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PhD Thesis
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**Motor Function, Attention and Cognitive Control
in Children with a Familial Risk of Schizophrenia or
Bipolar Disorder**

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Title: Motor Function, Attention and Cognitive Control in Children with a Familial Risk of Schizophrenia or Bipolar Disorder

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2 List of Publications

This thesis is based on the following three scientific papers:

- I. Burton BK, Hjorthøj C, Jepsen JR, Thorup AE, Nordentoft M, Plessen KJ. Research Review: Do motor deficits during development represent an endophenotype for schizophrenia? A meta-analysis. *Journal of Child Psychology and psychiatry* 57:4 (2016), pp 446-456.
- II. Burton BK, Thorup AAE, Jepsen JR, Poulsen G, Ellersgaard D, Spang KS, Christiani CJ, Hemager N, Gantriis D, Greve A, Mors O, Nordentoft M, Plessen KJ. Motor Impairments among Children with a Familial Risk of Schizophrenia or Bipolar Disorder at 7 Years Old – The Danish High Risk and Resilience Study VIA 7. *Submitted and under review*
- III. Burton BK, Vangkilde S, Petersen A, Theil Skovgaard L, Jepsen JR, Hemager N, Christiani CJ, Spang KS, Ellersgaard D, Greve A, Gantriis D, Heike Eichele, Mors O, Nordentoft M, Thorup AAE, Plessen KJ. Sustained attention and cognitive control among 7-year-old children with a familial risk of schizophrenia or bipolar disorder. *Manuscript*

3 Dansk Resumé

3.1 Baggrund

Individer med skizofreni og deres børn udviser både motoriske og opmærksomhedsmæssige afvigelser i forhold til kontroller. Hvorimod individer med bipolar lidelse og deres børn udviser både fremragende og forringede kognitive evner, selvom skizofreni og bipolar lidelse betragtes som en neuroudviklingslidelse med genetisk overlap. Tidligere studier har ikke undersøgt motorisk funktion blandt børn med familiær risiko for bipolar lidelse med en omfattende og valideret motorisk test. Kognitiv kontrol og 'tilpasning til fejl' er ikke tidligere vurderet i en større gruppe af børn med smalt aldersspektrum af forældre med skizofreni eller bipolar lidelse. På grund af det genetiske overlap mellem disse to sygdomme og det faktum at det motoriske og kognitive system er tæt relateret og interagerer under udvikling, er det relevant at undersøge specificitet af motoriske afvigelser, vedvarende opmærksomhed og kognitive kontrol hos børn med en familiær risiko for skizofreni eller bipolar lidelse.

3.2 Formålet

1: Evaluere eksisterende studier mhp at undersøge om førstegradsslægtninge til personer med skizofreni udviser forsinket motorisk udvikling eller forringelse af specifikke motoriske evner sammenlignet med personer uden en genetisk disposition (Papir I)

2: Undersøge om børn med en familiær risiko for skizofreni udviser mere udtalte motoriske vanskeligheder sammenlignet med kontroller. Børn med en familiær risiko for bipolar lidelse forventes at udvise mindre udtalte motoriske vanskeligheder sammenlignet med kontroller (papir II)

3: Undersøge om børn med en familiær risiko for skizofreni eller bipolar lidelse sammenlignet med kontroller vil i) udvise deficits i vedvarende opmærksomhed med længere reaktionstid over tid (vigilance), lavere reaktionstids konsistens generelt igennem testen samt lavere konsistens mellem blokkene. Endvidere ii) udvise deficits i kognitiv kontrol ved mindre nøjagtighed (accuracy), længere reaktionstid og større reaktionstid variabilitet gennem en test, som kræver kognitiv kontrol (Paper III).

3.3 Metode

Paper I: Vi anvendte PRISMA retningslinjerne for udførelsen af den systematisk litteratur gennemgang og meta-analyse. Vi søgte i videnskabelige databaser efter studier der afrapporterede motorisk funktion blandt individer yngre end 21 år og første-gradsslægtning (barn af eller søskende) til et individ med skizofreni. Studierne blev klassificeret i henhold til motorisk funktion og opdelt i motoriske domæner. Separate meta-analyser baseret på motoriske domæner blev præsenteret i 'forest plots'. Vi vurderede publikationsbias ved hjælp af Eggers test og 'funnel plot asymmetri' med en "Duval og Tweedie Trim and Fill analysis".

Paper II: Vi har etableret en prospektiv kohorte af 7-årige børn med ingen, en, eller to forældre med skizofreni eller bipolar lidelse. Vi undersøgte motorisk funktion blandt 514 børn vha Movement Assessment Battery for Children-Second Edition, der omfatter tre subdomæner: Fin og hånd motorik, bold evner og balance.

Paper III: Vi undersøgte vedvarende opmærksomhed ved hjælp af CPT-2. Kognitiv kontrol og 'tilpasning til fejl' blev målt ved anvendelse af et Erik Flanker paradigme for 7-årige børn med en familiær risiko for skizofreni eller bipolar lidelse sammenlignet med kontroller.

3.4 Resultater

Paper I: Tre og tyve studier mødte inklusionskriterier, med et samlet antal $n = 18.582$ og n varierende mellem motor domæner fra $n = 167$ til 8619. Børn under 4 år som er barn af en forældre med skizofreni udviste forsinket fin- og grov-motorisk udvikling ($k=3$, $n=167$, Hedges $g=0,644$, $CI=[0,328, 0,960]$, $p<0,001$), og forsinket gang-milepæl ($k=3$, $n=608$, $g=0,444$, $CI=[0,108, 0,780]$, $p=0,01$); børn og unge udviste forringet koordinationsevne ($k=8$, $n=8619$, $g=0,625$, $CI=[0,453, 0,797]$, $p<0,0001$) og abnorme bevægelser f.eks ufrivillige bevægelser ($k=6$, $n=8365$, $g=0,291$, $CI=[0,041, 0,542]$, $p=0,02$) sammenlignet med kontroller. Ved at måle på antallet af 'bløde neurologiske tegn' kunne der ikke påvises nogen forskel mellem at være førstegradsslægtninge af skizofreni sammenlignet med kontroller ($k=4$, $n=548$, $g=0,238$, $CI=[-0,106, 0,583]$, $p=0,18$). Korrigeres for publikationsbias ændrede dette ikke resultatet yderligere. Personer med en familiær risiko for skizofreni udviste forsinket fin- og grov-motorisk udvikling sammenlignet med børn af forældre med andre psykiske lidelser ($k=2$, $n=275$, $g=0,847$, $CI=[0,393, 1,300]$, $p<0,001$).

Paper II: Børn med en familiær risiko for skizofreni udviste ringere motorisk funktion sammenlignet med kontroller mht fin og håndmotorik (mean difference= -1.42, 95% CI: [-2.08– -0.77], $t_{(510)}=-4.27$, $p<0.0001$) og balance (mean difference= -1.38, 95% CI: [-2.03– -0.72], $t_{(508)}=-4.12$, $p<0.0001$), men ikke i forhold til bold færdigheder (mean difference= -0.39, 95% CI: [-0.97– 0.19], $t_{(510)}=-1.33$, $p=0.18$). Børn med en familiær risiko for bipolar lidelse udviste ingen signifikant forskel sammenlignet med kontroller i alle tre motor subdomæner: fin og håndmotorik: (mean difference= -0.69, 95% CI: [-1.44– 0.07], $t_{(512)}=-1.79$, $p=0.075$), balance (mean difference= -0.68, 95% CI: [-1.44– -0.08], $t_{(510)}=-1.75$, $p=0.08$), og boldevner (mean difference= -0.36, 95% CI: [-1.03– 0.31], $t_{(511)}=-1.05$, $p=0.29$). Drengene præsterede ringere i fht piger i subdomænerne fin og håndmotorik (mean difference= -2.29, 95% CI: [-2.87– -1.72], $t_{(510)}=-7.83$, $p<0.0001$) og balance (mean difference= -2.21, 95% CI: [-2.78– -1.63], $t_{(507)}=-7.52$, $p<0.0001$), hvorimod drengene udviste bedre boldevner end pigerne (mean difference= 0.80, 95% CI: [0.29– 1.31], $t_{(509)}=3.10$, $p=0.002$) med en signifikant gruppe*subdomæne interaktion.

Paper III: Vi kunne bekræfte hypotesen at børn med familiær risiko for skizofreni udviste svækket vedvarende opmærksomhed på CPT-2 med nedsat vigilance sammenlignet med børn med familiær risiko for bipolar lidelse (mean difference=0.01, 95% CI: [0.002– 0.019], $t_{(484)}=2.36$, $p=0.0018$), men kun en trend-signifikant forskel fra kontroller (mean difference=0.007, 95% CI: [-0.0002– 0.014], $t_{(209)}=1.91$, $p=0.058$). Der kunne ikke påvises en forskel i vedvarende opmærksomhed blandt børn med familiær risiko for bipolar lidelse og kontroller (mean difference= -0.003, 95% CI: [-0.012– 0.0054], $t_{(484)}=-0.74$, $p=0.46$). Børn med familiær risiko for skizofreni udviste lavere reaktionstids konsistens generelt igennem testen i forhold til kontroller (mean difference=2.23, 95% CI: [0.42– 4.03], $t_{(242)}=2.43$, $p=0.016$) og i forhold til børn med familiær risiko for bipolar lidelse (mean difference=3.4, 95% CI: [1.3– 5.49], $t_{(485)}=3.20$, $p=0.0015$). Derudover udviste drenge lavere generel reaktionstid konsistens i forhold til piger (mean difference=2.65, 95% CI: [1.03– 4.27], $t_{(307)}=3.22$, $p=0.0014$). Børn med familiær risiko for skizofreni udviste lavere konsistens mellem blokkene i forhold til kontroller (mean difference=5.37, 95% CI: [0.54– 10.19], $t_{(223)}=2.19$, $p=0.029$) og i forhold til børn med familiær risiko for bipolar lidelse (mean difference=8.85, 95% CI: [3.3– 14.4], $t_{(488)}=3.13$, $p=0.0018$).

Endvidere udviste drenge lavere konsistens mellem blokkene i forhold til piger (mean difference=7.58, 95% CI: [3.29–11.86], $t_{(288)}=3.48$, $p=0.0006$). Børn med familiær risiko for bipolar lidelse udviste ingen forskel i forhold til kontroller mht generel reaktion tid konsistens og reaktionstids konsistens mellem blokkene.

Vi kunne bekræfte vores anden hypotese at der kunne påvises en gruppe forskel mht kognitiv kontrol målt i et flanker paradigme; i accuracy ($F_{(2,494)}=3.06$, $p=0.048$), gennemsnitlig reaktionstid ($F_{(2,447)}=3.17$, $P=0.043$) samt for variationskoefficienten ($F_{(2,340)}=8.15$, $P=0.0003$). Piger med familiær risiko for skizofreni udviste signifikant lavere accuracy under inkongruente trials (mean difference= -0.16, 95% CI: [-0.29– -0.015], $T_{(490)}=-2.19$, $p=0.029$) i forhold til pigerne i kontrolgruppen. Børn med en familiær risiko for bipolar lidelse udviste lavere accuracy under inkongruente trials i forhold til kontroller. Derudover udviste børn med familiær risiko for skizofreni langsommere gennemsnitlig reaktionstid i forhold til kontroller, hvor reaktionstiden var hurtigere i kongruente trials og blandt ældre børn. Endvidere udviste børn med familiær risiko for skizofreni højere RT variabilitet i forhold til kontroller (mean difference=0.05, 95% CI: [0.03–0.076], $T_{(209)}=3.84$, $p=0.0002$) og i forhold til børn med familiær risiko for bipolar lidelse (mean difference=0.04, 95% CI: [0.01–0.074], $T_{(491)}=2.71$, $p=0.007$). RT variabiliteten var højere for inkongruente trails, for yngre børn og drenge udviste signifikant højere variationskoefficient end piger.

Endelig påviste vores resultater en korrelation mellem vedvarende opmærksomhed og motor funktion ($F_{(1,468)}=16.38$, $p<0.0001$), således at lav motorisk funktion korrelerer med en nedsat RT konsistens mellem blokkene.

3.5 Konklusion

Denne afhandling illustrerer at på gruppe niveau er en forskel på børns motorisk funktion og vedvarende opmærksomhed afhængig af barnets familiære risiko for skizofreni, bipolar lidelse eller ingen. Det Danske High Risk og Resilience study har bidraget til at påvise at børn før puberteten med familiær risiko for skizofreni har nedsat motoriske funktion og svækket vedvarende opmærksomhed samt afvigelser i evne til at udvise kognitive kontrol sammenlignet med kontroller. Børn med en familiær risiko for bipolar lidelse udviste ingen signifikant forskel i motorisk funktion, vedvarende opmærksomhed eller kognitive kontrol (med undtagelse af mindre accuracy under inkongruente trials) sammenlignet med kontrol børn. Denne afhandling bidrager til forståelsen af neuroudviklingsmæssige sårbarheder i barndommen og resultaterne indikerer, at motoriske vanskeligheder og svækket vedvarende opmærksomhed formentlig kan betragtes som en mulig samhörig endophenotype for skizofreni. Dette afspejler en forskellig udviklingsprofil med afvigelse af motorisk og opmærksomhedsfunktion på trods af det genetiske overlap mellem skizofreni og bipolar lidelse. Fremtidige studier bør følge denne kohorte mhp at klarlægge om disse motoriske og opmærksomhedsmæssige vanskeligheder i 7 års alderen er transitoriske eller persisterer gennem udvikling. Endvidere anbefales det at denne kohorte følges til børnene er voksne, således at man kan klarlægge hvilke sårbarheder der er prædikative for sygdom og hvilke faktorer der er beskyttende.

4 English summary

4.1 Background:

Individuals with schizophrenia and their offspring display motor impairments and attention deficits, whereas individuals with bipolar disorder and their children display both excellent and impaired cognitive abilities, even though schizophrenia and bipolar disorder are considered neurodevelopmental disorders with shared genetic liability. Previous studies, however, have not assessed motor function in children with a familial risk of bipolar disorder with a comprehensive motor tool. Moreover, previous studies on cognitive control and error adaptation in children of parents with schizophrenia or bipolar disorder have also been marked by small sample sizes and wide age-ranges. Hence, given the genetic overlap between these two disorders, and the fact that motor and cognitive systems are tightly interconnected during development, an investigation addressing the specificity of motor aberrations, sustained attention, and cognitive control abilities in children with a familial risk for both disorders would fill a gap in the literature.

4.2 Objectives:

- 1:** To evaluate the existing studies to assess if first-degree relatives to individuals with schizophrenia display delayed motor development or impairment in specific motor abilities compared with individuals without a genetic predisposition (Paper I).
- 2:** To examine if children with a familial risk of schizophrenia display more pronounced motor impairments than controls and whether children with a familial risk of bipolar disorder would show less pronounced motor deficits compared with controls (Paper II)
- 3:** To examine if children with a familial risk of schizophrenia or bipolar disorder compared with controls will i) display deficits in sustained attention with more longer reaction time as a function of time (vigilance) and lower overall reaction time (RT) consistency and lower between block RT consistency during a task requiring attention and ii) display deficits in cognitive control with less accuracy, higher RT, and greater coefficient of variation during a task requiring cognitive control compared with controls (Paper III).

