*	<.001*	<.001*	<.001*
Control[b]		(0.62)	(0.40)	(0.57)	(0.59)	(0.51)	(0.54)	(0.66)	(0.49)	(0.50)
FHR-BP vs.	*P*-value*	.091	.882	.103	.039	.323	.139	.053	.054	.240
Control[b]	(Cohen d)	(0.28)	(0.06)	(0.28)	(0.34)	(0.19)	(0.25)	(0.32)	(0.31)	(0.21)
FHR-SZ vs.		.047*	.019	.116	.197	.089	.118	.043	.270	.065
FHR-BP		(0.30)	(0.33)	(0.25)	(0.22)	(0.27)	(0.25)	(0.31)	(0.19)	(0.28)

B) Odds ratio (OR) and statistical significance that an FHR child will be classified as 1.5 SD above the mean of the control group compared to an individual from the control group, and for FHR-SZ vs. FHR-BP										
Primary Caregiver Report										
FHR-SZ vs.		3.7 (2.0-6.9)	2.7 (1.4-5.0)	2.4 (1.3-4.6)	2.7 (1.5-4.8)	3.0 (1.6-5.5)	2.5 (1.3-4.7)	2.7(1.4-5.2)	2.7 (1.4-5.1)	5.3 (2.4-11.6)
Control		<.0001*	.0020*	.0058*	.0012*	.0005*	.0038*	.0030*	.0026*	<.0001*
FHR-BP vs.	OR (CI)	2.5 (1.2-5.1)	2.1 (1.0-4.4)	2.6 (1.3-5.2)	2.5 (1.3-4.9)	2.0 (1.0-4.1)	1.6 (.74-3.4)	1.4 (.6-3.2)	2.3 (1.1-4.7)	3.0 (1.2-7.6)
Control	*P*-value	.0146*	.0396	.0082	.0065	.0642	.2339	.4165	.0267	.0168
FHR-SZ vs.		1.5 (0.8-2.7)	1.3 (0.7-2.3)	0.9 (0.5-1.7)	1.1 (.6-1.9)	1.5 (0.8-2.8)	1.6 (0.8-3.1)	1.9 (0.9-4.0)	1.2 (0.6-2.2)	1.7 (0.9-3.4)
FHR-BP		.185	.473	.853	.844	.212	.172	.078	.617	.119
Teacher Report										
FHR-SZ vs.		4.0 (2.2-7.4)	2.5 (1.4-4.7)	3.1 (1.7-5.8)	5.2 (2.7-10.1)	2.4 (1.3-4.3)	3.4 (1.7-6.5)	3.8 (2.1-6.9)	2.6 (1.4-4.8)	2.6 (1.4-4.9)
Control		<.0001*	.0036*	.0004*	<.0001*	.0046*	.0003*	<.0001*	.0025*	.0032*
FHR-BP vs.	OR (CI)	2.3 (1.1-4.6)	1.1 (.5-2.4)	2.1 (1.1-4.4)	3.2 (1.6-6.8)	1.8 (.9-3.5)	2.2 (1.0-4.6)	2.1 (1.1-4.2)	1.9(.9-3.8)	1.4(.6-3.0)
Control	*P*-value	.0233*	.8830	.0364	.0018*	.1034	.0437	.0315	.0829	.4247
FHR-SZ vs.		1.8 (1.0-3.2)	2.4 (1.1-4.9)	1.4 (0.8-2.6)	1.6 (0.9-2.9)	1.3 (0.7-2.5)	1.5 (0.8-2.9)	1.8 (1.0-3.2)	1.4 (0.7-2.6)	1.9 (0.9-3.8)
FHR-BP		.059	.020	.243	.101	.354	.180	.048	.311	.070

(A) GEC analysed with Welch's ANOVA and post hoc Games-Howell. Clinical scales analysed by MANOVA and post hoc Games-Howell.

(B) Odds ratios analysed by logistic regression.

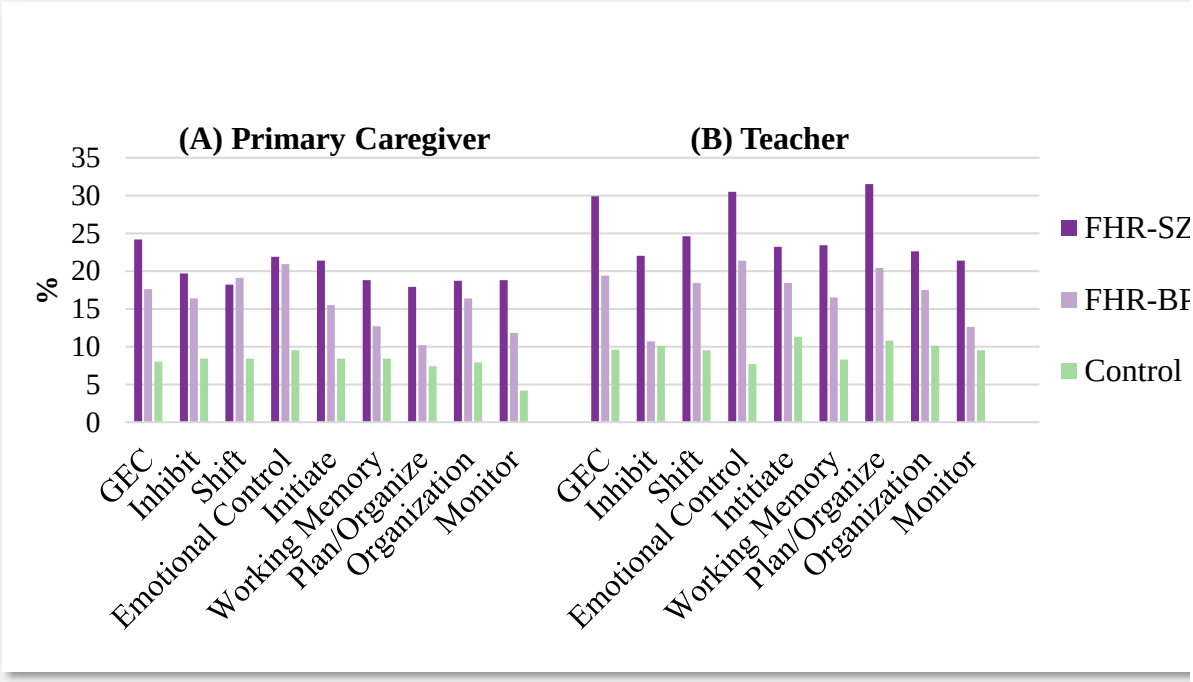
FHR-BP: familial high risk of bipolar disorder; FHR-SZ: familial high risk of schizophrenia spectrum disorder.

[a]Control N=190. [b]Control N= 168.

*Significant P-value. Fore GEC an alfa level below .05 is considered significant. For clinical scale scores an alfa level below .00625 are considered significant after Bonferroni adjustment for multiple comparisons.

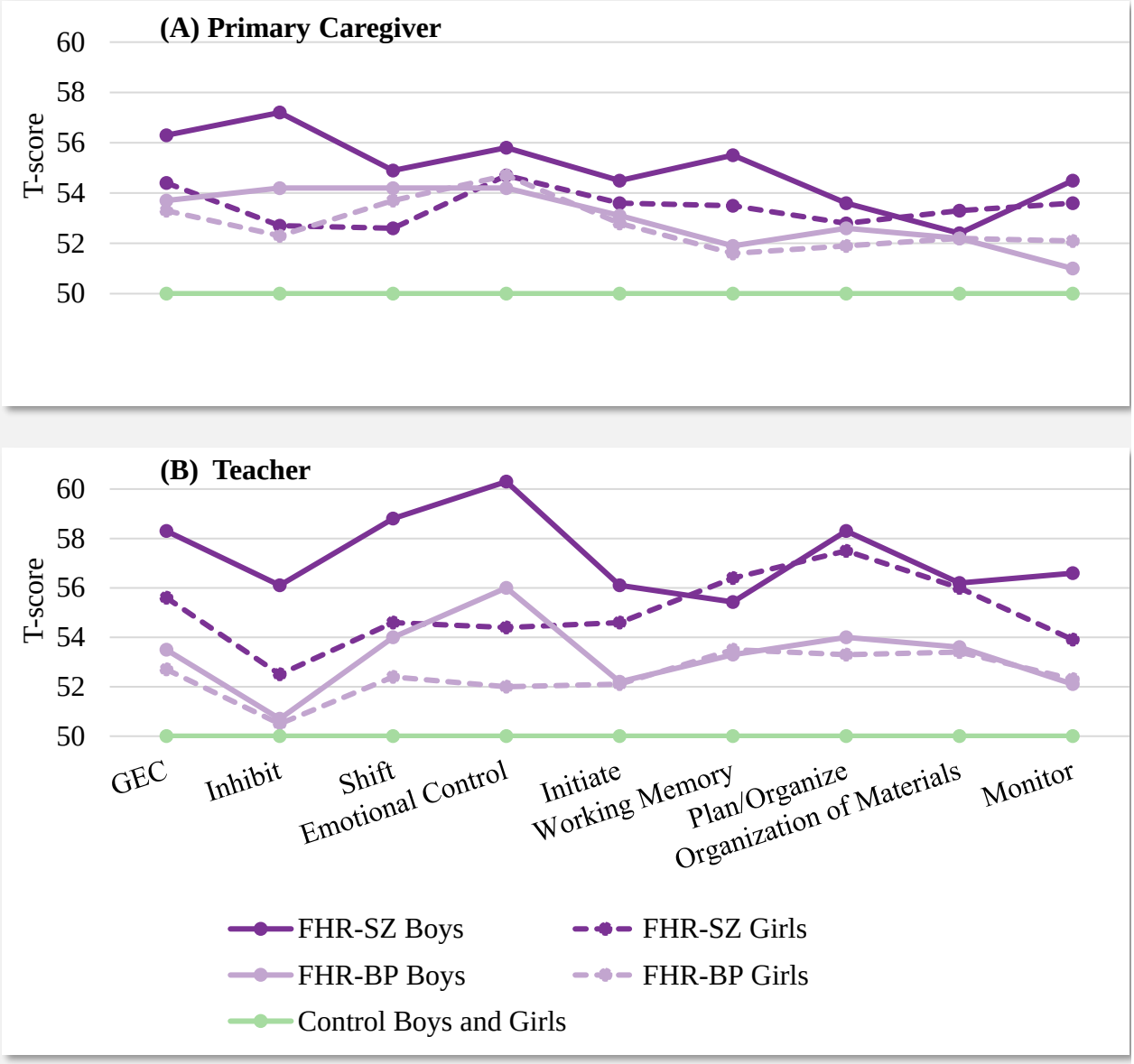
7 primary caregiver and 5 teacher BRIEF reports had missing items that prohibited calculation of 1 or more scales.

Figure 1. Prevalence of children scoring above cut-off (1.5 SD above the mean of the control group) on the BRIEF in each of the three risk groups.



BRIEF: Behavior Rating Inventory of Executive Functions; FHR-BP: Familial High-Risk Bipolar disorder; FHR-SZ: Familial High-Risk schizophrenia; GEC: Global Executive Composite.

Figure 2. BRIEF T-scores of female and male participating children as rated by their primary caregiver (A) and teacher (B)



BRIEF: Behavior Rating Inventory of Executive Functions; FHR-BP: Familial High-Risk Bipolar disorder; FHR-SZ: Familial High-Risk schizophrenia; GEC: Global Executive Composite.

Control group standardized as reference group with T-score mean=50 and SD=10 on boys and girls separately.

Paper III.

Emotion regulation in 7-year-old children with familial high risk for schizophrenia or bipolar disorder compared to controls - The Danish High Risk and Resilience Study - VIA 7, a register-based cohort study (Submitted)

Emotion regulation in 7-year-old children with familial high risk for schizophrenia or bipolar disorder compared to controls – The Danish High Risk and Resilience Study – VIA 7, a population-based cohort study

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Wordcount:

Abstract (244)

Introduction (777)

Method (1413)

Results (279)

Discussion (1650)

Abstract:

Emotion regulation is a predictor of overall life-outcome. Problems of emotion regulation are associated with multiple psychiatric disorders and could be a potential treatment target for improving wellbeing and functioning. Children at familial high risk of severe mental illness have a markedly increased risk of various psychopathology and constitute a group at significant risk of emotion regulation problems. Investigations of emotion regulation in children at familial high risk of severe mental illness are sparse, and there is a general need for standardized measures of spontaneous emotion regulation. We applied a new assessment manual of emotion regulation; the Tangram Emotion Coding Manual; TEC-M, to a population-based cohort of 522 7-year-old children born to parents diagnosed with either schizophrenia or bipolar disorder and matched controls. The TEC-M is an ecologically valid, clinician-rated observational test-measure. We aimed to compare emotion regulation between risk groups and to investigate associations between emotion regulation and psychopathology and daily life functioning, and between emotion regulation and an acknowledged questionnaire-based dysregulation profile. In this early developmental phase, we found no between group differences in emotion regulation. We found a significant but weak negative association between emotion regulation and both child psychopathology and the presence of a dysregulation profile and a weak positive association between emotion regulation and current level of functioning. These findings contribute to the understanding of emotion regulation in familial high-risk children and further studies of emotion regulation in children at familial high risk of severe mental illness are warranted.

Keywords: Emotion Regulation, Schizophrenia Spectrum Psychosis, Bipolar Disorder, Familial High Risk, Offspring,

Abbreviations:

ADHD: Attention-Deficit/Hyperactivity Disorder

CBCL: Child Behavior Checklist

CBCL-DP: Child Behavior Checklist – Dysregulation Profile

EmReg: TEC-M Measure of Overall Emotion Regulation Ability

FHR-SZ: Familial High Risk for Schizophrenia

FHR-BP: Familial High Risk for Bipolar Disorder

TEC-M: Tangram Emotion Coding Manual

Introduction

Emotions guide the individual in identifying what is potentially harmful and what is believed to be advantageous in relation to the individual's immediate well-being as well as general future functioning (Campos et al., 1994; Gross et al., 2019; Kimhy et al., 2016; Lazarus, 1991). Emotion regulation (ER) involves the initiation, maintenance, modification, and termination of emotions, but also the choice of response (behavioural as well as emotional) in a given situation (Campos et al., 1994; Gross, 2002). Emotion regulation enables the individual to organise behavioural responses appropriate to the social context and the society that the individual is a part of (Barrett et al., 2001; Thompson, 2011).