4.3 Methods

Paper I: We applied the PRISMA guidelines and conducted a systematic review and meta-analysis. We performed the literature search in scientific databases searching for studies reporting motor function in unaffected individuals younger than 21 years with a first-degree relative with schizophrenia (i.e., offspring or sibling). We classified studies according to motor outcome, and performed separate meta-analyses that we presented in forest plots. We assessed publication bias using Eggers test and funnel plot asymmetry with a Duval and Tweedie's Trim and Fill analysis.

Paper II: We established a prospective cohort of 7-year-old children, with no, one, or two parents with schizophrenia or bipolar disorder. We investigated motor function in 514 children using the Movement Assessment Battery for Children–Second Edition which contained three subdomains: manual dexterity, aiming and catching, and balance.

Paper III: We compared sustained attention and cognitive control abilities of 7-year-old children with a familial risk of schizophrenia or bipolar disorder with controls. We assessed sustained attention using Conners' Continuous Performance Test II and the Erik Flanker paradigm to determine cognitive control and error adaptation.

4.4 Results

Paper I: Twenty-three studies met inclusion criteria, with a total sample size $n = 18582$. Sample sizes varied across motor domains from $n = 167$ to 8619 . Infants from affected families with schizophrenia were delayed in their gross and fine motor development ($k=3$, $n=167$, Hedges' $g=0.644$, $CI = [0.328, 0.960]$, $p < 0.001$), and walking milestone ($k=3$, $n=608$, $g=0.444$, $CI = [0.108, 0.780]$, $p=0.01$); children and adolescents showed impaired coordination ($k=8$, $n=8,619$, $g=0.625$, $CI = [0.453, 0.797]$, $p < 0.0001$) and abnormal movement ($k=6$, $n=8,365$, $g=0.291$, $CI = [0.041, 0.542]$, $p = 0.02$) compared with controls. Neurological soft signs did not yield reliable effects between first-degree relatives of schizophrenia compared with controls ($k=4$, $n=548$, $g=0.238$, $CI = [-0.106, 0.583]$, $p = 0.18$) and correcting for publication bias did not change the result. Finally, individuals with a familial risk of schizophrenia showed poorer gross and fine motor skills than children of parents with other mental disorders ($k=2$, $n=275$, $g=0.847$, $CI = [0.393, 1.300]$, $p < 0.001$).

Paper II: We could confirm the hypothesis that children with a familial risk of schizophrenia demonstrated impaired motor function compared with controls in the subdomains of manual dexterity (mean difference = -1.42 , 95% $CI: [-2.08, -0.77]$, $t_{(510)} = -4.27$, $p < 0.0001$) and balance (mean difference = -1.38 , 95% $CI: [-2.03, -0.72]$, $t_{(508)} = -4.12$, $p < 0.0001$), but not the subdomain of ball skills, including aiming and catching (mean difference = -0.39 , 95% $CI: [-0.97, 0.19]$, $t_{(510)} = -1.33$, $p = 0.18$). The second hypothesis of expecting less pronounced, but present motor deficits in children with a familial risk of bipolar disorder was not confirmed. Children with a familial risk of bipolar disorder did not differ significantly from controls in all three subdomains of manual dexterity (mean difference = -0.69 , 95% $CI: [-1.44, 0.07]$, $t_{(512)} = -1.79$, $p = 0.075$), balance (mean difference = -0.68 , 95% $CI: [-1.44, -0.08]$, $t_{(510)} = -1.75$, $p = 0.08$), and aiming and catching (mean difference = -0.36 , 95% $CI: [-1.03, 0.31]$, $t_{(511)} = -1.05$, $p = 0.29$). Finally, boys performed at a lower level than girls in the domains of manual dexterity (mean difference = -2.29 , 95% $CI: [-2.87, -1.72]$, $t_{(510)} = -7.83$, $p < 0.0001$) and balance (mean difference = -2.21 , 95% $CI: [-2.78, -1.63]$, $t_{(507)} = -7.52$, $p < 0.0001$). In contrast, however, boys outperformed girls in the domain of aiming and catching (mean difference = 0.80 , 95% $CI: [0.29, 1.31]$, $t_{(509)} = 3.10$, $p = 0.002$) with a significant 'sex-by-subdomain' interaction.

Paper III: We could confirm our first hypothesis measured on CPT-2 that children with a familial risk of schizophrenia displayed a deficit in sustained attention in terms of reduced vigilance compared with children with a familial risk of bipolar disorder (mean difference = 0.01 , 95% $CI: [0.002, 0.019]$, $t_{(484)} = 2.36$, $p = 0.0018$), but only differed at trend significance from controls (mean difference = 0.007 , 95% $CI: [-0.0002, 0.014]$, $t_{(209)} = 1.91$, $p = 0.058$). Children with a familial risk of bipolar disorder did not differ from controls (mean difference = -0.003 , 95% $CI: [-0.012, 0.0054]$, $t_{(484)} = -0.74$, $p = 0.46$). Moreover, groups differed in terms of overall RT consistency and between block RT consistency. Children with a familial risk of schizophrenia displayed lower overall RT consistency compared with controls (mean difference = 2.23 , 95% $CI: [0.42, 4.03]$, $t_{(242)} = 2.43$, $p = 0.016$) and compared with children with a familial risk of bipolar disorder (mean difference = 3.4 , 95% $CI: [1.3, 5.49]$, $t_{(485)} = 3.20$, $p = 0.0015$). Moreover, boys exhibited lower overall RT consistency than girls (mean difference = 2.65 , 95% $CI: [1.03, 4.27]$, $t_{(307)} = 3.22$,

$p=0.0014$). Children with a familial risk of schizophrenia displayed lower between block RT consistency compared with controls (mean difference=5.37, 95% CI: [0.54–10.19], $t_{(223)}=2.19$, $p=0.029$) and compared with children with a familial risk of bipolar disorder (mean difference=8.85, 95% CI: [3.3–14.4], $t_{(488)}=3.13$, $p=0.0018$). Moreover, boys exhibited lower between block RT consistency than girls (mean difference=7.58, 95% CI: [3.29–11.86], $t_{(288)}=3.48$, $p=0.0006$). Children with a familial risk of bipolar disorder did not differ from controls.

We could confirm our second hypothesis that group differed in terms of cognitive control abilities measured in a Flanker paradigm; accuracy ($F_{(2,494)}=3.06$, $p=0.048$), mean reaction time ($F_{(2,447)}=3.17$, $P=0.043$) and coefficient of variation ($F_{(2,340)}=8.15$, $P=0.0003$). Girls with a familial risk of schizophrenia displayed significant lower accuracy during incongruent trials (mean difference= -0.16, 95% CI: [-0.29– -0.015], $T_{(490)}=-2.19$, $p=0.029$) compared with girls in the control group. Children with a familial risk of bipolar disorder displayed lower accuracy during incongruent trials compared with controls. Moreover children with a familial risk of schizophrenia displayed slower mean reaction time compared with controls, that reaction times were faster in the congruent condition and among older children. Furthermore, children with a familial risk of schizophrenia displayed higher RT variability compared with controls (mean difference=0.05, 95% CI: [0.03–0.076], $T_{(209)}=3.84$, $p=0.0002$) and compared with children with a familial risk of bipolar disorder (mean difference=0.04, 95% CI: [0.01–0.074], $T_{(491)}=2.71$, $p=0.007$). RT variability was higher in the incongruent condition, young children and boys exhibited a significant higher coefficient of variation than girls.

Motor skill performance had a significant negative predicting effect ($F_{(1,468)}=16.38$, $p<0.0001$) on sustained attention indicating that lower level of motor performance/scores correlated with a decrease in between block RT consistency.

4.5 Conclusion

This thesis illustrates the differences on a group level in pre-pubertal children's motor function and sustained attention depending on the child's familial risk for schizophrenia, bipolar disorder or not. The Danish High Risk and Resilience study has provided evidence for impaired motor performance, deficits in sustained attention and subtle deviations in the cognitive control abilities in pre-pubertal children with a familial risk of schizophrenia compared with controls. Children with a familial risk of bipolar disorder displayed no significant differences in motor performance nor deficits in sustained attention or cognitive control (except for less accuracy during incongruent trials) compared with controls.

By assessing offspring of individuals with these two severe mental disorders, this study contributes to the understanding of neurodevelopmental vulnerability in childhood. Our results might indicate that motor deficits and deficits in sustained attention are a possible interrelated endophenotypes for schizophrenia, indicating deviation of developmental paths and different profiles of motor- and attentional functions despite the genetic liability for schizophrenia and bipolar disorder. Future studies should follow this cohort to identify whether these motor impairments and attentional deficits at the age of 7 years persist or are transitory during development. Furthermore, it would be valuable to follow this cohort until at least adulthood to verify which vulnerabilities predict disorder and which factors yield resilience.

5 Introduction and background

5.1 Familial risk of severe mental disorders.

Schizophrenia and bipolar disorders are related, complex, severe mental disorders. Individuals with schizophrenia present with symptoms of hallucinations, delusions, reduced motivation and diminished cognitive functions.¹ Bipolar disorder is characterized by cyclical and recurrent episodes of affective dysregulation (mania and depression), which impair daily functioning.² Schizophrenia is considered a neurodevelopmental disorder^{1;3}, whereas the case for bipolar disorder is not as strong.^{4;5} Individuals who develop schizophrenia in adulthood show subtle cognitive, motor and social abnormalities in childhood, long before psychotic symptoms emerge.⁶ Cohort studies show that adults with mania and depression have a history of anxiety and sleep disturbances in childhood and depression in adolescence.^{7;8} A follow-up study of bipolar offspring provided insight into the developmental path of bipolar disorder by documenting transition from either no diagnosis or anxiety spectrum disorders or unipolar depression to bipolar disorder.⁹

Severe mental disorders like schizophrenia and bipolar disorder are heritable through transmission of genetic substrates from the biological parent or as a result of genetic mutation. Offspring of a parent with a severe mental disorder have a 32%, 95% CI= [0.24- 0.42] probability of developing a severe mental disorder in adulthood¹⁰ and a 55% probability of developing any kind of mental disorder¹⁰. This is in contrast to the 1% lifetime prevalence risk of developing schizophrenia and 0.8 -1% lifetime prevalence risk of developing bipolar disorder for individuals without a genetic risk.¹¹ The interaction of genetic and environmental factors affecting the developing neurological system results in various phenotypic presentations of behavior,¹² despite the shared genetic liability for schizophrenia and bipolar disorder.¹³ Therefore the risk to develop, not only the disorder of the parents, but also another severe mental disorder, is increased.¹⁰ Children of a parent with schizophrenia have a 1.62 times the risk of developing bipolar disorder or major depression and 7.4 times the risk of developing schizophrenia compared to offspring of parents without schizophrenia.¹⁰ Carrying a familial risk of bipolar disorder the risk of developing schizophrenia or major depression is increased to the double (RR = 2.03), whereas the risk is 4.06 times increased of developing bipolar disorder as the parents.¹⁰

5.1.1 Gene - environment interactions

Despite the considerable genetic risk, environment factors also contribute to the risk of developing a severe mental disorder.¹⁴ Environmental exposures that interfere with prenatal development, such as maternal infections¹⁵ (influenza,¹⁶ toxoplasmosis,¹⁷ cytomegalovirus infection¹⁸) and lack of maternal vitamin D during pregnancy,¹⁹ preterm birth and obstetric complications²⁰ are associated with an increased risk of developing schizophrenia in adulthood. Furthermore, urbanicity and migration increase the risk of developing schizophrenia²¹. Moreover, low educational achievement and poor school performance are associated with schizophrenia^{22;23}, as opposed to bipolar disorder, in which both excellent and extremely poor school performance were associated with increased risk of bipolar disorder.^{24;25} Furthermore, head injury^{26;27}, parental loss²⁶, cannabis use during adolescent²⁸ and stressful life events in adulthood^{29;30} are associated with an increased risk of both bipolar and schizophrenia.

Familial risk of severe mental disorders may be further explained by the environment in which children of parents with severe mental disorders are raised. Research suggests that a secure attachment between children and their caregivers is a protective factor against mental disorders.³¹ Adverse life events such as bullying, childhood maltreatment³² and childhood trauma³³⁻³⁶ are associated with development of psychosis in early adulthood. However, little is known about the impact of environmental factors associated with being reared by a parent with a severe mental disorder. A Danish register study documents a greater tendency for children of a parent with a severe mental disorder to live with a single parent compared with the general population.³⁷ Further the risk of family dissolution was 2 to 3 times greater, if a parent was diagnosed with severe mental disorder (parental schizophrenia had the greatest risk) compared with the general population.³⁷

It has proven difficult to differentiate between the environmental and genetic contribution to the familial risk of severe mental disorders, one of the reasons being the presence of gene-environment interactions.³⁸ Individuals with a genetic risk are more vulnerable to environmental risk factors than those without a genetic risk.³⁸ Furthermore, evidence suggests that individual differences, such as factors fostering resilience, influence the impact and sensitivity of environmental exposure,³⁹ which may be mediated through genetic factors to some degree.⁴⁰ However, not all individuals who either carry a genetic risk variant or are exposed to environmental risk factors or both will develop severe mental disorder in adulthood.⁴¹ Symptoms of vulnerability during childhood can be transitory.⁴²

5.1.2 The concept of endophenotypes and intermediate phenotypes

The genetic underlying liability for severe mental disorders has created the basis for the concept of an endophenotype. Early measurable processes of vulnerability, which are unseen by the unaided eye, may be present in affected and in unaffected family members.⁴³ An endophenotype is associated with the disorder, heritable, state-independent (present in active disease and present in remission), present within the affected individuals and in their unaffected relatives in a higher frequency than in the general population.⁴³ Further an endophenotype is co-segregated with the disorder within the families, which require the endophenotype more prevalent in ill relatives of the affected individual than in the well relatives of the affected individual. Finally the endophenotype is more strongly associated with the disease than with other mental disorders.⁴³ An endophenotype is a reliable measurable component reflective of a developmental process that lies within the pathway between the disorder and genotype and implicates a vulnerability to the disorder.^{43;44} An endophenotype should thus not be regarded as a risk factor or an indicator of an elevated risk for a disorder, but rather as a manifestation of the underlying disease liability.⁴⁴ A biomarker, on the other hand, is any objectively measurable indicator of a normal biological process (e.g., HCG hormone of pregnancy), pathological process of a disorder (e.g., prostate specific antigen for prostate cancer) or pharmacologic responses to a therapeutic intervention. A defining characteristic of an endophenotype is its heritability, which stands in contrast to a biomarker, where this is not part of the definition.⁴⁴

An intermediate phenotype – “quantifiable biological mediators of genetic risk”⁴⁵ in relation to mental disorders is recommended as a tool for investigating the complex relationship between genes, neural circuits and behavior.⁴⁵ However, researchers define the term “intermediate phenotype” differently. Many view it as synonymous with the endophenotype concept.⁴⁶⁻⁴⁸ Others argue that an intermediate phenotype may be visible for the unaided eyes, which

distinguishes an intermediate phenotype from an endophenotype⁴⁴. However, the term “intermediate phenotype” is often used in the literature to describe the genetic influences on the neural circuits in the brain linked to behavior and disease.⁴⁹ Additionally, it has been argued that an endophenotype is related to a specific response measure, whereas an intermediate phenotype rather defines an operational definition, such as personality or clinical constellations⁵⁰. Throughout this dissertation and its empirical works, we consistently chose to use the concept of an *endophenotype*.