The development of adaptive emotion regulation begins at birth and continues to advance during childhood, adolescence, and potentially throughout life (Charles & Carstensen, 2009b; Plessen & Kabicheva, 2010; Schweizer et al., 2020). In the first years of life, the development of emotion regulation is highly dependent on the communicative feedback from the primary caregivers, but as the processes of emotion regulation mature, it changes from being mostly non-conscious and externally regulated to being more conscious and internally regulated (Plessen & Kabicheva, 2010).

Adaptive and appropriate emotion regulation is a prerequisite for adequately adjusting to varying social contexts, and emotional dysregulation can have vast negative consequences for the individual as well as for society as a whole (Moffitt et al., 2011; Philippot, 2004; Thompson, 2011). Emotion regulation in childhood and adolescence is an important predictor of overall outcomes throughout life, such as academic, occupational, and family functioning (Graziano et al., 2007; Moffitt et al., 2011).

Behaviours associated with inadequate or maladaptive emotion regulation are seen in multiple psychiatric disorders. Specifically, problems with emotion regulation are core symptoms of bipolar disorder and schizophrenia spectrum disorder and are often seen in, e.g. attention-deficit/hyperactivity disorder (ADHD), disruptive behaviour disorder, and autism spectrum disorders (Aldao et al., 2016; Fernandez et al., 2016; Kring & Werner, 2004). Studies in offspring of mothers with bipolar disorder suggest that problems with emotion regulation are present from infancy (Johnson et al., 2014). The capacity of emotion regulation is less studied in offspring of parents with schizophrenia, but studies imply that problems with emotion regulation are present from early childhood (4 and 7 years of age; 4-17 years of age) (Díaz-Caneja et al., 2018; Donatelli et al., 2010). Moreover, several studies have reported that children born to parents with severe mental illnesses such as schizophrenia and bipolar disorder are at a markedly increased risk of a wide array of psychiatric disorders (Ellersgaard et al., 2018; Rasic, Hajek, Alda, & Uher, 2014b; Thorup et al., 2017) Thus, children of parents with a severe mental

illness comprise a unique group of individuals, who potentially have emotion regulation difficulties due to their augmented risk of a broad spectrum of psychiatric disorders.

Most studies investigating emotion regulation in children are based on parent-, teacher- or self-rated questionnaires. These questionnaires often focus on the occurrence of dysregulated behaviour and do not yield information about the context or the social mechanisms related to emotion regulation. Observational measures of emotion regulation could help fill in this gap in knowledge and complement previous findings (Compas et al., 2017; Wakschlag et al., 2007). Also, the need for ecologically valid assessments of spontaneous emotion regulation has been highlighted in a meta-analytic review (Aldao et al., 2010). To this end, we developed the Tangram Emotion Coding Manual (TEC-M (Hagstrøm et al., 2019). The TEC-M provides an assessment of children´s emotion regulation in an ecologically valid setting, in which the child participates in a frustrating puzzle task designed to prompt emotional reactions, in a social context, where only the child's primary caregiver is present during the task. The TEC-M allows for a standardised, lab-based, and clinician-rated assessment including observations of related mechanisms.

Employing the TEC-M, we aimed to investigate differences in emotion regulation across familial risk status in a population-based cohort of 522 7-year-old children consisting of children born to parents diagnosed with either schizophrenia or bipolar disorder and control children with neither parent diagnosed with schizophrenia nor bipolar disorder (Thorup et al., 2015b). We hypothesised that children with a familial predisposition of severe mental illness would display more inadequate emotion regulation than children without this familial risk. Secondly, we aimed to investigate potential associations, both within each risk status group, as well as across risk groups, between emotion regulation of the child and dimensional measures of child psychopathology, psychopathological symptom severity, daily life functioning, and a categorical emotional/behavioural dysregulation profile from The Child Behavior Checklist (CBCL-DP). We hypothesised that an increased dimensional psychopathological load and a positive dysregulation profile would be negatively associated with emotion regulation.

Materials and methods

Procedures

The Danish High Risk and Resilience Study – VIA 7 (The VIA 7 Study), a nationwide population-based cohort study, was approved by the Danish Data Protection Agency (J.nr.:2012-58-0004). The Danish National Committee on Health Research Ethics concluded that approval was not necessaire due to the observational nature of the study. We obtained informed written consent from all participants and custody holders, including a separate written consent to contact the child's teachers. Trained psychologists, medical doctors, and nurses

performed all assessments under the supervision of a senior specialist in child neuropsychology (JRMJ) and a specialist in child and adolescent psychiatry (AT). Child assessors were blinded to the risk status of the child.

Participants

We composed a cohort of 522 children (aged 6.9-8.4 years) using the Danish Psychiatric Central Research Register (Mors, Perto, & Mortensen, 2011b) and the Danish Civil Registration System (Pedersen, 2011b). The groups comprised children with familial high risk for bipolar disorder (FHR-BP) or schizophrenia spectrum psychosis (defined as schizophrenia, delusional disorder or schizoaffective disorder) (FHR-SZ). Children in the control group were likewise drawn from the registers and matched on sex, age, and municipality to the FHR-SZ children. FHR-BP children comprised a non-matched sample but were comparable on age and sex to the children in the two other groups. All children and parents had to be born and living in Denmark. The VIA 7 study design has been described in detail elsewhere (Thorup et al., 2015b). A total of 465 children and their primary caregivers participated in the frustration task designed to measure emotion regulation (Figure 1). The participating adult was always the primary caregiver, defined as the adult who, at the time of the study, knew the child the best and cared for the child on a daily basis. This could be either one of the biological parents (independent of potential diagnosis of the parent), a step-, or foster parent. TEC-M data of 57 children was not included in the study. Technical and administration problems accounted for 43.9 % of missing data (N=28; lack of sound/picture, inappropriate film angle etc.), but missing data was also due to, e.g. refusal to be videotaped or dis-participation. Missingness analyses revealed no significant differences between participants and non-participants neither on sex (p=.314) nor age (p=.714). Likewise, participation rates (p=.279) and reason for missing (p=.438) did not differ between risk groups.

Measures

The Tangram Emotion Coding Manual (TEC-M)

The Tangram Emotion Coding Manual (TEC-M) (Hagstrøm et al., 2019) was developed to assess behaviours reflecting children's emotion regulation while performing a difficult puzzle task (the Tangram Construction Task, (Hudson & Rapee, 2001)) in the context of the interaction between the primary caregiver and the child.

The TEC-M is a standardised manual for coding The Tangram Construction Task; a frustration task originally used in samples of children with anxiety focusing on the dyadic interaction using a different manual than the TEC-M (Hudson & Rapee, 2001; Esbjørn, Christiansen & Steele, unpublished manuscript). The TEC-M is theoretically founded on The Process Model of

emotion regulation, which is an elaborated and well-recognised schematic model of the processes involved in emotion regulation (Gross, 1998, 2014b, 2015a; Hagstrøm et al., 2019). TEC-M was developed as a tool to measure emotion regulation abilities across potential diagnoses as well as in typically developing children.

In the Tangram Construction Task, the child is instructed to solve as many puzzles as possible within five minutes. The child and the primary caregiver are told that most children can solve these puzzles, but that some find it a bit difficult. The primary caregiver is handed a booklet with the solutions to the puzzles. The primary caregiver is instructed to support the child, but it is emphasised that the primary caregiver should only help the child if it is genuinely needed. The task purpose is to frustrate the child and elicit emotional responses from both the child and the primary caregiver. Hence the puzzle task is considerably more difficult than communicated to the participants. The session is videotaped with only the child and the primary caregiver in the room during the task. The video-recording is used for subsequent qualitative coding according to the manual, focusing on the child and primary caregiver. Eight items are coded for parental personal and interpersonal behaviour (intrusiveness, avoidance, control, verbal reappraisal, tension, positive expressions, negative expressions, and support sensitivity), and eleven items are coded for child behaviour (situation rejection, avoidance/resignation, control, narration, verbal reappraisal, reassurance-seeking, tension, incongruent positive affect, positive expressions, negative expression, and aggression). All child and parent items are scored on a four-point frequency scale (never, rarely, sometimes, often) and a three-point intensity scale (mild, moderate, marked). One item assessing the parent-child dyad (emotional warmth) is scored from 0-3.

The primary outcome measure of the TEC-M, the emotion regulation scale; EmReg, represents an assessment of the child's overall emotion regulation and is scored based on the scores of the other items while taking into account all factors of the evaluated test situation, such as the child's level of frustration, parental behaviour, and perceived level of difficulty. The EmReg score is scored on a five-point scale, where a score of one represents very poor emotion regulation and a score of five represents excellent emotion regulation. In the primary validation study, the TEC-M was found to have high levels of inter- and intra-rater reliability and satisfactory content validity (the first author of the present paper participated in the validation study) (Hagstrøm et al., 2019).

Two trained raters (KR and KSS) conducted the coding of all videos from The Danish High Risk and Resilience Study - VIA 7. Reliability and harmonising ratings on TEC-M coding were carried out with regular intervals. Both raters coded a subset of 14 videos enabling the

calculation of inter-rater reliability (IRR). IRR was found to be in the excellent range (Cicchetti, 1994) for the EmReg; ICC= 0.79 (95% CI 0.34-0.93) when analysing the degree of rating consistency between raters, across subjects, assessed with intra-class correlation coefficient (ICC) based on raw data estimates by method of Two-way Mixed-effects model, average measures and absolute agreement type (McGraw & Wong, 1996).

The Child Behavior Checklist (CBCL)

Primary caregivers filled out the CBCL (Achenbach & Rescorla, 2001)**.** Beyond the CBCL-Total score, an emotional/behavioural dysregulation profile (CBCL-DP) can be computed from the CBCL. The CBCL-DP comprises three symptom scales from the CBCL (Aggressive Behavior, Anxious/Depressed, and Attention Problems)(Achenbach & Rescorla, 2001; Althoff, 2010). Two versions of the CBCL-DP are generally used, the stringent CBCL-DP70 (i.e. T-scores above or equal to 70 on all of the three individual symptom scales) or the broader CBCL-DP210 (i.e. a sum of the three symptom scale T-scores above or equal to 210) (Aitken et al., 2019). A CBCL-DP score above the cut-off, suggestively predicts subsequent psychopathology and poor functioning (Biederman et al., 2012). We computed a normalised CBCL-DP T-score (mean=50 and SD=10) from our study sample's control group for boys and girls separately, with higher scores indicating more problem behaviour. In this study, we utilised both the stringent CBCL-DP70 and the broader CBCL-DP210.

The Attention deficit/Hyperactivity Disorder-Rating Scale (ADHD-RS)

Primary caregivers and the child's teacher independently filled out the ADHD-RS (Barkley et al., 1999; DuPaul et al., 1998; Makransky & Bilenberg, 2014) Danish version. Higher scores on ADHD-RS reflect worse symptom severity. ADHD-RS composite scores (ADHD-RS-comp) were calculated as the mean from the primary caregiver and teacher-rated ADHD-RS item 1-18, thus excluding conduct disorder item scores (Martel et al., 2015). A normalising T-score was calculated by the same method as described for CBCL-DP.

Children´s Global Assessment Scale (CGAS)

The child's current level of daily functioning was assessed with the CGAS (Shaffer et al., 1983). Higher CGAS scores reflect higher level of functioning.

Statistical analysis

Participant characteristics

Between-group differences of participant characteristics were analysed using one-way ANOVAs, chi-square tests or the Mantel-Haenszel linear-by-linear test of associations, as appropriate (table 1).

Group differences in emotion regulation

The primary outcome measure; EmReg, was approximately normally distributed for both the total cohort and for the three high-risk groups separately as evaluated from indicators of skewness, kurtosis, histograms and boxplots. Assessing between-group differences of emotion regulation employing ANOVA with post hoc Tukey-Kramer was thus considered not to increase the risk of type I errors (Blanca et al., 2017).

Association between emotion regulation and dimensions of psychopathology and general functioning

Spearman's rank-order correlation analyses were performed as a monotonic relationship was evaluated between EmReg and the continuous dependent variables. For dichotomous dependent variables, Pearson correlations were performed.

We used IBM SPSS Statistics, version 25.0, for all statistical analyses.

Results

Participant characteristics

There was no difference between groups regarding age and sex. Compared to the control group, children from both FHR groups had significantly lower general levels of functioning (CGAS) and were rated higher on the dimensional measure of psychopathology (CBCL). Likewise, primary caregivers from both FHR groups had significantly lower levels of functioning than primary caregivers from the control group (Table 1) These results correspond to the results of the full VIA 7 cohort (Ellersgaard et al., 2018).

Group differences in emotion regulation

We found no significant difference between the three groups on EmReg as determined by a one-way ANOVA, (F (2,462) = 1.155, p = .316) (Table 2).

Associations between emotion regulation and dimensions of psychopathology and general functioning

Correlation analyses using Spearman's rank-order correlation on the total cohort revealed a statistically significant, weak and inverse correlation between the EmReg score and ADHD-RS-comp; (r_s(460) = -.170, p = < .001) and CBCL-Total; (r_s(445) = -.132, p = .005). Pearson's correlation between EmReg and the broader CBCL-DP210 were significant, weak and negative; r(444) = -.177, p = <.001. The stringent CBCL-DP70 was non-significantly correlated with the EmReg score (Table 3). CGAS was significantly, weak and positively correlated with EmReg (r_s(462) = .150, p = .001) (Table 3).

All within-group associations were likewise weak. Associations between EmReg and ADHD-RS were only significant in the FHR-SZ group ($r_s(177) = -.273$, $p = < .001$). CBCL-DP210 was significantly associated with EmReg in both the FHR-SZ and the control group, and in the control group associations between EmReg and the CBCL-Total and the CGAS were likewise significant. The only significant association in the FHR-BP group was between EmReg and CGAS (Table 3).

Discussion

We did not find any group differences between the two familial high-risk groups and the control group on the primary outcome measure of emotion regulation; EmReg, measured by the TEC-M. We did, however, find statistically significant, weak associations between emotion regulation (the EmReg score) and general functioning (CGAS), a dimensional measure of psychopathology (CBCL), ADHD symptom severity (ADHD-RS), and between emotion regulation and a dysregulation profile (CBCL-DP210) in the total cohort.

Evidence of the stringently defined dysregulated profile; CBCL-DP70, was only found in very few FHR-SZ children and none of the FHR-BP nor the control children. The insignificant results regarding the association between EmReg and CBCL-DP70 may thus be due to the small number of children found with a dysregulation profile (type II error). Associations between EmReg and the broader defined dysregulation profile; CBCL-DP210, were highly significant for the total cohort and in the FHR-SZ group; the group with the highest frequency of a CBCL-DP210 profile. The non-significant associations between EmReg and the CBCL-DB210 in the FHR-BP group and the control group may also be due to the small number of children identified with the dysregulation profile in these groups (Type II error).