Various endophenotypes are suggested to underlie in schizophrenia such as neuromotor deviation such as neurological soft signs^{51;52} auditory-evoked P50 paradigms, working memory, mismatch negativity, continuous performance functional magnetic resonance imaging activation during continuous performance test and oculomotor-delayed response.⁵³ Executive function/working memory, verbal learning and memory are suggested endophenotypes for bipolar disorder.⁵⁴

5.1.3 Why study children with a familial risk of severe mental disorders

Detection of endophenotypes is important for identifying individuals at risk at an early stage. Ideally, we aim to identify only those children who are likely to develop a severe mental disorder and avoid unnecessary false alarms. Preventing the development of severe mental disorders is of high priority. Some cases of severe mental disorders may be preventable to some degree by modification of the environment³⁸. Given a child presents with multiple vulnerabilities (e.g., genetic disposition, environmental exposures and presence of endophenotypes), a tailored intervention that supports normal development and enhances resilience could be considered.

One way of investigating vulnerabilities /endophenotypes and resilience factors is the assessment of unaffected first-degree relatives of individuals with a severe mental disorder, in which the genetic disposition is present, without the manifestations of clinical symptoms of the disorder. Assessing children of parents with severe mental disorders provides information of early vulnerabilities and possibly resilience factors, which together may contribute the understanding of the complex underlying pathology.⁵⁵ Furthermore, the comparison of offspring of parents with schizophrenia and bipolar disorder and with children without this vulnerability enables the identification of differences and similarities across defined vulnerabilities. Such comparisons may help illuminate whether children display distinct profiles of abilities during development which depends on their familial risk status.

5.2 Motor function in children at risk of severe mental disorders

5.2.1 Motor function and development in humans

Motor development encompasses many developmental transitions during childhood and is inherently tied to transitions in other areas of development, such as intellectual development and self-control. Studies suggest an association between early motor problems and later cognitive difficulties.⁵⁶ Moreover and due to this relationship between cognitive and motor development, this focus may also contribute to understand the early signs of vulnerability to mental disorders. The presence of primitive reflexes, defined as involuntary movement elicited by external stimuli, at birth is an essential aspect of early motor development. These reflexes

disappear around 12 months. Persistence of primitive reflexes is considered a warning sign of a neurological problem.⁵⁶ In the first 15-18 months of life the child achieves ocular control and control over voluntary movement, such as postural control, manual control and locomotion. Postural control is the development of stability, balance and orientation. It entails first achieving head control and thereafter trunk control to achieve the ability of sitting and standing. Manual control involves reaching and grasping. Reaching refers to moving the hand from an initial location to a target location, whereas grasping describes shaping of the hand around an object.⁵⁶ Evidence suggests that newborns have the ability of prefunctional eye-hand coordination to some extent, which serves as an attentional mechanism rather than intentional behavior.⁵⁷ It is suggested that an orientation response is involved in the mechanism of voluntary reaching meaning that when a child fixates on an object and a new object appears, a reduction in motor activity occurs as the child attends the new stimulus.⁵⁷ Reaching and grasping are essential for managing tools like a spoon, fork or knife and later a crayon or pencil, which requires manual dexterity. Locomotion refers to rolling, creeping/crawling, and walking.⁵⁶

Motor development depends on and interacts with other systems such as vision, proprioception and musculoskeleton strength. Exteroceptive information from the visual system is important for achieving stability and postural control⁵⁶. Information from the proprioceptive system about sensation of movement in the muscles, joint and tendons (kinesthesia), tactile and vestibular information from the inner ear concerning maintaining equilibrium, controlling eye movement and sensing motion, play an important role in achieving normal motor development.⁵⁶ The muscular tonus and skeletal strength is critical for posture and performing movements.⁵⁶

Motor developmental delay in an individual may have numerous reasons. First, deficits in the neuro-motor systems may arise from the genetic substrate from the biological parents in addition to environmental exposures during development. Second, environmental exposures could be intrauterine mal-development owing to maternal infection and malnutrition, obstetric complications affecting the neuro-motor- and the cognitive system. Lastly, the lack of motor stimulation and training during development may also delay motor development.

5.2.2 Motor problems in individuals with neurodevelopmental disorders

Abnormal motor development is a well-known element of many childhood neurodevelopmental disorders such as attention-deficit/hyperactive disorder, autism, developmental coordination disorder, retardation, schizophrenia and the non-progressive disorder of cerebral palsy and Down syndrome.⁵⁶ Limited studies have assessed motor function in adolescents with bipolar disorder or their relatives.^{58;59} A study reports significantly more total soft signs in adolescents with attention deficits disorder compared with adolescents with bipolar disorder⁵⁸ and another study reports higher frequency of neurological soft signs in adolescents with bipolar disorder than in controls.⁵⁹ Furthermore, adults with bipolar disorder and their first-degree relatives display a higher frequency of neurological soft signs (subtle neurological abnormalities in motor coordination, sensory integration, and sequencing of complex motor acts)⁶⁰ compared with controls.^{61;62}

Various motor deficits occur in medicine-naïve individuals diagnosed with schizophrenia such as abnormal involuntary movements, catatonic symptoms, psychomotor slowing and parkinsonian signs.⁶³⁻⁶⁵ Furthermore, neurological soft signs and neurological abnormalities have repeatedly

been reported in individuals with schizophrenia,⁶⁶⁻⁷⁵ in pre-morbid groups,⁷⁶⁻⁷⁸ and in adult first-degree relatives.

5.2.3 Motor development in childhood prior to developing schizophrenia or bipolar disorder

A British birth cohort study has documented that motor developmental delay (i.e., delayed walking milestones, independent of sex and social status) precedes the onset of schizophrenia.²³ A Finnish birth cohort study found an association between delayed achievement of the standing and walking milestones increased risk of developing schizophrenia in adulthood. These motor effects were more pronounced among boys.⁷⁹ Furthermore, a birth cohort from New Zealand has documented delayed motor development at the age of 3, 5 and 9 years among individuals who develop schizophrenia in adulthood, whereas those individual who develop mania displayed superior motor performance in childhood compared with controls.⁸⁰ Children (0–15 years) who later developed schizophrenia displayed significantly more abnormal movements compared to their healthy siblings, and subjects from families without mental disorder, when assessing motor function in home videos.⁸¹ Furthermore, studies in adolescents with prodromal symptoms reported that those who developed manifest psychosis had significantly more movement abnormalities coded according to the Dyskinesia Identification System: Condensed User Scale⁸² than those who did not develop psychosis.⁸³

5.2.4 Motor function in first-degree relatives of individuals with schizophrenia and bipolar disorder

In the first to establish a high-risk cohort study in 1952, where 12 children born to mothers diagnosed with a schizophrenia spectrum disorder were followed until the age of 27-35 years, the authors observed neurodevelopmental aberrations in five of the children before the age of two and described this behavior as a neurointegrative disorder (pandysmaturity)⁸⁴. The follow-up study illustrated that the five children with pandysmature behavior before the age of two developed schizophrenia in adulthood.⁸⁵

Since then other high-risk studies have been conducted. The Copenhagen High Risk Study (CHRS) from 1962 is one of the largest studies conducted to date (n=207 offspring of mothers with schizophrenia). The CHRS provided evidence for delayed motor milestone in children born to mothers with schizophrenia.⁸⁶ These results were replicated by the Swedish high risk cohort.⁸⁷ However, the Finnish high risk study did not find delayed motor milestones in offspring of mothers with schizophrenia.⁸⁸

The Swedish high risk study assessed children of mothers with schizophrenia and children born to mothers with affective disorders. They only found motor impairments in children with a familial risk of schizophrenia, whereas children born to mothers with an affective disorder were comparable to controls in the domains of eye-hand coordination.⁸⁹

An Israeli longitudinal high risk study documented that individuals who exhibit a high level of hyperactivity and poor attention in childhood were more likely to develop schizophrenia in adulthood.⁹⁰ Similarly, both the New York high risk study and the Finish high risk study documented impaired motor skills as a predictor for developing schizophrenia in adulthood.^{88;91}

These cohort studies measured motor performance in various ways that vary in validity. Some studies obtained retrospective reports from mothers with schizophrenia or affective disorders.⁸⁶ Other studies used validated measures like the Bayley Scale of Infant Development,⁹²⁻⁹⁴ Griffiths developmental scale^{89;95} and Lincoln-Oseretsky Motor

Developmental Scale.^{91;96} Some studies also used measures constructed and validated in adults with schizophrenia, like the Neurological Evaluation Scale⁶⁰ (a measure of neurological soft signs), to assess children with no symptoms of psychosis^{97;98} and thus, these measures may lack sensitivity⁹⁹.

Measuring motor performance in children of parents with bipolar disorder explicitly is limited. One study have assessed motor speed (coordination speed on grooved pegboard) in offspring of bipolar parents, sample sizes were small (n=28) and a comprehensive motor test has not been used.¹⁰⁰ Other high-risk studies have assessed motor function in offspring of parents with an affective disorder consisting of unipolar and bipolar disorder but not assessed exclusively a bipolar sample.^{89;91}

5.3 The cognitive control system

5.3.1 Definitions

The executive functions refer to a collection of cognitive top-down processes, which include the abilities of planning, reasoning and problem solving.¹⁰¹ These processes are crucial for functioning in daily life in that they facilitate successful school and job performance as well as social functioning and promote physical and mental health.¹⁰¹ Cognitive control is an executive function that refers to the ability to monitor information processing and behavior towards a goal in the presence of a conflict.¹⁰² The cognitive control system is considered to consist of three core functions: inhibitory control, working memory and cognitive flexibility.¹⁰¹⁻¹⁰³ This dissertation focuses on inhibitory control, whereas other executive functions, such as working memory and cognitive flexibility are beyond the scope of this dissertation.

Inhibitory control is the ability to focus attention and control behavior, thoughts, and emotions in order to achieve a goal, while ignoring, inhibiting or overriding prepotent responses and irrelevant internal and external stimuli.¹⁰¹ Definitions of inhibitory control vary, but in the vast majority of the literature, definitions of inhibitory control distinguish between response suppression and interference control.¹⁰⁴ Response suppression refers to “the ability to prevent or suppress a highly practiced automatic or dominant response” (Mullane 2009)¹⁰⁴. Other terms for response suppression include, prepotent response inhibition,^{105;106} behavioral inhibition¹⁰⁷ and response inhibition.¹⁰⁸ Interference control is defined as “the ability to filter out competing information that is irrelevant to the task being performed” (Mullan 2009)¹⁰⁴. Interference control is used interchangeably with terms such as executive attention,¹⁰⁹ conflict resolution,¹¹⁰ and resistance to distractor interference.¹¹¹

In addition to definitions of inhibitory control that disentangle response suppression and interference control, other descriptions divide interference control into selective attention and cognitive inhibition¹⁰¹. Selective attention allows a person to selectively pay attention to a certain stimuli, while ignoring others. Cognitive inhibition is the ability to suppress unwanted thoughts and memories¹⁰¹ or information from working memory.¹⁰⁷

Children suffering from neurodevelopmental disorders such as autism, attention-deficit/hyperactivity disorder (ADHD), intellectual disabilities and schizophrenia often display deficits in the development of the executive control system or the cognitive control system.¹¹²⁻

5.3.2 Cognitive control

In order to attain our goals effectively in the everyday life with an increasing flow of information, it is necessary to attend selectively to relevant information and evade distraction by irrelevant information. Several neurocognitive tasks try to mimic the challenges to override prepotent responses, e.g. in a response competition paradigm, where distractors interfere with the relevant target. These distractors can be congruent with the target, incongruent or neutral to the target and thus represent a possibility to test the individual ability to attend to the target, however, typically, response time to congruent and neutral distractors is faster than response time to incongruent distractors information. When a conflict situation occurs i.e. incongruent distractors the hypothesis of conflict monitoring suggests that the conflict signal triggers strategic downstream adjustments of cognitive control to adjust behavior, which in turn serves to prevent the emergence of new conflicts in performance of the subsequent trials.^{116;117} It is anticipated that a conflict situation appeals for selective attention, which helps both enhancing target processing and suppression of irrelevant information.¹¹⁸

5.3.3 Error adaptation

It is human to make mistakes. How does committing an error, however, change our behavior to prevent future mistakes? Error adaptation is the theory of the ability to adapt behavior after an erroneous response by slowing response speed in the subsequent trial to improve accuracy and avoid additional errors.¹¹⁹ There are different types of behavioral post-error adjustment. These include post-error slowing (PES),¹²⁰ post-error reduction of interference (PERI)^{121;122} and post-error improvement in accuracy (PIA).^{123;124} Each is discussed in turn.

5.3.3.1 Post-error slowing

After an erroneous response the immediate subsequent response to the following trial will typically show an adaptation effect if the participant demonstrates a behavioral adaptation response to errors (*Figure 1*). This is reflected by a slower reaction time in the following trial after an error compared to the reaction time (RT) in trials following correct trials.¹²⁰ This phenomenon is called post-error slowing (PES) and is suggested to reflect abilities to accomplish cognitive control and as a marker of compensatory reorganization and adaption.¹²⁵

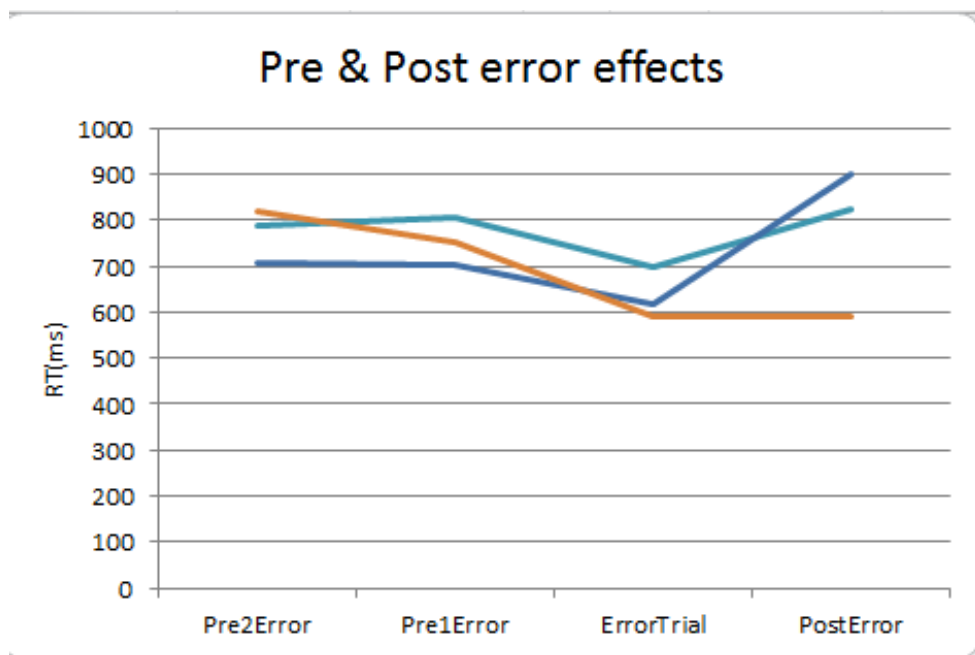
However, it is not clear to date whether the underlying mechanism of PES represents an adaptive effect of cognitive control or not.¹²⁶⁻¹²⁸ It is suggested that the conflict monitoring system becomes activated after an erroneous response, which triggers cognitive control to reduce excitatory input to the motor response resulting in slower reaction time and more accurate responses in the next trial.¹¹⁷ In other words, PES represents an increased motor threshold after an error, implemented by general motor inhibition to avoid future mistakes.¹¹⁷

Another understanding has been put forward, suggesting that an increase in selective suppression or inhibition occurs in the subsequent trial after an error. Thus irrelevant information in post-error trials interfere less with response processing after an error response than after a correct response because of an increased inhibitory control of the motor system established after errors.¹²¹

Other theories suggest that PES is not a result of cognitive control, but a reflecting of an unspecified orienting response.^{126;128} This is based on the fact that a fair amount of research reports a decrease in accuracy after an error, even though it is logical to expect accuracy to

increase following an error as a result of cognitive adaptation.^{126;128;129} These unexpected findings may be reconciled by proposing that PES may not represent adaptive behavior mediated from cognitive control, but the result of a more basic orienting response. PES may thus correlate in reaction time to an automatic orienting response to infrequent events (i.e the feedback given to the error response or the internal realization of the mistake in a non-feedback paradigm), which in turn inhibits the subsequent response and thereby creates PES.¹²⁸

Figure 1: Post-error effects in a trial complex before (pre2error and pre1error) and after an error (post error). Blue lines illustrate post-error slowing, whereas the orange line illustrates no post-error slowing. These graphs are simulated data to show the principal of post-error effects.