Better emotion regulation was positively related to higher levels of daily functioning, although we cannot infer causation, this could possibly suggest an underlying importance of apt emotion regulation for success in everyday activities like school and leisure time activities, and in initiating and maintaining social relations to peers. This is supported by findings of emotion regulation being associated to academic performance as early as age five, and that academic performance is found relatively stable after 1. grade (Graziano et al., 2007). Further, good emotion regulation is recognised as a psychological competence that can increase the individual's wellbeing and chances of overcoming adverse life events or minor obstacles in daily life (National Scientific Council on the Developing Child, 2015). Apt emotion regulation is thus likely a critical resilience factor in life.

On account of the higher prevalence of psychopathology in FHR-SZ and FHR-BP children in this FHR population as documented with diagnostic interviews (Ellersgaard et al., 2018) and the significantly worse psychopathological symptom severity measured dimensionally (Table 1), we expected to find poorer emotion regulation in the two high-risk groups compared to the control group. We did nevertheless not find any significant differences in emotion regulation between the three groups. It is, however, essential to consider that the participating children are at an age where their emotion regulation is still developing and maturing (Plessen & Kabicheva, 2010; Schweizer et al., 2020). Thus, later in the maturational development an abnormal emotion regulation may emerge in the FHR groups (Dickson et al., 2018; Reichenberg et al., 2010b). Poorer emotion regulation was modestly associated to worse ADHD symptom severity and more signs of psychopathology in the total cohort. These results could suggest that emotion regulation difficulties are not specific to offspring with a predisposition for schizophrenia or bipolar disorder but rather related to developmental disorders such as ADHD. Yet another consideration is that emotion regulation in all forms (as is true of all other types of regulation) requires resource capacity, and that different forms of emotion regulation require different forms of cognitive capacity (Urry & Gross, 2010). This entails two different presumptions 1) regulation capacity as a depletable resource, and 2) differences in cognitive capacity in different cognitive domains. Regarding the first presumption, it could be speculated that the Tangram Construction Task was not demanding or lengthy enough to elucidate emotion regulation difficulties in average to high-capacity children and only children with an inherent low capacity to regulate would show emotion regulation difficulties. Following this hypothesis, the association between ADHD symptom load and poor emotion regulation could be explained by an inherent low capacity to regulate in children with ADHD. The second presumption of cognitive capacity again supports the association between poor emotion regulation and ADHD, as ADHD is defined on the basis of dysfunctional regulation of, e.g. attention (Petrovic & Castellanos, 2016).

We chose to analyse associations across the whole study cohort regardless of risk status as well as within-group. This was done considering two different conceptualizations of emotion regulation in children with FHR for severe mental illness. The first being, that emotion regulation and emotion regulation development is inherently affected by, and should be primarily understood in relation to, the specific psychiatric disorder of the parent. The second, that emotion regulation is related to the child's own potential psychopathology. Herewith not neglecting the fact that both scenarios are intrinsically connected to genetic and environmental dispositions related to high-risk status. The fact that we find associations between emotion regulation and measures of psychopathology including ADHD symptom severity across groups

and no differences in emotion regulation between groups, could again indicate that emotion regulation is more related to the child's own psychopathology than FHR status. However, it is essential to note that when analyzing associations by group, significant association was only found in the FHR-SZ group and most likely this carries the significant result of the total group association. However, it is likewise important to note that only very few FHR-BP and control children fulfilled the criteria for an ADHD diagnosis which could account for the nonsignificant results within these groups.

We know from a previous study of the same cohort that the FHR-SZ children as a group have poorer cognitive functioning than control children (Hemager et al., 2018) and we also found expected differences in parental and primary caregiver educational attainments, employment status, and daily life functioning, measured by the Personal and Social Performance Scale between FHR-groups and the control group (Ellersgaard et al., 2018) (table 1).These factors could affect the child's capabilities of solving the puzzles as well as increase frustration levels. However, we did not control for these factors as this could potentially remove key effects of being an FHR child and introduce the risk of overcorrection and thus rendering the results unrepresentative.

Utilising a population-based cohort, we wished to increase the knowledge of emotion regulation in children with a familial high risk of schizophrenia or bipolar disorder compared to controls by using a test that was easy to apply and ecologically valid. The finding of non-different emotion regulation between groups indicates that TEC-M may not be sensitive enough in this specific population at this age as previous findings indicate that problems with emotion regulation are present in children with familial high risk of severe mental disorders (Díaz-Caneja et al., 2018; Donatelli et al., 2010; Johnson et al., 2014). Even though the test is designed to resemble a naturalistic situation, it is a lab-setting and thus does not entail all the demands of everyday life. Evaluation of real-life emotion regulation may potentially be more valid in this population at this age.

A considerable strength is the uniqueness of the sizeable register-based study sample of same-aged children. Further, most studies of emotion regulation rely on questionnaires (Compas et al., 2017; Wakschlag et al., 2007) that can be subject to recall biases. To overcome this methodological limitation, we investigated emotion regulation with an ecologically valid clinician-rated observational test-measure thus adding to previous knowledge of emotion regulation investigations employing other methods. A further strength contributing to the validity of the results of the study is the interrater reliability (IRR) which was found in the excellent range regarding the emotion regulation ability measure, EmReg. This indicates a high

degree of agreement, suggesting that a negligible amount of measurement error was introduced by the two independent raters despite a rather small sample of 14 cases. The ICC confidence intervals of the IRR are somewhat wide, indicating a risk that the ICC value might not hold the standard of excellence. However, this is to be expected due to the low number of cases assessed for IRR. The high IRR corresponds to the results found in the TEC-M validation study, supporting the validity of the IRR in the present study (Hagstrøm et al., 2019). However, the present study also has some limitations. Emotion regulation partly develops through social interaction and in childhood, especially in close interaction with the primary caregiver (Plessen & Kabicheva, 2010). Severe mental illness can potentially affect the primary caregivers' ability to support their child's emotion regulation development (National Scientific Council on the Developing Child, 2015). As we used parental lifetime diagnoses in the inclusion process, the cohort includes children of parents with current illness as well as of parents that might have been ill shortly and in remission/well for many years and even before the birth of the child. Also, the severity of illness of parents in the cohort may vary significantly. This limitation could account for why we, in the present study, did not find any significant group differences in emotion regulation ability of the children. It could be speculated that a more uniform sample with more narrow inclusion criteria, e.g. diagnosis given no later than the year before the child's birth or, a requirement of active illness during the child's lifetime would have revealed a different result.

Conclusion

To our knowledge, this is the first study to compare emotion regulation between FHR-SZ and FHR-BP children applying an ecologically valid clinician-rated observational test. At age seven emotion regulation in familial high-risk children did not differ from controls, although poorer emotion regulation was associated to a higher level of psychopathology and more ADHD symptoms. Also, emotion regulation efficacy correlated positively with daily life functioning of the child. These findings contribute to the understanding of emotion regulation in familial high-risk children and the difficulties related to poor emotion regulation. Identification of poor emotion regulation is important as maladaptive emotion regulation is associated with adverse outcomes, and conversely, adaptive emotion regulation is associated with a positive outcome and general wellbeing. Improving emotion regulation may be a relevant mean to improve the overall outcome and wellbeing of the individual and further studies with observational measures of emotion regulation in familial high-risk children are warranted.

Acknowledgements

The authors would like to express their gratitude to the dedicated families participating in the study, to M. Skjærbæk, A. Ranning, A. Søndergaard, M. Gregersen, H. Jensen, C. Gregersen,

D-M. Henriksen, H. Stadsgaard, K. Zahle and M. Melau for contributing to data collection; to C. Bøcker Pedersen and M. Gjørtz Pedersen for retrieving the register extract; to M. Chaine and J. Ohland for help with data management and Emma Louise Sillehoved for data entry; to P.B. Mortensen T. Werge, D. Hougaard and A. Børglum for collaboration in iPSYCH; and B. Hoff Esbjørn for collaboration preceding the TEC-M development.

Declarations

The study was approved by the Danish Data Protection Agency (J.nr.:2012-58-0004) and follows all present laws concerning personal data. The Danish Ministry of Health granted the permission to draw data from Danish national Registers. The Danish National Committee on Health Research Ethics evaluated the study and concluded that further approval was not required due to the observational nature of the study. Verbal and written informed consent was obtained for all participants or custody holders, including a separate written consent to contact the child's teacher. The study was funded by TrygFonden, the Mental Health Services of the Capital Region of Denmark, The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Aarhus University, and the Beatrice Surovell Haskell Fund for Child Mental Health Research of Copenhagen.

Funding: This work was supported by TrygFonden, the Mental Health Services of the Capital Region of Denmark, The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) (Grant Nos. R102-A9118 and R155-2014-1724), Aarhus University, and the Beatrice Surovell Haskell Fund for Child Mental Health Research of Copenhagen (Grant No J.NR 11531).

Conflicts of interest: The authors have no conflicts of interest to disclose.

Ethics approval: The VIA 7 study was approved by the Danish Data Protection Agency (J.nr.:2012-58-0004). The Danish National Committee on Health Research Ethics evaluated the study and concluded that further approval was not required due to the observational nature of the study.

Consent to participate: Verbal and written informed consent was obtained for all participants or custody holders, including a separate written consent to contact the child's teacher.

Availability of data and material: Access can be granted upon reasonable request.

Code availability: Access can be granted upon request.

Author contributions: All authors contributed to the study conception and design. KSS wrote the manuscript and performed data analysis with input from all authors. KSS, DE, NH, CC, BKB, ANG, DG, MG collected the data. KSS and KR coded and typed all TEC-M assessments. All co-authors critically revised the manuscript and approved the final version.

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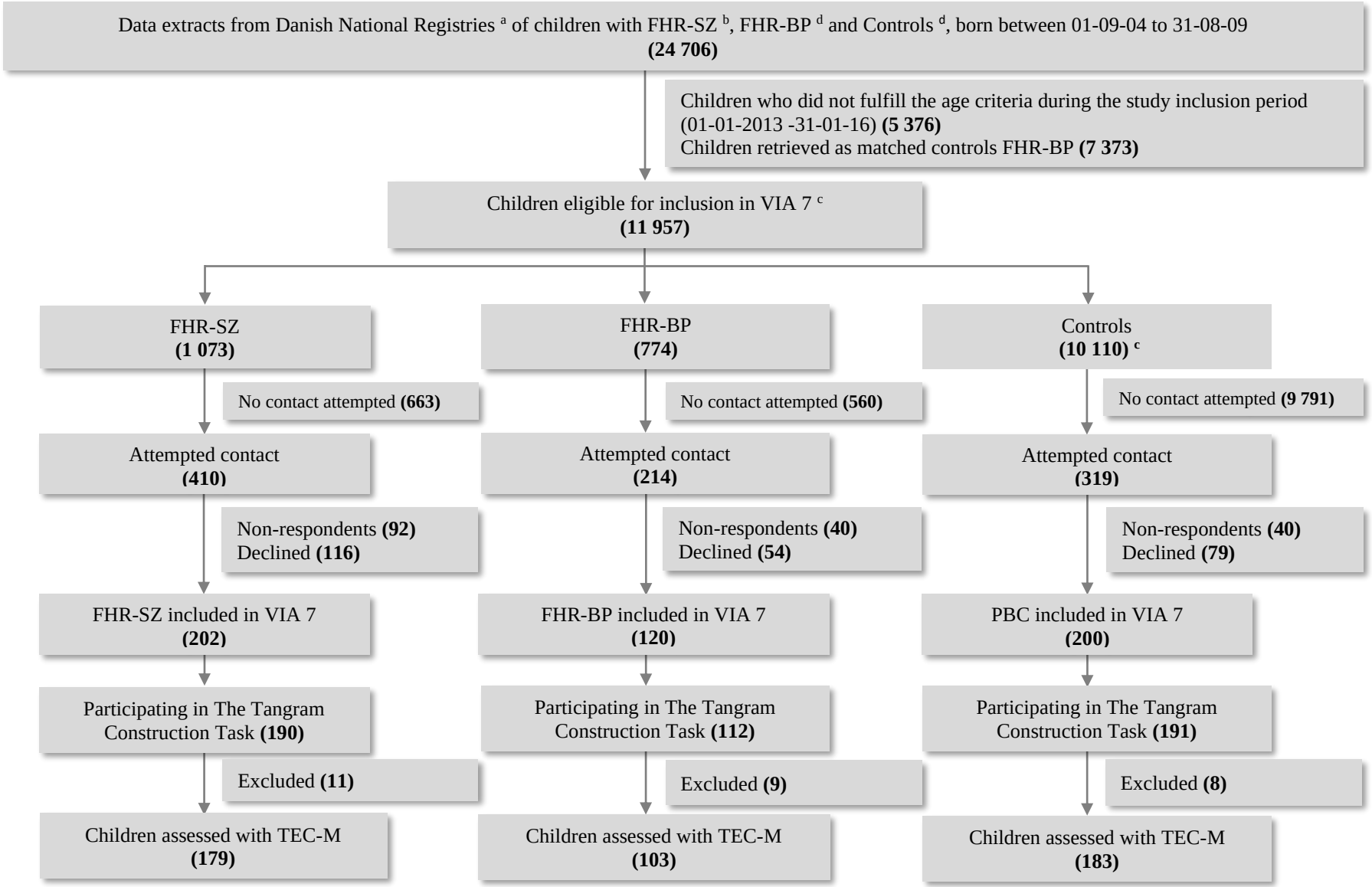
Figure 1. Flowchart of inclusion of children in The Danish High Risk and Resilience Study Via 7, and participation in The Tangram Cunstruction Task[1] and assessed with the Tangram Emotion Coding Manual[1] (TEC-M) for emotion regulation ability.



FHR-SZ: Children of parents with schizophrenia spectrum disorders. FHR-BP: Children of parents with bipolar disorder. Controls: Population-based control children of parents with no diagnoses of schizophrenia spectrum disorders or bipolar disorder.

FHR: Familial High Risk; BP: Bipolar disorder: PBC: Population based control; SZ: Scizophrenia.

[a] Danish Civil Registration System and Danish Psychiatric Central Research Register. [b] Parents with both a diagnosis of schizophrenia and bipolar disorder were assigned to the schizophrenia high risk group as per the ICD-10 hierarchy. [c] Up to 10 controls were retrieved for each child in the schizophrenia spectrum disorder group and the bipolar disorder group. Controls were matched to cases on sex, municipality and exact age.