An orienting reflex including reduced perceptual sensitivity and motor inhibition was already suggested earlier in the field of motor development (Holsten in 1982)⁵⁷. An orientation response is involved in the mechanism of voluntary reaching, a motor activity that is reduced while infants attend to new stimuli (see 5.2.1 Motor function and development in humans).

5.3.3.2 Post-error improvement of accuracy

The adaptation process may lead to an improved accuracy in the subsequent trial. In other words, it is often observed that the accuracy is improved in the post-error trials compared to the post-correct trials after committing an error, thus demonstrating improved accuracy as a consequence of post-error adjustments, called *post-error improvement of accuracy* (PIA).¹²⁴ In cases where PIA and PES do not co-occur the difference may be due to differences in the time course.¹²⁴ This suggestion is based on the fact that PES is more pronounced in short response stimuli intervals, where accuracy decreases, whereas PIA is present mostly in longer inter-trial intervals.¹²⁴ Furthermore the type of error may influence selective attentional post-error adjustments.¹³⁰ Flanker-errors (errors due to flankers interfering) may reflect insufficient selective attention in contrast to non-flanker errors (premature responses or motor failure), which are anticipated not to initiate adjustment of selective attention. Consequently, when assessing cognitive error adaptation, it is suggested to distinguish between error types when

measuring PES and only assess trials with flanker-errors and avoiding including premature responses (non-flanker errors) in the assessment of PES.¹³⁰

5.3.3.3 Post-error reduction of interference

Interference control is the ability to focus on the target while ignoring competing irrelevant information.¹⁰⁴ Cognitive interference emerges from task-irrelevant information, represented by the flankers, which can either be congruent or incongruent. Irrelevant information is difficult to ignore and will influence RT, and therefore, RT is shorter in congruent trials than in incongruent trials¹²⁹. This is known as the interference effect¹²⁹. As a consequence of post-error adjustments and cognitive adaptation the interference effect is reduced after erroneous trials compared with after correct trials.^{122;131} The irrelevant information is filtered out more easily after an error due to an increase of alertness and cognitive adaptation. This is described as *post-error reduction of interference* (PERI). PERI reflects cognitive control processes that trigger improved interference resolution in post-error trials.¹²²

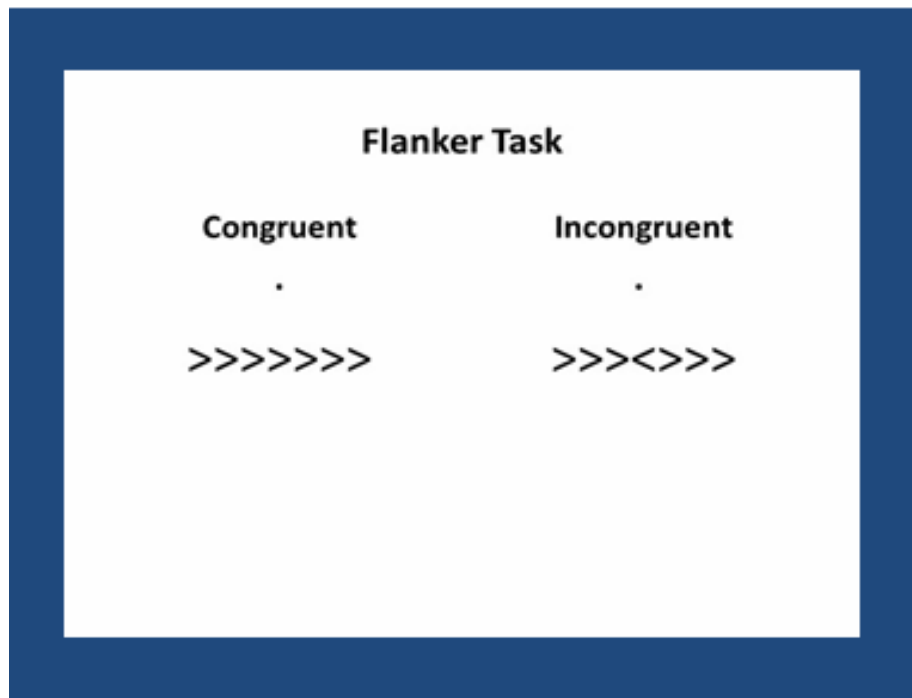
5.3.4 Measuring cognitive control

Different instruments measure inhibitory control. Examples of these are the Flanker task¹³² and Simon task,¹³³ which measure interference control by estimating reaction time in a non-verbal computerized task¹⁰⁴. Furthermore, the stop signal task¹³⁴ and go/no go task have been classified as instruments for measuring response inhibition. This dissertation will focus on interference control as measured by the Flanker task and response suppression/response inhibition as measured by one type of go/no-go task, the Conner's Continuous Performance Task-2 (CPT 2).¹³⁵

In a Flanker task a central stimulus (target) is flanked by irrelevant information (i.e. flankers) which is either congruent with the target or incongruent (*Figure 2*). Reaction time (RT) is one of the primary outcomes of the flanker task. In congruent trials, in which the central target points in the same direction as the flankers, reaction time is shorter and accuracy is higher. In incongruent trials, in which the flankers are in the opposite direction of the central target, reaction time is usually longer and accuracy lower. These incongruent trials represent a conflict and are believed to activate the conflict monitoring function in the brain. Research implicates the anterior cingulate cortex (ACC) as one of the areas that detects conflicts and responds by sending a signal to the cognitive control system to adjust behavior.¹³⁶

Measuring post-error slowing is documented in the literature in various ways. PES is traditionally calculated as the mean post-error RT (after errors of commission) minus the mean post-correct RT¹³⁷. In line with models of inattention (Sonuga-Barke see below), researchers suggest that the aspects of motivation and energy state should be incorporated into the measurement of post-error slowing¹³⁷. A recent model suggests that avoidance of contamination by global fluctuations in performance during the experiment, such as global changes in motivation or response caution should be considered when assessing post-error slowing. Therefore it is suggested to calculate PES from consecutive sequences of trials (PES complex) (*Figure 1*) consisting of the error trial (ErrorTrial), and the two previous correct trials before the error trials (Pre1Error) and (Pre2Error) followed by a correct post-error trial (PostError) (*Figure 1*).

Figure 2: Congruent and incongruent trial in a Flanker task. The test person is instructed to fixate on the dot on the computer screen and assess whether the central target arrow (below the dot) point to the right > or whether the central target arrow point to the left <. The interference effect consists of three arrows which surround the central target arrow and either are congruent to the central target >>> > >>> or incongruent <<< < <<<.



5.3.5 Cognitive control in children with a familial risk of schizophrenia and bipolar disorder

The ability to monitor one's own behavior, detect errors and to subsequently adapt behavior develops throughout childhood and adulthood in pace with the emergence of cognitive control. Several neuro-physiological measures associated with error adaptation show distinct neurodevelopmental trajectories from childhood to early adulthood.¹³⁸ Thus, it is important to explore the correlation of measures of error adaptation from a developmental perspective to understand how individual deviations of maturational tracks may correlate with the emergence of neuropsychiatric disorders.

Current evidence indicates that deficits in self-monitoring of one's own cognitive actions are associated with psychotic symptoms.¹³⁹⁻¹⁴³ Moreover, the interpretation of psychotic symptoms, such as errors in perception, suggests that patients with psychosis have difficulties correcting erroneous perceptions, which may originate in a deficient monitoring system. However, previously published studies report conflicting results with respect to the adaptation to errors (post-error slowing) in tasks measuring error adaptation in individuals with schizophrenia. Several studies report diminished post-error slowing in individuals with schizophrenia compared with controls^{144;145}, whereas others document normal post-error slowing in individual with schizophrenia.¹⁴⁶⁻¹⁴⁹ One of these studies assessed a prodromal high-risk sample and demonstrated that these individuals had normal post-error slowing compared with controls.¹⁴⁸

The error adaptation literature on individuals with bipolar disorder is limited. A recent study did not find a significant difference in post-error slowing between women with bipolar disorder and controls.¹⁵⁰ A study reported that first-degree relatives to individuals with bipolar disorders (n=24) had a slower reaction time in incongruent trials and greater individual variability than controls in a Flanker task.¹⁵¹

The development of cognitive processing is ongoing in children and adolescents. Despite the immaturity of the developing cognitive control system, neurophysiological measures, such as the error related negativity (ERN) may represent an endophenotype /biomarker for certain psychiatric disorders.¹⁵² Furthermore, children and adolescents with a familial risk of developing bipolar disorder may show specific deficits in cognitive flexibility, possibly representing an endophenotype for bipolar disorder.^{153;154}

5.4 Attention capacity in children with a familial risk of severe mental disorders

5.4.1 Definitions

Attention consists of three major systems: orienting system (selective attention), executive system (divided attention/multi-tasking attention) and the alerting and vigilance system (sustained attention).^{155;156} Attention is subjected to both external and internal control. Unexpected noise, movement or light changes in the surroundings can elicit an involuntary or automatic orientation of attention to the external event. The involuntary control of attention is named exogenous attention, while the voluntary control of attention is related to conscious decision making and is known as endogenous attention.

Models in ADHD research suggest dividing attention into networks of attention. The executive control network is associated with goal directed behavior, error detection, conflict resolution, target detection and inhibition of automatic response.¹⁵⁵ The alerting network is involved in obtaining a vigilant state and maintaining readiness to react. The orienting network entitles the attention to sensory stimuli and involves often the visual system and the oculo-motor system.¹⁵⁵ Developmental models of ADHD advocate viewing deficits of context dependent nature such as motivation and energetic state in addition to deficits of executive functions when assessing attention.¹⁵⁷

Individuals with schizophrenia and bipolar disorder exhibit deficits in attention, information processing and reward processing.¹⁵⁸ In subgroups of individuals with schizophrenia, with dominating negative symptoms, non-executive functions in attention such as motivation, and reward processing are dysfunctional¹⁵⁸. In individuals with bipolar disorders, motivation decreases in the depressive periods and increases to an excessive level in the manic periods¹⁵⁸. Several models suggest that dopamine plays an important role for the neurocognitive symptoms in schizophrenia and in bipolar disorder.^{159;160} Excess release of dopamine (hyperdopaminergic) underpins positive symptoms in schizophrenia and manic symptoms in bipolar disorder.^{159;160} Diminished release of dopamine is associated with negative symptoms in schizophrenia and depression in bipolar disorder.¹⁵⁸ Dopamine is involved in cognitive circuits. However, the abnormal phasic striatal dopamine signaling is not only critical for attention and reward processing, which is documented in both schizophrenia and bipolar disorders, but also for the motor and associative parts of the striatum.⁶ In sum, the dopaminergic circuits and signaling occurs in brain areas responsible for attention, executive function, reward processing and motor function. These brain areas, involved in the dopaminergic circuits, reflect the relationship and the interactions between the attentional and motor system and these systems

also underlie symptoms of attention, cognitive control and motor deficits seen in schizophrenia and to some extent in bipolar disorder.

5.4.2 Measuring sustained attention

Attention may be measured in various ways, dependent upon the choice of systems such as motor, working memory or vision that facilitates the measure of attention. Within a reaction time-dependent paradigm, reaction time is used as the main metric of attention capacity. Attention capacity can also be assessed in RT-independent paradigms e.g. paradigms based on theory of visual attention.¹⁶¹ In TVA, accuracy-based perceptual measures of visual attention (e.g., short term memory capacity, speed of information processing, attentional selectivity) are derived as distinct components of attention. When measuring attention in individuals who may have deficits within the motor system or visual system per se, it is important to distinguish effects of these deficits on attention from actual attentional deficits.

The present thesis measures sustained attention in a reaction time-dependent paradigm using Conner's performance test (CPT). This test is designed to measure sustained attention and response inhibition by providing different measures, such as overall reaction time (RT) consistency across the entire test and between block RT consistency, vigilance, reaction time processing speed and response inhibition. Between block RT consistency is the inconsistency or fluctuations in individual performance within one task and is considered to reflect both deficits in temporal processing¹⁶² and poor state regulation.¹⁵⁷ Errors of commission, i.e., number of responses to the non-target (X), is a measure for the ability of response inhibition driven by executive function and motivation,¹⁶³ whereas the rate of errors of omission gives a measure for errors due to inattentiveness.¹³⁵

5.4.3 Attention abilities in children with a familial risk of schizophrenia or bipolar disorder

Deficits in attention have been documented in adults suffering from schizophrenia and bipolar disorder in clinical and in experimental settings.^{164;165} Children's attention span, i.e., the length of time for which they are able to sustain focused attention, increases with age and is accompanied by a decrease in RT intra-individual variability, increase in RT consistency and a general improvement of cognitive control.¹⁶⁶ Adults with schizophrenia showed subtle cognitive impairments in sustained attention, executive function and working memory already as children.^{91;167} Several high risk studies have established that children with a familial risk of schizophrenia show deficits in sustained attention compared with controls.^{168;169} Moreover studies assessing children of parents with schizophrenia suggest that poor attention skills during mid-childhood predict schizophrenia in adulthood.^{170;171} Moreover, it has been proposed that deficits in sustained attention, as measured by Conner's continuation performance test, may represent an endophenotype for schizophrenia.^{172;173}

The presence of deficits of attention is not as well documented in children of parents with bipolar disorder, even not for those who develop bipolar disorder in adulthood. A review reported between 0% - 67% occurrence of attention deficits hyperactivity disorder (ADHD) among children of parent with bipolar disorder¹⁷⁴. However, a recent review concluded that ADHD in childhood did not predict bipolar disorder in adulthood, despite the presence of various deficits in attention during childhood among those who developed bipolar in adulthood.¹⁷⁵ Only those children with a life-time psychiatric diagnosis reported attention problems (ADHD RS questionnaire) in offspring of bipolar disorders but otherwise did not differ

from offspring without a life-time psychiatric diagnosis when measuring sustained attention on the Talland Letter Cancellation Test.¹⁷⁶ The prevalence of lifetime diagnosis of ADHD in a longitudinal Dutch cohort study of children of parent with bipolar disorder was 5 %.¹⁷⁷ Similarly the Amish offspring study of bipolar parents reported that attention deficits pattern were not common in their sample of 100 children of parents with bipolar disorders.¹⁷⁸ In sum, owing to the conflicting reports as to which children with a familial risk of bipolar disorder have attentional deficits or not, it would be relevant to consider whether the attention deficits is assessed by a direct measure or derived by a questionnaire rated by parents or teachers.

5.5 The relationship between motor function, error adaptation, and attention

According to the hypothesis of neurodevelopmental disorder^{1;6;179;180} and as established in birth cohorts and high-risk studies, both cognitive- and motor impairments are evident in childhood in individuals developing schizophrenia in adulthood.^{85;91;181;182} This is reflected in brain mapping studies, in which evidence suggests that motor development and cognitive development is interrelated owing to the abundant connection between the cerebellum and the dorsolateral prefrontal cortex.¹⁸³ The important role of the cerebellum in coordination and motor skills is well-known.¹⁸⁴ Growing evidence verifies that the cerebellum also has non-motor functions, including executive function, spatial cognition, memory, language, affect, timing, and associative learning.¹⁸⁵⁻¹⁹¹ Similarly, the dorsolateral prefrontal cortex is involved in the development of motor function beyond cognitive control, such as executive function and attention. Recent theories conceptualize schizophrenia as a disorder of poor coordination (cognitive dysmetria) in domains of functioning, including movement and cognition.^{192;193}

The relationship and tight connection of the attentional system with the motor systems is also conceptualized in the premotor theory.¹⁹⁴ The theory proposed that shift of visual attention is a consequence of oculomotor programming, denoting that directing attention is connected to preparing an eye movement. In other words part of directing attention is mediated through the cerebral programming and preparation of an eye movement, even before the factual moving of the eye.¹⁹⁴

The achievement of age equivalent cognitive- and motor abilities is most likely due to a combination of genetic, heritable cognitive and motor capabilities, as well as an element of stimulation and training during development. The close interplay between motor and cognitive development is reflected in observations of related deficits in cognitive development with delayed motor function. Examples for this relationship are neurodevelopmental disorders, such as autism and attention deficit disorder (ADHD), in addition to schizophrenia, in which abnormalities in executive function are associated with motor deviations.

The literature is extensively larger regarding children of parents with schizophrenia compared to the literature of children with parent diagnosed with bipolar disorder. Although early cognitive abnormalities are reported in individuals with bipolar disorder and schizophrenia, the two disorders may have different developmental trajectories. The shared genetic liability and some of the environmental exposures (e.g., head injury, parental loss, and obstetric complications) contribute to increased risk of both disorders. Other pathways to bipolar disorder and schizophrenia are not fully shared.²⁶ Further research is needed to expose the differences and similarities during development.

5.6 Aims and hypothesis of the study

First, we aimed to search the literature, if abnormalities in motor function occur in unaffected first-degree relatives of individuals with schizophrenia during development (0 to 21 years of age) compared with controls. Specifically, we investigated whether children with a genetic risk of developing schizophrenia without manifest symptoms of psychosis display evidence for a motor impairment on a group level, which could represent an endophenotype.

Furthermore, we aimed to explore differences and similarities between 7-year-old children with a familial risk of schizophrenia or bipolar disorders and children without this vulnerability to determine whether children with familial risk display distinct profiles of their motor function, sustained attention, and cognitive control system.

We hypothesized that:

1. First-degree relatives to individuals with schizophrenia display delayed motor development or impairment in specific motor abilities compared with individuals without a genetic predisposition? (paper I)
2. Children with a familial risk of schizophrenia display more pronounced motor impairments compared with controls and children with a familial risk of bipolar disorder show less pronounced motor deficits compared with controls (paper II)
3. Children with a familial risk of schizophrenia or bipolar disorder will i) display deficits in sustained attention with longer reaction times as a function of time (vigilance), lower overall reaction time (RT) consistency and lower between block RT consistency during a task requiring attention and ii) display deficits in cognitive control with less accuracy, higher RT, and greater coefficient of variation during a task requiring cognitive control compared with controls (paper III).

6 Material and methods

6.1 Design of the papers

Paper I report the findings from a systematic review and meta-analysis of young (≤ 21 years) first-degree relatives of individuals with schizophrenia. Papers II and III are based on data derived in a case-control study: The Danish High Risk and Resilience Study VIA 7. Paper II reports the findings concerning motor function in children with a familial risk of schizophrenia or bipolar disorder compared with controls. Paper III reports the results of sustained attention and cognitive control function in children with a genetic risk profile compared with controls.

6.2 Settings

The present study presents baseline data (cross-sectional data) from a prospective case-control cohort in a longitudinal follow-up design, the “Danish High Risk and Resilience Study VIA 7”.¹⁹⁵ The cohort was established in Denmark between December 2012 and March 2016 and consists of 522 seven-year-old children with different familial risk profiles of schizophrenia, bipolar disorder or neither. The participants of the cohort (parents and the children) underwent a large test-battery of various domains, which included neurocognitive, motor function, psychopathology, social cognitive, home environment assessment, attachment style, genetic assessment, teacher’s opinion of the child and adverse life event assessment. This thesis will only report on the motor function, attention and cognitive control among the children.

Participants’ parents gave written informed consent. The Danish Data Protection Agency approved the study protocol. The Danish National Committee on Health Research Ethics received the protocol for approval and we obtained a general evaluation, but due to the absence of any intervention, ethical approval was not deemed further necessary by the authority.¹⁹⁵ We received permission to extract data from registers from the Danish Ministry of Health.

6.3 Participants

6.3.1 Identification of sample

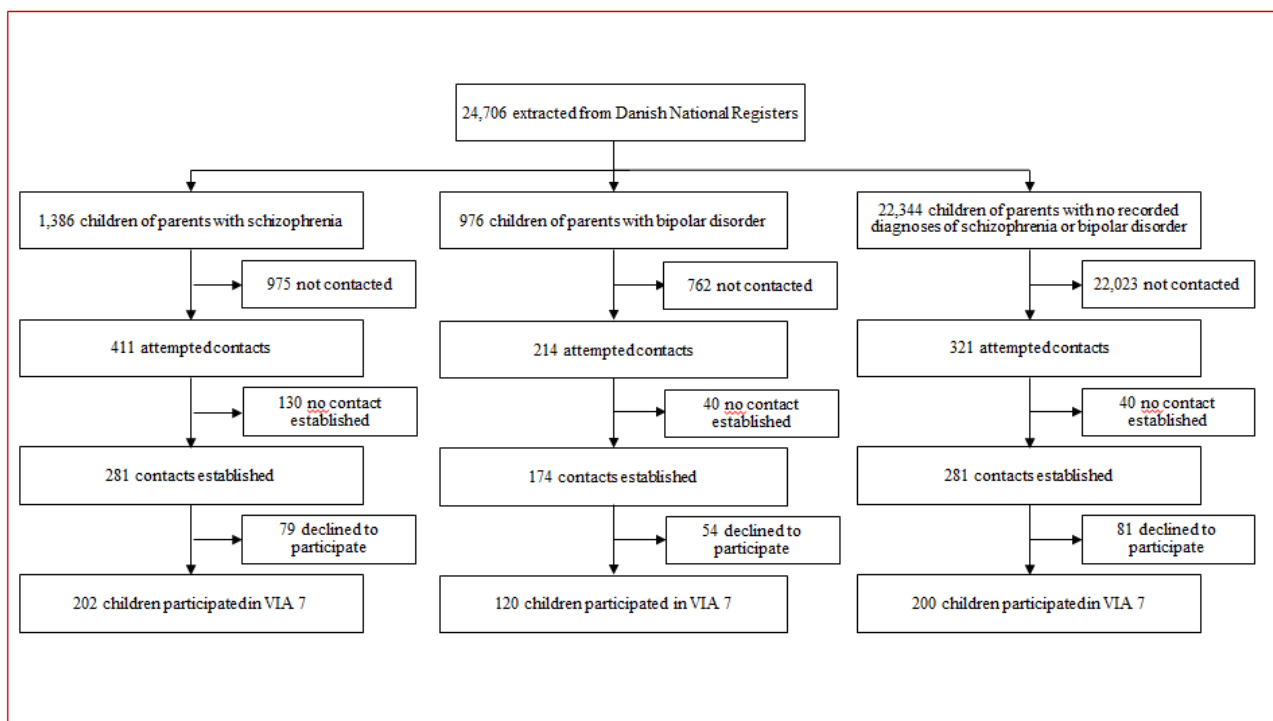
Our prospective cohort consists of 522 seven-year-old Danish children. Two-hundred-two children had at least one parent with a diagnosis of schizophrenia spectrum psychosis and 120 children had at least one parent with bipolar disorder. Two-hundred children had parents with neither of these diagnoses. We identified this cohort using a combination of registries. The Danish Psychiatric Central Research Register (DPCR)¹⁹⁶ provided diagnostic information based on in- and out-patient contact with psychiatry. The DPCR began to register in-patient contacts with the psychiatric services on April 1st, 1969 and out-patient contacts on January 1st, 1995. We extracted data from April 1st, 1969 to the end of 2011. Schizophrenia spectrum psychosis was defined as schizophrenia, delusional disorder, or schizoaffective disorder (ICD 10-codes: F20, F22 and F25 or ICD 8-codes: 295, 297, 298.29, 298.39, 298.99). Bipolar disorder was defined as ICD 10-code F31 or ICD 8-codes 296.19 or 296.39. The Danish Civil Registration System (DCRS) was used to identify children born in Denmark who turned seven years between September 1st, 2011 to August 31st, 2016. We also used the DCRS to link child data with parent

data. Participants/ children were not excluded based on additional psychiatric diagnoses of the parents because of the ICD-10 classification for mental and behavioural disorders, which is based on the hierarchical principle that the lowest numeric value is the main diagnosis. For example, a parent with schizophrenia could also have a diagnosis of bipolar disorder, whereas a parent with bipolar disorder could not have a diagnosis of schizophrenia. For each child with a familial risk of schizophrenia, ten eligible control children matched on age, sex and home address (municipality) were identified and selected. Second, we used the sex of the ill parent to appoint an index parent in the control family. For families with two ill parents, we used both parents to appoint an index parents in the control family. Children of parents with bipolar disorder were not matched to control children, but overall they were similar in terms of age, sex, and urbanicity.

6.3.2 Sample recruitment

Individuals identified from the registers were selected randomly and invited to participate in the VIA 7 study (Figure 3). We randomly enrolled one of the ten eligible controls for each child with a familial risk of schizophrenia. Siblings, including twins, of participating VIA 7 children were eligible for participation if the children came from a familial risk group, but not if the children came from control families. It was a requirement for all families that the child was not adopted or was a donor child with unknown genetic origin.

Figure 3: Sample flow chart



Initially, families received a letter by post. If the family did not respond to the letter, we contacted them by telephone, text message, or email. If the family could not be located at the address, either because of errors in the address or because the family had moved, an effort was made to find the right address through other means such as the telephone directory and the

hospital directory. For children in foster care, we contacted the children's social workers and biological parents with custody.

We met with each family and explained the purposes of the VIA 7 study, the implications of participation for them, and our legal obligations toward participants. Two researchers met each family throughout the assessment. The researcher who tested the child was blinded to the child's risk status. The other researcher interviewed and tested both parents, as well as one or two additional caregivers, if relevant. Stepparents and foster parents were interviewed, if they had lived at the same address with the child for at least the past 12 months. The child assessment, which included a home visit, took three to four days. At the end of the testing, the researchers offered the parent a general feedback of the child's function.

Nine families discontinued participation before they completed all assessments. However, all families agreed that we could use any data that we already had collected. Families stopped participation due to family circumstances such as an illness in the family, a death of a parent, a home fire or a change of residence.

6.3.3 Description of the cohort

A higher percentage of the biological parents were divorced and unemployed/on leave (sick leave, maternity, or retirement) in the familial risk groups than in the control group, and a larger proportion of children in the familial risk groups lived with a single parent. Index parents with schizophrenia and the healthy co-parent were both considerably less educated than index parents and healthy co-parents with bipolar disorder and control parents (*Table 1*).

Table 1: Characteristics of children and their parents participating in the Danish High Risk and Resilience Study VIA 7. Index parents refer to the biological parents with schizophrenia or bipolar disorder or, in the control group, the matched biological parent without any of these disorders.

	Schizophrenia familial-risk group	Bipolar disorder familial-risk group	Control group
Index Parent			
Total number of index parents	200	116	204
Female, N (%)	110 (55.0%)	64 (55.2%)	114 (55.9%)
Age at inclusion, mean (SD)	38.1 (6.1)	41.0 (7.0)	40.7 (4.8)
PSP, mean (SD)*	66.9 (15.8)	68.5 (13.9)	84.2 (10.1)
Unemployed or on leave	84 (48.8%)	46 (44.7%)	18 (9.3%)
Education			
Primary/ lower secondary education	50 (29.2%)	9 (8.5%)	8 (4.2%)
Upper secondary, vocational, short-cycle tertiary	73 (42.7 %)	44 (41.5%)	91 (47.6%)
Bachelor degree, equivalent or higher	48 (28.1%)	53 (50.0%)	92 (48.2%)
Biological co-parent			
Total number of co-parents	186	114	192
Female, N (%)	83 (44.6%)	51 (44.7%)	84 (43.8%)
Age at inclusion, mean (SD)	38.8 (6.4)	41.0 (5.4)	40.7 (4.2)
PSP, mean (SD)*	76.1 (14.2)	81.8 (13.3)	85.5 (8.5)
Unemployed or on leave	46 (26.4%)	14 (13.2%)	12 (6.4%)
Education, N (%)			
Primary/ lower secondary education	31 (17.5%)	5 (4.8%)	9 (4.8%)
Upper secondary, vocational, short-cycle tertiary	87 (49.2%)	43 (41.3%)	89 (47.8%)
Bachelor degree, equivalent or higher	59 (33.1%)	56 (53.8%)	88 (47.3%)
Child			
Total number of children	202	120	200
Age at inclusion, mean (SD)	7.8 (0.2)	7.9 (0.2)	7.8 (0.2)
Female, N (%)	93 (46.0%)	56 (46.7%)	93 (46.5%)
Two biological parents with SZ or/and BD, N (%)	7 (3.5%)	1 (0.8%)	-
CBCL score, mean (SD) **	27.2 (21.0)	23.3 (19.7)	17.0 (14.8)
CGAS, mean (SD) ***	68.2 (15.5)	73.5 (14.9)	77.7 (13.5)
Home environment			
Living with both biological parents, N (%)	81 (40.3%)	62 (53.0%)	169 (84.9%)
Living out of home, N (%)	11 (5.5%)	0 (0.0%)	1 (0.5%)
Living with index parent, N (%)	121 (59.9%)	81 (67.5%)	188 (94.0%)
Living with a single parent, N (%)	75 (37.3%)	37 (31.6%)	21 (10.6%)

* Personal and social performance scale (PSP) is a measure of personal and social functioning and ranges from 0 to 100 with higher scores reflecting better functioning.

** Child Behavior Check List (CBCL) is a parent-rated measure of problem behavior in children. Larger scores reflect more problems.

*** Children's Global Assessment Scale (CGAS) is a measure of general functioning in children rated by trained interviewers. The scale ranges from 0 to 100 with higher scores reflecting better functioning.