[1](Hagstrøm et al., 2019)

Table 1. Characteristics of child and adult participants evaluated with The Tangram Emotion Coding Manual (TEC-M)

	Study Group			*p*-value	*p*-value Pairwise comparison		
	FHR-SZ	FHR-BP	Controls		FHR-SZ vs. Controls	FHR-BP vs. Controls	FHR-BP vs. FHR-SZ
Children, N	179	103	183				
Female, N (%)	81 (45.3)	45 (43.7)	86 (47.0)	.859 [C]	-	-	-
Age at inclusion, mean (SD)	7.85 (0.21)	7.86 (0.21)	7.82 (0.20)	.200 [A]	-	-	-
CGAS, mean (SD)	67.7 (15.3)	73.6 (15.0)	77.7 (13.5)	.000 [A]	.000 [A]	.022 [A]	.001 [A]
Any Axis 1 diagnosis [1], N (%)	65 (36.3)	39 (37.9)	28 (15.4)	.000 [C]	.000 [C]	.000 [C]	.795 [C]
Any ADHD diagnosis [1], N (%)	36 (20.1)	9 (8.7)	13 (7.1)	.000 [C]	.000 [C]	.628 [C]	.012 [C]
Any DBD diagnosis [1], N (%)	10 (5.6)	4 (3.9)	2 (1.1)	.063 [C]	.017 [C]	.116 [C]	.526 [C]
CBCL (N=447), Mean (SD) [m]	27.6 (21.2)	22.2 (18.9)	16.9 (14.6)	.000 [A]	.000 [A]	.021 [A]	.021 [A]
CBCL-DP210 (N=446), N (%)	22 (12.7)	6 (6.3)	7 (4.0)	.008 [C]	.003 [C]	.395 [C]	.096 [C]
CBCL-DP70 (N=446), N (%)	7 (4.0)	0 (0.0)	0 (0.0)	.004 [C]	.007 [C]	-	.046 [C]
ADHD-RS-Comp (N=462), mean (SD)	12.8 (9.9)	10.5 (9.2)	8.7 (7.4)	.000 [A]	.000 [A]	.022 [A]	.001 [A]
Primary Caregivers [2], N	179	103	183				
Female N (%)	158 (88.3)	96 (93.2)	163 (89.1)	.398 [C]	-	-	-
Primary Caregiver is Index [3], N (%)	81 (45.3)	61 (59.2)	-	-	-	-	.024 [C]
PSP[3], mean (SD) [O]	72.6 (14.4)	74.8 (13.9)	84.3 (9.4)	.000 [A]	.000 [A]	.000 [A]	.153 [A]
Age at child´s birth, mean (SD)	30.53 (6.68)	31.57 (5.54)	32.29 (4.25)	.011 [A]	.003 [A]	.302 [A]	.130 [A]
Employed or studying [3], N (%) [P]	118 (66.3)	70 (68.0)	163 (90.6)	.000 [C]	.000 [C]	.000 [C]	.774 [C]
Education, N	176	102	181				
Primary/lower secondary, N (%)	31 (17.6)	5 (4.9)	5 (2.8)				
Upper secondary, vocational, short-cycle tertiary, N (%)	76 (43.2)	33 (32.4)	77 (42.5)	.000 [L]	.000 [L]	.248 [L]	.000 [L]
Bachelor degree, equivalent or higher, N (%)	69 (39.2)	64 (62.7)	99 (54.7)				

ADHD: Attention deficit/hyperactivity disorder; ADHD-RS-Comp: The modified version of the ADHD-Rating Scale parent-teacher composite score; BP: Bipolar disorder; CBCL-DP: Child Behavoir Checklist-Dysregulation Profile; CBCL-DP70: t-score above 70 on the three CBCL-DP subscales; CBCL-DP210: t-score above 210 on the combined CBCL-DP subscales; CGAS: Children's Global Assessment Scale; DBD: Disruptive behavior disorder; FHR: Familial high risk; PSP: The Personal and Social Performance Scale; SZ: schizophrenia spectrum disorder.

[1] Best estimate diagnosis made from diagnostics interviews (K-SADS-PL) with child and primary caregiver and all other available information on the child.

[2] Primary caregivers are defined as the parent or foster parent that knows the child best and spends most time with the child.

[3] Index is defined as the parent with a diagnosis of either schizophrenia spectrum disorder or bipolar disorder and their adult matched control.

[3] Employed or studying is defined as being under employment (including temporary leave) or adhering to an acknowledged education for a minimum of 15 hours weekly.
[A] ANOVA.
[C] Chi square test.
[L] linear by linear association.
[M] 173 FHR-SZ, 97 FHR-BP, 177 Controls.
[N] 179 FHR-SZ, 102 FHR-BP, 181 Controls.
[O] 177 FHR-SZ, 103 FHR-BP, 181 Control-group primary caregivers.
[P] 178 FHR-SZ, 103 FHR-BP, 180 Control-group primary caregivers.
In case information is not available for all participants an N indicates the number of informants.
In 8 cases data for the same primary caregiver is counted twice because of siblings with shared primary caregiver. A total of 10 sibling pairs participated.

Table 2. Emotion Regulation (EmReg) as measured with the Tangram Emotion Coding Manual (TEC-M)

	Study Group			*p*-value	*p*-value Pairwise comparison		
	FHR-SZ	FHR-BP	Controls		FHR-SZ vs. Controls	FHR-BP vs. Controls	FHR-BP vs. FHR-SZ
Children, N	179	103	183				
EmReg, mean [95% CI]	3.21 [3.06-3.36]	3.39 [3.21-3.56]	3.25 [3.11-3.40]	.316 [A]	-	-	-

EmReg: Emotion Regulation ability, higher scores represent better emotion regulation; FHR: Familial High Risk; SZ: Schizophrenia spectrum disorder; BP: Bipolar disorder.
[A] ANOVA.

Table 3. Correlation between emotion regulation (EmReg) and measures of psychopathology, symptom severity and daily life functioning.

	Total Cohort		FHR-SZ		FHR-BP		Controls	
	Correlation coefficient (df)	*p*-value	Correlation coefficient (df)	*p*-value	Correlation coefficient (df)	*p*-value	Correlation coefficient (df)	*p*-value
ADHD-RS-comp	-.170 (460) [S]	<.001	-.273 (177) [S]	<.001	-.107 (100) [S]	.284	-.130 (179) [S]	.082
CBCL-Total	-.132 (445) [S]	.005	-.111 (171) [S]	.147	-.177 (95) [S]	.082	-.173 (175) [S]	.021
CBCL-DP210	-.177 (444) [P]	<.001	-.199 (171) [P]	.009	-.194 (94) [P]	.058	-.156 (175) [P]	.039
CBCL-DP70	-.087 (444) [P]	.065	-.140 (171) [P]	.068	-	-	-	-
CGAS	.150 (462) [S]	.001	.137 ((177) [S]	.068	.201 (101) [S]	.042	.173 (180) [S]	.020

ADHD-RS-Comp: The modified version of the ADHD-Rating Scale parent-teacher composite score.
EmReg: Overall Emotion Regulation Scale. Higher scores equal better emotion regulation.
CBCL: Child Behavior Checklist. Higher scores equal more symptomatology.
CBCL-DP: Child Behavior Checklist Dysregulation Profile. DP70 and DP210 are dichotomous outcome measure of whether the child fulfils criteria for the profile. CBCL-DP70: t-score above 70 on the three CBCL-DP subscales; CBCL-DP210: t-score above 210 on the combined CBCL-DP subscales.
CGAS: Children's Global Assessment Scale. Higher scores equal better performance.
[S] Spearman's rank-order correlation.
[P] Pearson correlation.