6.4 Instruments

6.4.1 Paper I: Systematic review and meta-analysis of motor function in first-degree relatives of individual with schizophrenia.

This study was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and was registered at PROSPERO international prospective register of systemic reviews (registration number [CRD42012002591](#)) before the literature search.

Searches were performed in PubMed, PsycINFO, EMBASE, and the Cochrane Library. *Table 2* provides an overview of the search terms. References were examined for relevance and included if appropriate. No limitations were imposed regarding language, publication date, or country of origin.

Table 2: Search keywords

	AND		AND
	Clinical	Population	Outcome
OR	High risk	Child* [TIAB]	Motor
	High-risk	Adolescen* [TIAB]	Motor ability
	Clinical high risk	Infan* [TIAB]	Neurological soft signs
	Schizophrenia [TIAB]	Offspring	Motor milestones
	Psychos* [TIAB]		Functional outcome
	Psychotic [TIAB]		Movement abnormalities
	Mental illness [TIAB]		Developmental abnormalities
			Developmental disabilities
			Motor skills disorder
			Dyskines*
			Pandysmatur*

6.4.1.1 Inclusion criteria of studies

1. Investigates first-degree relatives (offspring or siblings) of individuals with schizophrenia
2. Assesses motor abilities or neurodevelopment
3. Includes a control group
4. Includes a sample ≤ 21 years of age.

6.4.1.2 Exclusion criteria

1. Manifest symptoms of schizophrenia in first degree relatives
2. Ultra-high-risk status in first-degree relatives (prodromal syndrome)
3. Reports no data on motor function of the child/adolescents

6.4.1.3 Outcome measures

We classified studies into six domains of motor function based on motor outcomes studies reported. We performed meta-analyses for each domain, and we reported the results within the following categories:

- *Gross and fine motor development*: assessed in infants aged 0–3.5 years using the Psychomotor Development Index (PDI) from the Bayley Scale of Infant Development¹⁹⁷. Test items for the PDI included motor skills, such as rolling, crawling, grasping, and using utensils.
- *Delay in walking*: age at which the child reached the milestone of walking. Categories were walking with support at the age of 10 months,⁸⁶ walking at 12 months,⁸⁸ or walking without support at the age of 18 months versus later.⁸⁷
- *Impaired coordination*: several measures of coordination were recorded including finger opposition, diadochokinesis, rapidly opening and closing the hand¹⁹⁸, placing matches into a box¹⁹⁹, patterned movements of arm and hand, tapping finger and foot, finger following, visual motor coordination (copying of simple geometric figures)²⁰⁰, finger-nose, finger pursuit, heel-knee, rapid alternation, and rapid finger movement. Furthermore, activities such as buttoning, writing¹⁸¹ or inability to draw⁸⁷ were recorded. Fine motor skills^{89;95} were assessed using the Eye and Hand Coordination subscale of the Griffiths Developmental Scale^{201;202}. Eye-hand coordination and finger dexterity were also assessed using the Lincoln–Oseretsky Motor Development Scale^{96;203}.
- *Abnormal movements*: defined as tremors, tics, spasms or athetoid movements¹⁸¹. Mirror movements, associated movements or involuntary movements were also included^{198;204}. Furthermore, choreoathetoid movements, abnormal facial movements, repetitive and spastic movements, hyper-/hypotonicity, bradykinesia, abnormal hand posture, abnormal posture⁸¹ or motor overflow²⁰⁰ were assessed. Finally, studies reporting a composite neuromotor measure where movement abnormalities were the main contributor^{81;89;204}.
- *Neurological soft signs*: assessed using the Neurological Evaluation Scale (NES)⁶⁰ or during a general neurological examination^{88;205}. One study divided the NES into repetitive-motor and cognitive-perceptual subscales⁹⁸. The data from the repetitive motor subscale only were used in this meta-analysis.
- *Fine and gross motor skills*: The Lincoln–Oseretsky Motor Development Scale²⁰³ was used to assess finger dexterity, eye-hand coordination, and gross activity of hands, arms, legs, and trunk in children 6–14 years old.⁹¹ One study²⁰⁶ assessed gross motor skills, such as hopping, walking in a line, and catching a ball, as well as fine motor skills, such as using pegboards, stringing beads, and the Porteus Maze Test²⁰⁷.

Individuals from the same sample could be included in several motor outcome domains. For example, if the study tested coordination and abnormal movements, the sample was included in both domains. Furthermore, if the study had an outcome measure comprising many different motor skills, we chose the most relevant motor outcome group to that specific outcome.

6.4.2 Paper II: Motor function

Motor abilities were assessed using the Movement Assessment Battery for Children–Second Edition (Movement ABC-2),²⁰⁸ which is a standardized test comprising three components: manual dexterity, aiming and catching, and balance. Manual dexterity measures abilities requiring fine motor skills using tasks, such as placing pegs, threading lace, and drawing a trail. The aiming and catching subdomain measures balls skills, with assessment of catching with two hands and throwing beanbags onto a mat. Finally, the balance subdomain, which measures static and dynamic balance, entails one-board balance, walking heel-to-toe forwards, and hopping on mats. All raters were trained, approved, and certified by a physiotherapist authorized in assessing Movement ABC-2 and were blinded to participants' clinical risk statuses when conducting assessments.

6.4.2.1 Data collection and inter-rater reliability

Movement ABC-2 assessments were preferably conducted in the same room where outlines for the assessment (i.e., throwing a ball, walking on a line) were designated. A few children were assessed at home at the wish of parents that examinations take place in familiar surroundings. Most assessments were recorded on video (n=469). We conducted regular inter-rater reliability assessments during data collection using the ratings of ten videos of children performing the Movement ABC-2. Intra-class correlation for single measures varied between ICC=0.71–1.0 except for the item walking heel-to-toe forwards (ICC=0.52). One single rater (BKB), blinded to risk status, consistently scored the item 'drawing trail 2'. Intra-rater reliability for ten sets of 'drawing trail 2' between the rater and the instructing physiotherapist was ICC=0.98, and the within-rater reliability across four weeks was ICC=0.97.

6.4.3 Paper III: Cognitive control, error adaptation and sustain attention.

6.4.3.1 Eriksen Flanker Task

Cognitive control and error adaptation was assessed using a modified visuospatial task involving an interference effect, the Eriksen Flanker Task paradigm¹³² implemented in E-prime 2 software tool (Psychology Software Tools, 2012). We instructed the child to fixate on a dot on the computer screen and to press the right mouse button when the central target arrow point to the right > and press the left mouse button when the central target arrow point to the left < as precise and fast as possible. The interference effect consists of three arrows which surround the central target arrow and either are congruent to the central target >>> > >>> or incongruent <<< < <<<. See paper III for description of exact instruction.

6.4.3.2 Conners' Continuous Performing Test II

Sustained attention was assessed using a go/no-go task: Conners' Continuous Performing Test II (CPT-2),¹³⁵ where the child had to press the mouse button every time a letter appears on the computer screen (go) except for the letter X, where the child is supposed to inhibit the response and omit to press (no-go). See paper III for further details.

6.5 Statistical analysis

6.5.1 Paper I: meta-analysis

The meta-analysis was conducted using a random effect model. Effect sizes were calculated as (Hedges' g) to avoid bias for small study samples and results presented as forest plots. Meta-regression including age as moderator was performed for outcome measures larger than five studies. Funnel plots and Egger's test of intercept in a random effects model were assessed to estimate the potential publication bias. A 'Trim and Fill' analysis was performed to quantify the effect of missing studies on the observed effect size and re-calculate the meta-estimate based on hypothetical studies which could have generated a symmetrical funnel plot.²⁰⁹ Analyses were performed in Comprehensive Meta-Analysis (2.0).²¹⁰

6.5.2 Paper II.

The effect of familial risk group was tested in a mixed-model analysis with repeated measures over the three subdomains of the Movement ABC-2 (manual dexterity, aiming and catching, and balance). Matched, non-matched children and controls were included in the model as random effects. The model was adjusted for age and sex, as well as all two-way, three-way and four-way interactions of familial risk group, sex, age, and motor subdomains. The statistical analysis was performed in SAS using the PROC MIXED command. Logistic regression was used assessing the binary outcome of having definite motor problems (children who scored $\leq 5^{\text{th}}$ percentile) or not, while adjusting for age and sex. Finally, we explored the significance of the following variables in the repeated mixed model analysis: handedness, 'living with both biological parents', 'living with index parent', 'living with single parent' and 'personal and social performance score' (PSP) of the biological index parent and the biological healthy co-parent, in addition to 'education level' for index and biological co-parent.

6.5.3 Paper III.

The effect of familial group was analyzed in a mixed-model analysis with repeated measure over the trials congruent and incongruent, where matched cases, the non-matched cases and controls were included in the model as random effects. Covariates included age, sex, and condition (congruent or incongruent trials). Beyond these independent variables, we considered all two-way and three-way interactions of group, sex, age and condition. Statistically nonsignificant interaction terms were eliminated via backward stepwise regression, with the constraint that the model at each step had to be hierarchically well formulated. All lower-order terms that is sex, age, group and condition, were included in the model regardless of statistical significance and owing to their biological plausibility. The effect of sustained attention (vigilance, overall RT consistency, between block RT consistency) across groups was tested by using a univariate Analysis of Covariance (ANCOVA) in a mixed model analysis, where matched cases, non-matched cases and controls were included in the model as random effects. Covariates included age and sex. Beyond these independent variables, we considered all 2- and 3-way interactions of group, sex and age. Both statistical analyses were performed in SAS (version 9.4) using the PROC MIXED command.

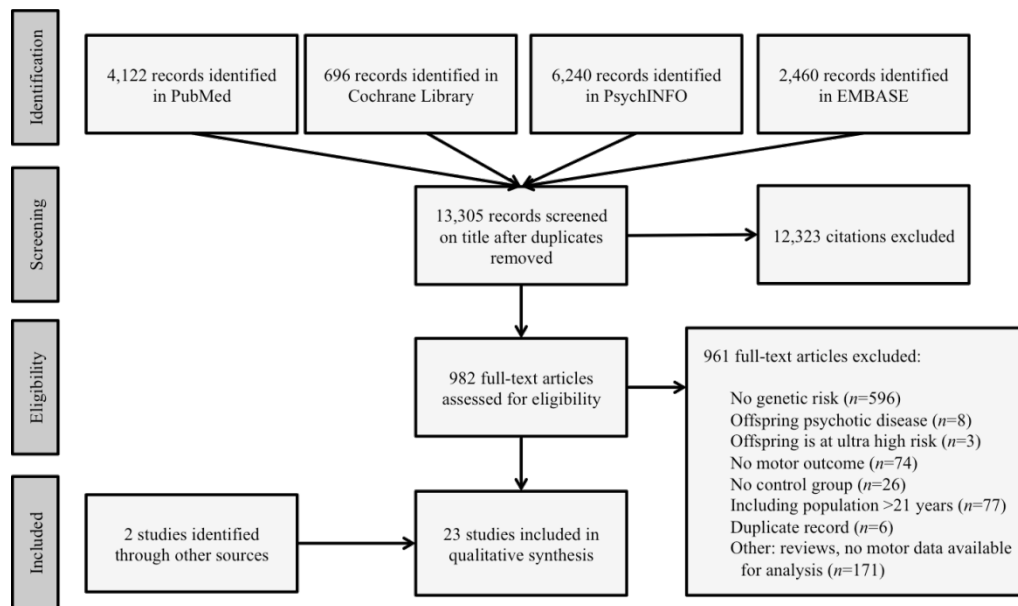
Multiple linear regression was used to test the relationship between sustained attention and motor performance. Attention was assessed as between block RT consistency from CPT-2. Motor performance was measured by Movement ABC-2 as total standard score.

7 Results

7.1 Results from Paper I

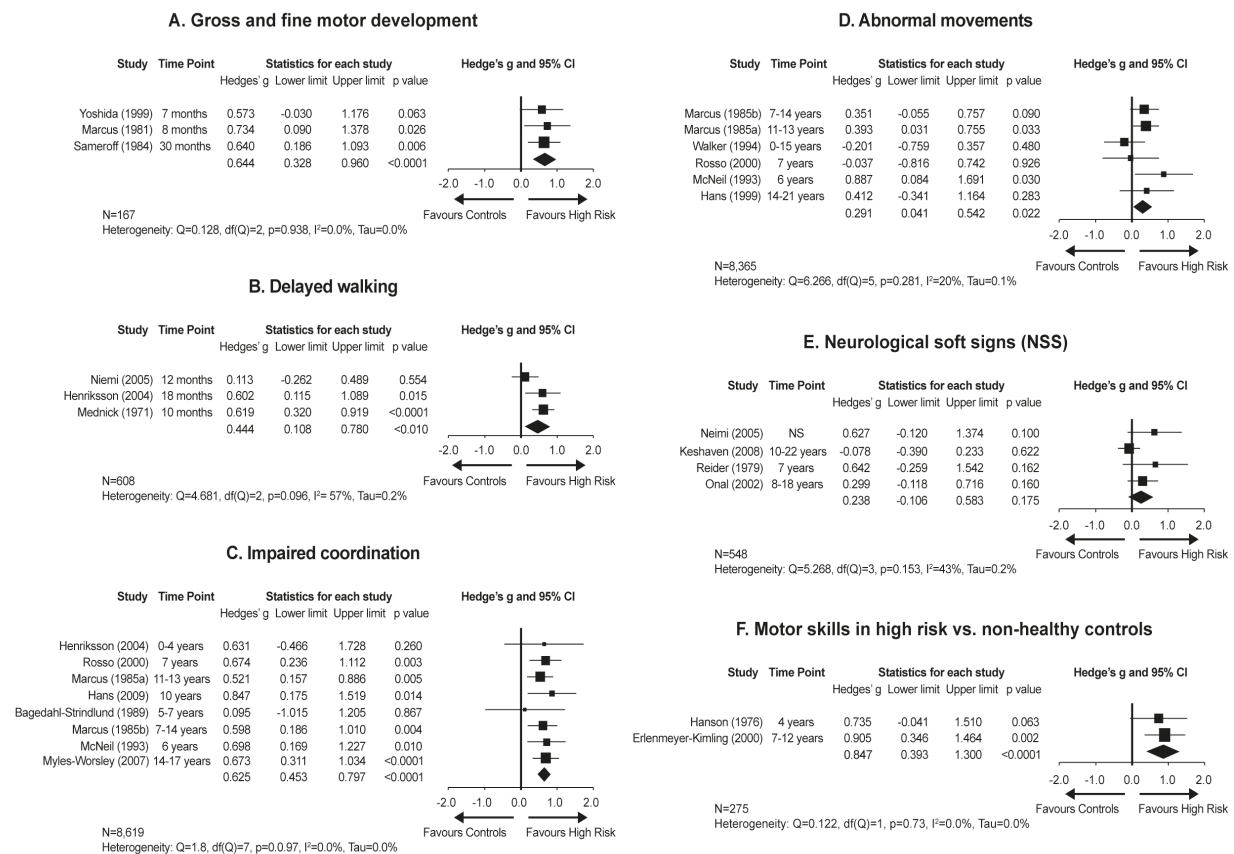
The systematic literature search identified 23 studies with a total sample size of $N=18,582$, which fulfilled the inclusion criteria (1. unaffected first-degree relatives of individual with schizophrenia 2. Assessing motor abilities 3. Including a control group 4. Sample ≤ 21 years) (Figure 4). Motor function was categorized into domains of specific motor function to compare similar motor abilities. Sample sizes across domains varied from 167 to 8619.

Figure 4: PRISMA flow chart



The effect across studies that assessed gross and fine motor development in infancy ($k=3$, $n=167$, Hedges' $g=0.644$, $CI=[0.328, 0.960]$, $p<0.001$), walking milestone ($k=3$, $n=608$, $g=0.444$, $CI=[0.108, 0.780]$, $p=0.01$), coordination ($k=8$, $n=8,619$, $g=0.625$, $CI=[0.453, 0.797]$, $p<0.0001$), and abnormal movements ($k=6$, $n=8,365$, $g=0.291$, $CI=[0.041, 0.542]$, $p=0.02$), demonstrated poorer abilities in first-degree relatives of individuals with schizophrenia compared with controls (Figure 5). Neurological soft signs did not yield reliable effects ($k=4$, $n=548$, $g=0.238$, $CI=[-0.106, 0.583]$, $p=0.18$) and correcting for publication bias did not change this result. Young unaffected first-degree relatives of individuals with schizophrenia did not differ from controls with respect to neurological soft signs. Individuals with a familial risk of schizophrenia, however, displayed poorer gross and fine motor skills than children of parents with other mental disorders skills ($k=2$, $n=275$, $g=0.847$, $CI=[0.393, 1.300]$, $p<0.001$). The current findings thus suggested that motor deficits during development may represent a potential endophenotype for schizophrenia reflecting an underlying, neurodevelopmental vulnerability. The specificity of this finding needed further exploration employing longitudinal designs and groups of first-degree relatives with other mental disorders for comparison.

Figure 5: Forest plots with effect size and heterogeneity of the six motor domains



7.2 Results from Paper II

In a cross-sectional case-control study of 198 children with a familial risk of schizophrenia, 119 children with a familial risk of bipolar disorder and 197 controls, 7 years of age, motor function was assessed with the Movement ABC-2.

We could confirm the hypothesis that on group level children with a familial risk of schizophrenia demonstrated impaired motor function compared with controls. Whereas the hypothesis of children with a familial risk of bipolar disorder showed less pronounced motor deficits compared with controls was not confirmed. Children with a familial risk of bipolar disorder did not differ significantly from controls. Age, sex and subdomain had a significant effect on motor function. The interactions of group-by-subdomain and sex-by-subdomain showed the effect of group and sex was not the same for each subdomain. No other interactions were significant. Children with a familial risk of schizophrenia performed significantly poorer on the subdomain of manual dexterity (mean difference= -1.42, 95% CI: [-2.08– -0.77], $t_{(510)}=-4.27$, $p<0.0001$) and balance (mean difference= -1.38, 95% CI: [-2.03– -0.72], $t_{(508)}=-4.12$, $p<0.0001$), whereas they performed comparable with controls in the subdomain of aiming and catching (mean difference= -0.39, 95% CI: [-0.97– 0.19], $t_{(510)}=-1.33$, $p=0.18$). Children with a familial risk of bipolar disorder displayed motor performance not significantly different from controls in all three subdomains, namely manual dexterity (mean difference= -0.69, 95% CI: [-1.44– 0.07], $t_{(512)}=-1.79$, $p=0.075$), balance (mean difference= -0.68, 95% CI: [-

1.44– -0.08], $t_{(510)}=-1.75$, $p=0.08$), and aiming and catching (mean difference=-0.36, 95% CI: [-1.03–0.31], $t_{(511)}=-1.05$, $p=0.29$) (Figure 6A and Table 3).

Boys performed poorer than girls in the domains of manual dexterity (mean difference= -2.29, 95% CI: [-2.87– -1.72], $t_{(510)}=-7.83$, $p<0.0001$) and balance (mean difference= -2.21, 95% CI: [-2.78– -1.63], $t_{(507)}=-7.52$, $p<0.0001$). In contrast, however, boys outperformed girls in the domain of aiming and catching (mean difference= 0.80, 95% CI: [0.29–1.31], $t_{(509)}=3.10$, $p=0.002$) with a significant ‘sex-by-subdomain’ interaction (Figure 6B and Table 3).

Table 3: Mean difference of standard scores of Movement ABC-2 between familial risk of schizophrenia or familial risk of bipolar disorder and controls adjusted for sex, age, subdomains and the interaction group-by-subdomain and sex-by-subdomain.

	T-test (degree of freedom) T(F)	Standard error (SE)	Mean difference [95% CI]	P-value
Schizophrenia familial risk-group versus control				
Manual dexterity	-4.27 (510)	0.33	-1.42 [-2.08– -0.77]	<0.0001
Ball skills: Aiming and catching	-1.33 (510)	0.29	-0.39 [-0.97–0.19]	0.18
Balance	-4.12 (508)	0.33	-1.38 [-2.03– -0.72]	<.0001
Bipolar disorder familial risk-group versus control				
Manual dexterity	-1.79 (512)	0.39	-0.69 [-1.44–0.07]	0.075
Ball skills: Aiming and catching	-1.05 (511)	0.34	-0.36 [-1.03–0.31]	0.29
Balance	-1.75 (510)	0.38	-0.68 [-1.44– -0.08]	0.08
Sex differences				
Boys versus girls*				
Manual dexterity	-7.83 (510)	0.29	-2.29 [-2.87– -1.72]	<0.0001
Ball skills: Aiming and catching	3.10 (509)	0.26	0.80 [0.29–1.31]	0.0021
Balance	-7.52 (507)	0.29	-2.21 [-2.78– -1.63]	<0.0001

*Girls are the reference level

Figure 6A: Mean difference in Movement ABC-2 subdomains between children with a familial risk of schizophrenia (dark purple dashed line) or familial risk of bipolar disorder (light purple solid line) compared with controls (green horizontal line).

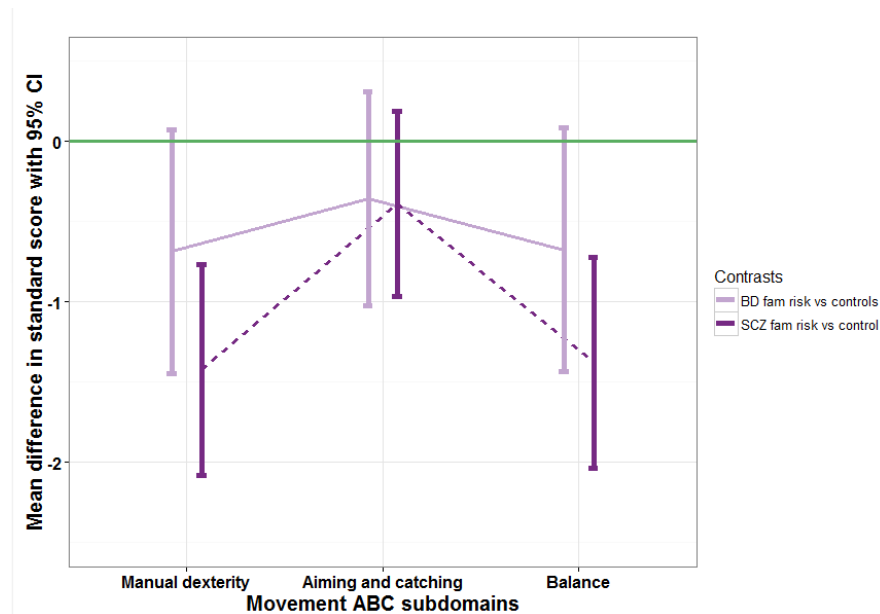
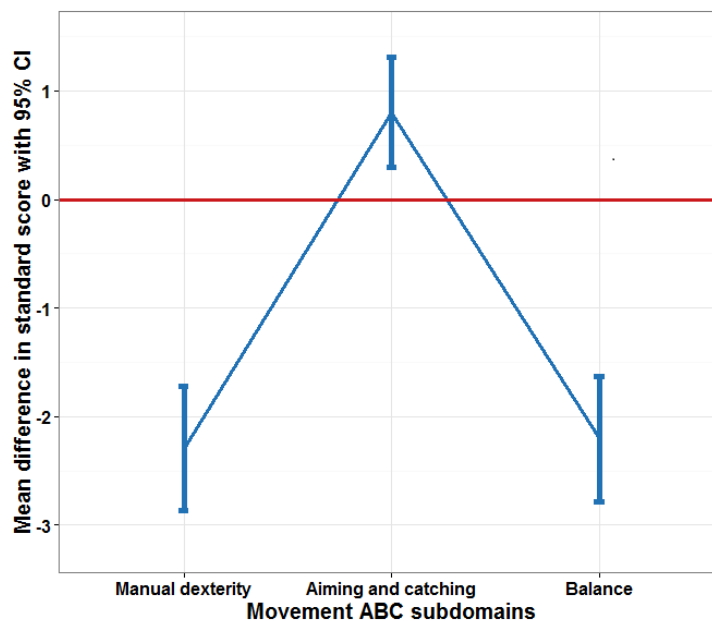


Figure 6B: Mean difference between sexes in each subdomain of Movement ABC-2. Boys compared with girls (girls are the reference group, illustrated with the red horizontal line).



The odds of having definite motor problems ($\leq 5^{\text{th}}$ percentile) were 2.02 (95% CI: [1.23–3.32]) times higher for children with familial risk of schizophrenia compared with controls. The odds of having definite motor problems were comparable for children with familial risk of bipolar disorder and controls (1.57 (95% CI: [0.88–2.79])). Handedness of the child did not influence motor function ($F_{(1,508)}=1.86$, $p=0.173$) nor did the child's living arrangement (whether the child lived with both biological parents ($F_{(1,506)}=0.05$, $p=0.83$), with the index parent ($F_{(1,509)}=0.09$, $p=0.77$) or with a single parent ($F_{(1,507)}=1.0$, $p=0.32$)). However, the education level of the index parents was positively related to children's motor performance

($F_{(1,471)}=7.79$, $p=0.0055$). The effect of group disappeared when we accounted for the personal and social performance level (measured on the personal and social performance scale) of the healthy biological co-parent. The parent's personal and social performance level had a positive influence on the child's motor abilities ($F_{(1,415)}=14.4$, $p=0.0002$).

7.3 Results from Paper III

7.3.1 Sustained attention (CPT-2)

We could confirm our first hypothesis that groups differed in terms of overall sustained attention in terms of vigilance and overall RT consistency, as well as between block RT consistency during the CPT-2 task (see *Table 4* for definition of variables). Vigilance differed across groups ($F_{(2,336)}=3.30$, $p=0.038$), with no effect of age ($F_{(1,455)}=1.22$, $p=0.27$), sex ($F_{(1,280)}=1.72$, $p=0.19$) or any significant two or three-ways interactions. Post-hoc tests indicated that children with a familial risk of schizophrenia displayed reduced vigilance compared with children with a familial risk of bipolar disorder (mean difference=0.01, 95% CI: [0.002–0.019], $t_{(484)}=2.36$, $p=0.0018$), but only differed at trend significance from controls (mean difference=0.007, 95% CI: [-0.0002–0.014], $t_{(209)}=1.91$, $P=0.058$). Children with a familial risk of bipolar disorder did not differ from controls (mean difference=-0.003, 95% CI: [-0.012–0.0054], $t_{(484)}=-0.74$, $P=0.46$) (*Table 5*).

Overall RT consistency differed across groups ($F_{(2,362)}=5.81$, $p=0.0033$), sex ($F_{(1,307)}=10.35$, $p=0.0014$), but not with age ($F_{(1,458)}=0.95$, $p=0.33$) and none of the two or three-ways interactions reached significance. Post-hoc tests indicated that children with a familial risk of schizophrenia displayed lower overall RT consistency compared with controls (mean difference=2.23, 95% CI: [0.42–4.03], $t_{(242)}=2.43$, $p=0.016$) and compared with children with a familial risk of bipolar disorder (mean difference=3.4, 95% CI: [1.3–5.49], $t_{(485)}=3.20$, $p=0.0015$). Moreover, boys exhibited lower overall RT consistency than girls (mean difference=2.65, 95% CI: [1.03–4.27], $t_{(307)}=3.22$, $p=0.0014$) (*Table 5*).

Between block RT consistency differed with respect to group ($F_{(2,349)}=5.35$, $P=0.0051$), sex ($F_{(1,288)}=12.12$, $P=0.0006$), but not with age ($F_{(1,452)}=0.36$, $P=0.55$) and none of the two or three-ways interactions were significant. Post-hoc tests indicated that children with a familial risk of schizophrenia displayed lower between block RT consistency compared with controls (mean difference=5.37, 95% CI: [0.54–10.19], $t_{(223)}=2.19$, $P=0.029$) and compared with children with a familial risk of bipolar disorder (mean difference=8.85, 95% CI: [3.3–14.4], $t_{(488)}=3.13$, $P=0.0018$). Moreover, boys exhibited lower between block RT consistency than girls (mean difference=7.58, 95% CI: [3.29–11.86], $t_{(288)}=3.48$, $P=0.0006$) (*Table 5*).

Table 4: Definitions of CPT-2 and Flanker task variables, means and standard deviations.

Task/ Concept	Variable	Definition	Children with a familial risk of schizophrenia	Children with a familial risk of bipolar disorder	Controls
CPT-II			N=190	N=116	N=187
Vigilance	Hit RT block change	The slope of change in hit RT across the different blocks (a positive slope indicates a slowing of RT as a function of time on the task)	0.03 (0.04)	0.02 (0.04)	0.03 (0.04)
Overall RT consistency	Hit RT SE	Consistency of response time as measured by the standard error for responses to target	19.1 (9.56)	15.84 (7.53)	17.0 (9.55)
Between block RT consistency	Variability SE	Measure of response time consistency calculated as the standard deviation of the standard error values for each sub-block	41.13 (25.37)	32.41 (22.11)	36.19 (24.19)
Reaction time (RT)	Raw Hit RT	Average speed (RT) of correct responses across the entire test	519.99 (95.87)	494.70 (78.96)	502.8 (92.08)
Accuracy	Omission	Number of none response to target letters (non-X)	36.72 (29.83)	27.72 (20.03)	31.68 (29.16)
	Commissions	Number of responses to the non-target (X)	24.81 (6.24)	26.24 (4.99)	24.96 (5.62)
Flanker Task			N=192	N=116	N=192
Mean RT	Mean RT for congruent trials	Mean RT of correct responses across the flanker task for all congruent trials	910.21 (230.31)	839.0 (173.94)	850.87 (203.5)
	Mean RT for incongruent trials	Mean RT of correct responses across the flanker task for all incongruent trials	1253.9 (428.96)	1124.7 (348.59)	1138.72 (368.98)
Accuracy	Accuracy for congruent trials	Number of correct responses for congruent trials	0.90 (0.08)	0.91 (0.08)	0.91 (0.08)
	Accuracy for incongruent trials	Number of correct responses for incongruent trials	0.77 (0.20)	0.80 (0.15)	0.81 (0.14)
	Coefficient of variability (CV) for congruent trials	Standard deviation of RT with-in subjects divided by mean RT with-in subject for congruent trials	0.45 (0.14)	0.41 (0.14)	0.41 (0.14)
	Coefficient of variability (CV) for incongruent trials	Standard deviation of RT with-in subjects divided by mean RT with-in subject for incongruent trials	0.53 (0.15)	0.49 (0.16)	0.48 (0.15)
	Post-error slowing (PES)	Post-error slowing was calculated as the difference in RT between post-error trial (E+1) and the associated pre-error trial (E-1) for each individual.	182.11 (318.64)	188.60 (241.2)	163.11 (251.78)
Error adaptation	Post error improvement in accuracy (PIA)	Accuracy in post-error trials minus accuracy in post-correct trials	-0.07 (0.09)	-0.08 (0.09)	-0.07 (0.09)
	Post-error reduction of interference (PERI)	Interference (incongruent mean RT-congruent mean RT) of post-correct trials minus interference of post-error trials	6.15 (331.8)	-30.42 (291.02)	28.92 (255.7)

Table 5: Mean difference of raw scores in CPT-2 between familial risk of schizophrenia or familial risk of bipolar disorder and controls adjusted for sex and age. No three way or two way interactions were significant.