Co-authorship declarations

GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
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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	
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Title of the PhD thesis	Age seven and at familial high risk for severe mental disorder - Emotion Regulation, Executive Functions, and Psychopathology; The Danish High Risk and Resilience Study - VIA 7 - a register-based cohort study of children with a familial high risk for schizophrenia or bipolar disorder and their matched controls

2. The declaration applies to the following article	
Title of article	The Strengths and Difficulties Questionnaire; Seven-year-old children with familial high risk of schizophrenia or bipolar disorder and controls
Article status	
Published ☐ Date:	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).	

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	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	C
5. Conducting the analysis of data	A
6. Interpretation of the results	A
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.[1]
Katrine Spang contributed to data collection of all the presented data with chief responsibility of the main outcome measure. Katrine Spang performed all statistical analyses, wrote first and final draft independently, and is the corresponding author. Co-authors contributed with continues feedback on content, analyses and interpretation during the writing of the manuscript.

Latest update of the declaration: December 2018

4. Material from another thesis / dissertation[ii]	
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[iii]

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

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GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
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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	Katrine Søborg Spang
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2. The declaration applies to the following article	
Title of article	Executive functions in seven-year-old children of parents with schizophrenia or bipolar disorder compared with controls
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☒ Date: 26/2-2020	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).	

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	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	C
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.[1]
Katrine Spang contributed to data collection of all the presented data. Katrine Spang performed all statistical analyses, wrote first and final draft independently, and is the corresponding author. Co-authors contributed with continues feedback on content, analyses and interpretation during the writing of the manuscript.

Latest update of the declaration: December 2018

4. Material from another thesis / dissertation[II]	
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.	

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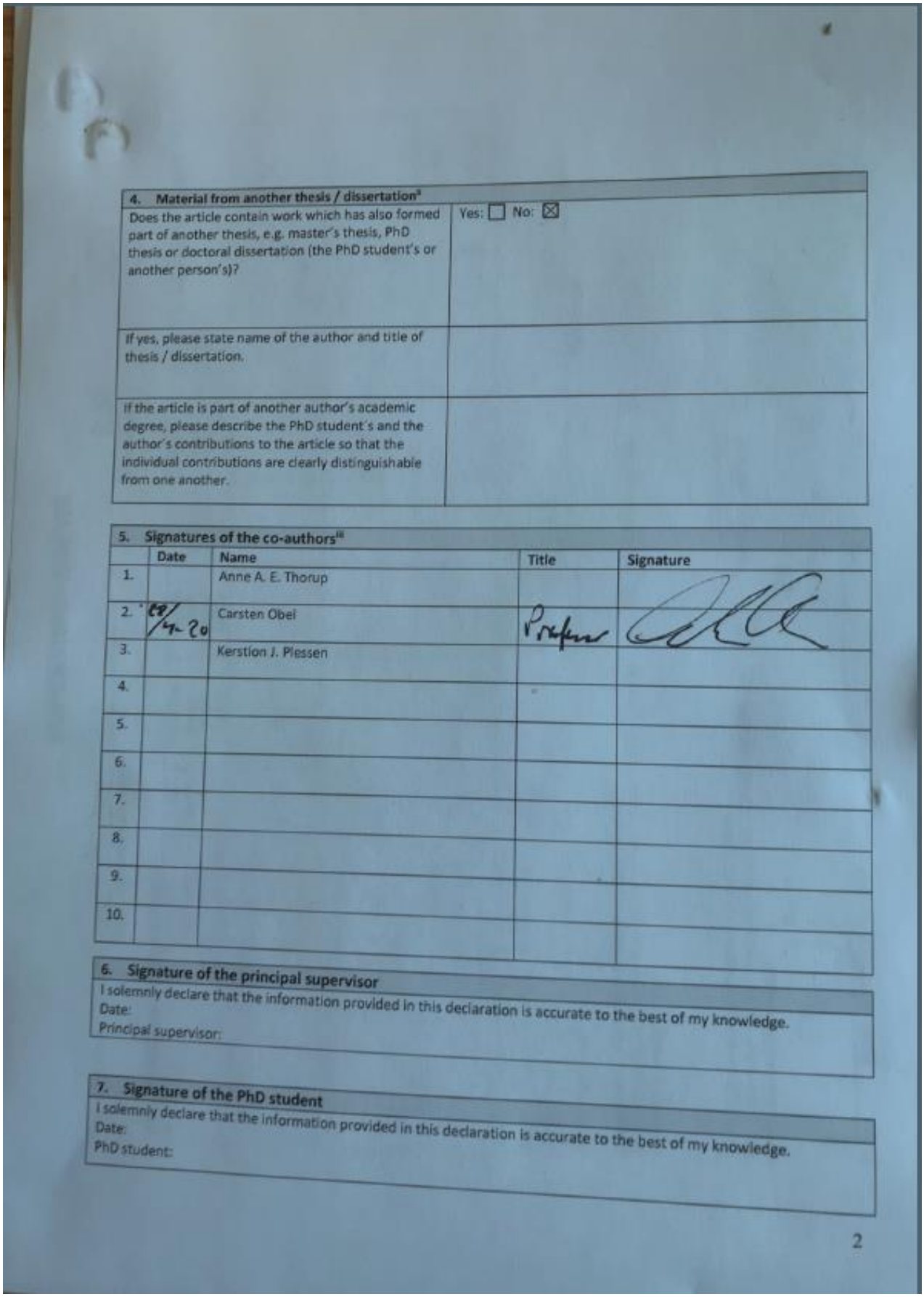
10.				

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: 30.09.20 Principal supervisor: Anne AE Thorup

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: 30/4-20 PhD student:

2



4. Material from another thesis / dissertation[9]	
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[10]				
	Date	Name	Title	Signature
1.		Anne A. E. Thorup		
2.	28/4-20	Carsten Obel	Profes	
3.		Kerstion J. Plessen		
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:

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: PhD student:

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GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

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	Katrine Søborg Spang
E-mail	katrine.soeborg.spang@regionh.dk
Name of principal supervisor	Anne A. E. Thorup
Title of the PhD thesis	Age seven and at familial high risk for severe mental disorder - Emotion Regulation, Executive Functions, and Psychopathology; The Danish High Risk and Resilience Study - VIA 7 - a register-based cohort study of children with a familial high risk for schizophrenia or bipolar disorder and their matched controls

2. The declaration applies to the following article	
Title of article	Emotion regulation in 7-year-old children with familial high risk for schizophrenia or bipolar disorder - The Danish High Risk and Resilience Study - VIA 7, a register-based cohort study
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☒ Date: 28/4-2020	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).	

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	A
2. Development of the key methods	C
3. Planning of the experiments and methodology design and development	B
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	B
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.[1]
Katrine Spang contributed to data collection of all the presented data with chief responsibility of the main outcome measure. Katrine Spang developed the key assessment measure in collaboration primarily with co-PhD-student, Julie Hagstrøm. Katrine Spang performed all statistical analyses, wrote first and final draft independently, and is the corresponding author. Co-authors contributed with continues feedback on content, analyses and interpretation during the writing of the manuscript.

Latest update of the declaration: December 2018

4. Material from another thesis / dissertation[ii]	
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[iii]

	Date	Name	Title	Signature
1.		Anne A. E. Thorup		
2.				
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: 300420

Principal supervisor: Anne A E Thorup

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: 30/4-20

PhD student: Kathrine Sørup

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