	T-test (degree of freedom) T(F)	Standard error (SE)	Mean difference [95% CL]	P-value
Schizophrenia familial risk-group versus control				
Vigilance	1.91 (209)	0.0037	0.007 [-0.0002; 0.014]	0.058
Overall RT consistency	2.43 (242)	0.92	2.23 [0.42; 4.04]	0.016
Between block RT consistency	2.19 (223)	2.45	5.37 [0.54; 10.19]	0.029
Reaction time	1.8 (243)	9.57	17.26 [-1.582; 36.10]	0.072
Omissions	1.86 (269)	3.56	6.63 [-0.39; 13.66]	0.064
Commissions	-0.47 (488)	0.61	-0.28 [-1.49; 0.91]	0.636
Bipolar disorder familial risk-group versus control				
Vigilance	-0.74 (484)	0.004	-0.0032 [-0.01; 0.005]	0.46
Overall RT consistency	-1.09 (485)	1.07	-1.17 [-3.27; 0.93]	0.27
Between block RT consistency	-1.22 (488)	2.84	-3.47 [-9.06; 2.11]	0.22
Reaction time	-0.44 (486)	11.42	-5.08 [-27.53; 17.37]	0.65
Omissions	-1.37 (488)	4.16	-5.69 [-13.88; 2.48]	0.17
Commissions	1.93 (488)	0.70	1.35 [-0.027; 2.74]	0.054
Schizophrenia familial risk-group versus Bipolar Disorder				
Vigilance	2.36 (484)	0.004	0.01 [0.002; 0.019]	0.019
Overall RT consistency	3.20 (485)	1.06	3.4 [1.3; 5.49]	0.0015
Between block RT consistency	3.13 (488)	2.82	8.845 [3.3; 14.40]	0.0018
Reaction time	1.97 (486)	11.34	22.34 [0.062; 44.62]	0.049
Omissions	2.98 (488)	4.13	12.33 [4.21; 20.46]	0.003
Commissions	-2.35 (488)	0.697	-1.64 [-3.01; -0.27]	0.019

7.3.2 Cognitive Control (Flanker task)

We could confirm our second hypothesis that groups differed in terms of cognitive control abilities measured in a Flanker paradigm. The test for fixed effects in a repeated mixed model for the effect of accuracy revealed significance across familial risk groups ($F_{(2,494)}=3.06$, $p=0.048$), condition ($F_{(1,492)}=4.23$, $P=0.04$) and age ($F_{(1,498)}=4.09$, $p=0.044$), but no significant effect of sex ($F_{(1,498)}=2.70$, $p=0.10$). The interaction group-by-age-by-condition (congruency) reached significance ($F_{(2,492)}=3.93$, $p=0.020$), the interaction sex-by-age-by-condition (congruency) attained significance ($F_{(1,492)}=3.91$, $p=0.049$) and the interaction group-by-condition reached significance ($F_{(2,492)}=4.02$, $p=0.019$). The remaining two-way interactions were not significant, but remained in the model to maintain the hierarchical formulation. Post-hoc tests indicated that girls with a familial risk of schizophrenia displayed significant lower accuracy during incongruent trials (mean difference = -0.16, 95% CI: [-0.29; -0.015], $T_{(490)}=-2.19$, $p=0.029$) compared with girls in the control group. Moreover, children with a familial risk of bipolar disorder displayed lower accuracy during incongruent trials compared with controls (Table 6).

Reaction time differed across groups ($F_{(2,447)}=3.17$, $p=0.043$), across conditions ($F_{(1,493)}=4.22$, $p=0.04$) and with age ($F_{(1,547)}=4.61$, $p=0.032$), but not with respect to sex ($F_{(1,468)}=0.85$, $p=0.35$). Moreover, the interaction of group-by-sex-by-condition reached significance ($F_{(2,493)}=3.45$, $p=0.033$). No other interactions reached significance. Post hoc test indicated children with a

familial risk of schizophrenia displayed slower mean reaction time compared with controls, that reaction times were faster in the congruent condition and among older children (*Table 6*).

RT variability (measured with the coefficient of variation) differed across groups ($F_{(2,340)}=8.15$, $p=0.0003$), across conditions ($F_{(1,499)}=322.53$, $p<0.0001$), across sexes ($F_{(1,288)}=7.4$, $p=0.007$) and with age ($F_{(1,470)}=4.62$, $p=0.032$). Post-hoc tests indicated that children with a familial risk of schizophrenia displayed higher RT variability compared with controls (mean difference=0.05, 95% CI: [0.03–0.076], $T_{(209)}=3.84$, $p=0.0002$) and compared with children with a familial risk of bipolar disorder (mean difference=0.04, 95% CI: [0.01–0.074], $T_{(491)}=2.71$, $p=0.007$). RT variability was higher in the incongruent condition, young children and boys exhibited a significant higher coefficient of variation than girls (*Table 6*).

Table 6: Mean difference of mean reaction time (RT) between familial risk of schizophrenia or familial risk of bipolar disorder and controls adjusted for sex, age, condition (congruency) and the interaction group-by-sex-by-congruency and all 2 ways interactions. Mean difference of accuracy between familial risk of schizophrenia or familial risk of bipolar disorder and controls adjusted for sex, age, condition (congruency) and the interaction age-by-group-by-condition and age-by-sex-condition and all two ways interaction.

	T-test (degree of freedom) T(F)	Standard errors (SE)	Mean difference [95% CI]	P-value
Schizophrenia familial risk-group versus control				
Boys				
RT_mean Congruent	2.33 (372)	78.9	184 [28.8; 339.18]	0.02
RT_mean Incongruent	3.23 (555)	90.74	293 [115.2; 471.7]	0.0013
Accuracy Congruent	-0.59 (490)	0.0336	-0.0197 [-0.09; 0.05]	0.55
Accuracy Incongruent	-1.71 (490)	0.0711	-0.122 [-0.261; 0.018]	0.087
Coefficient Variance	3.56 (106)	0.0184	0.065 [0.029; 0.102]	0.0006
Girls				
RT_mean Congruent	2.31 (366)	78.39	181.42 [27.3; 335.5]	0.02
RT_mean Incongruent	1.94 (568)	92.2	178.6 [-2.59; 359.9]	0.053
Accuracy Congruent	-0.58 (490)	0.033	-0.019 [-0.08; 0.046]	0.563
Accuracy Incongruent	-2.19 (490)	0.07	-0.155 [-0.29; -0.015]	0.029
Coefficient Variance	1.76 (101)	0.018	0.033 [-0.004; 0.069]	0.08
Bipolar disorder familial risk-group versus control				
Boys				
RT_mean Congruent	-0.95 (504)	100.16	-95.41 [-292; 101.3]	0.341
RT_mean Incongruent	-0.27 (716)	112.81	-30.45[-251.9; 191]	0.787
Accuracy Congruent	-1.02 (490)	0.0413	-0.042 [-0.123; 0.039]	0.309
Accuracy Incongruent	-2.78 (490)	0.087	-0.243 [-0.415; -0.07]	0.006
Coefficient Variance	0.15(262)	0.022	0.0034 [-0.041; 0.048]	0.88
Girls				
RT_mean Congruent	-0.72 (504)	107.34	-77.69 [-288.5; 133.1]	0.469
RT_mean Incongruent	-1.24 (719)	121.12	-150.65 [-388.4; 87.1]	0.214
Accuracy Congruent	-1.15 (490)	0.044	-0.051 [-0.138; 0.036]	0.249
Accuracy Incongruent	-3.14 (490)	0.093	-0.292 [-0.478; -0.11]	0.0018
Coefficient Variance	0.49 (226)	0.022	0.011 [-0.033; 0.055]	0.62

7.3.3 Explorative Analyses

7.3.3.1 Error adaptation

The test for fixed effects in a ANCOVA mixed model for overall effect of post-error slowing did not reveal a significant effect of familial risk groups ($F_{(2,492)}=0.30$, $p=0.74$), age ($F_{(1,492)}=0.29$, $p=0.29$), but a significant effect of sex ($F_{(1,492)}=5.17$, $p=0.02$). The post-hoc test indicated that boys exhibited less post-error slowing compared with girls (mean difference=-56.4, 95% CI: [-105.2– -7.64], $T_{(492)}=-2.27$, $p=0.02$).

Groups did not differ with respect to the post-error improvement of accuracy (PIA) among familial risk groups ($F_{(2,349)}=0.10$, $p=0.90$), nor with age ($F_{(1,467)}=0.24$, $p=0.62$) or sex ($F_{(1,293)}=0.59$, $p=0.44$) (Table 7).

The effect of post-error reduction of interference (PERI) revealed a significant effect of group ($F_{(2,491)}=4.19$, $p=0.016$), no effect of age ($F_{(1,491)}=3.19$, $p=0.075$), or sex ($F_{(1,491)}=3.15$, $p=0.076$), but a significant interaction of age-by-group ($F_{(2,491)}=4.27$, $p=0.015$). Our post-hoc analyses revealed that children with a familial risk of schizophrenia differed from controls, indicating that children with a familial risk of schizophrenia displayed less post-error reduction of interference compared with controls (mean difference=306.6, 95% CI: [70.87–542.3], $t_{(491)}=2.56$, $p=0.01$). The interaction age-by-group indicated that the effect of age was not the same for each group. In group of familial risk of schizophrenia, the performance of post-error reduction of interference improves with age, while in group of familial risk of bipolar disorder age has no effect on post-error reduction.

Table 7: Error adaptation. Mean difference of either post-error slowing, post-error improvement of accuracy and post-error reduction of interference between familial risk of schizophrenia or familial risk of bipolar disorder and controls adjusted for sex, age. No three ways or two ways interactions were significant, except for Post-error reduction of interference where the interaction age-by-group was significant. Post-error reduction of interference is adjusted for a significant interaction of age-by-group at the age of 7 beyond sex and age.

	T-test (degree of freedom) T(F)	Standard Error (SE)	Mean difference (95% CI)	P-value
Schizophrenia familial risk-group versus control				
Post-error slowing	0.62 (492)	28.36	17.7 [-38.03; 73.43]	0.53
Post-error improvement of accuracy (PIA)	0.16 (221)	0.0087	0.0014 [-0.016; 0.019]	0.87
Post-error reduction of interference (PERI)	2.56 (491)	119.97	306.6 [70.9; 542.3]	0.01
Bipolar disorder familial risk-group versus control				
Post-error slowing	0.68 (492)	32.73	22.37 [-41.93; 86.69]	0.49
Post-error improvement of accuracy (PIA)	-0.21(492)	0.01	-0.003 [-0.024; 0.017]	0.75
Post-error reduction of interference (PERI)	1.63 (491)	149.52	243 [-49.9; 537.5]	0.10

7.3.3.2 *The relationship between sustained attention and motor performance*

We tested the relationship between one measure of sustained attention (between block RT consistency) and motor skills performance (total score from Movement ABC-2) in a multiple linear regression, where “between block RT consistency” served as the dependent variable. Motor skill performance had a significant negative predicting effect ($F_{(1,468)}=16.38, p<0.0001$) on sustained attention indicating that poorer motor performance/scores correlated with a decrease in consistency. The effect of group remained significant ($F_{(2,346)}=3.71, p=0.026$) as well as the effect of sex ($F_{(1,303)}=5.81, p=0.017$), but not age ($F_{(1,438)}=0.15, p=0.69$). No two or three-ways interactions were significant.

8 Discussion

8.1 Summary of findings

This thesis builds on previous findings suggesting a tight relationship between the cognitive and the motor system during development.^{57;183;194} The increasing evidence that schizophrenia³ and bipolar disorder²¹¹ are neurodevelopmental disorders with a shared genetic liability warrants the investigation of the specificity of their developmental paths of cognition and motor function.^{13;212} The findings of this thesis supported the hypothesis that children with a familial risk of schizophrenia display (i) impaired motor abilities and (ii) deficits of overall sustained attention and cognitive control and finally (iii) a relationship between deficits of motor abilities and attention. Our analyses, however, did not confirm similar deficits for children with a familial risk of bipolar disorder. Our findings thus indicate that motor deficits and an impairment of sustained attention and cognitive control could represent interrelated endophenotypes for schizophrenia, indicating distinct developmental pathways for schizophrenia and bipolar disorder at the age of 7 years.

We used a standardized measurement of motor function for screening prepubescent children with familial risk of bipolar or of schizophrenia disorder and confirmed previous findings that it is possible to detect early developmental signs in children with a familial risk of schizophrenia using this fine-grained and objective motor test. Although previous studies have investigated motor function in offspring of individuals with schizophrenia, our studies provide new knowledge to the field by exclusively assessing children at the age of 7 years within a large and representative, community-based sample. Previous high-risk cohorts of children with a familial risk of schizophrenia have included a much broader age range in which puberty and varying developmental stages may influence results. Prior to the studies in this thesis, little to no information has been reported regarding motor function in prepubescent children of parental bipolar disorder exclusively. Previous high-risk-studies have assessed children with parents diagnosed with affective disorders including unipolar depression^{89;91}. The evaluation of motor function in children before puberty with a familial risk of bipolar disorder using a comprehensive motor test is thus novel.

Moreover, we used a validated instrument to assess sustained attention in children with a familial risk of schizophrenia or bipolar disorder to confirm previous findings^{176;213}. Again, no prior studies have investigated pre-pubertal children with a narrow age range and within a large population-based sample. To our knowledge, this is the first time cognitive control abilities have been assessed in children with familial risk of schizophrenia or bipolar disorder within a narrow age range, which is an advantage, because of important age-effects during the development of self-regulation. Finally, the relationship between deficits of motor abilities, attention and cognitive control in pre-pubertal children is novel.

8.2 Validity and generalizability

The VIA 7 case-control cohort consisted of 522 families from urban and rural areas all over Denmark, which were identified through the Danish registers. We attempted to contact 946 families. Of these 55% enrolled in the VIA 7 study. The drop-out rate after inclusion was 9 out of 522. At this point in time, it has not been possible to assess the families with whom we did not establish contact or those who declined to participate in a systematic drop-out analysis. Consequently, we do not have access to data of non-participating families', such as their

reasons for declining to participation, their level of functioning or other psychopathological or demographic characteristics. We thus cannot discern that they may have declined to participate due to a busy schedule in the context of a higher level of family-functioning, or whether a lower level of functioning and e.g. a higher paranoid attitude may have discouraged them from participating in this study. However, our sample is large, nationally representative, and consists of children within a narrow age range, which supports the generalizability of our findings.

A potential limitation of our study involves construction of the diagnostic groups. Parents were invited on the background of their lifetime diagnostic status for a schizophrenia spectrum disorder or bipolar disorder, or the absence of such a diagnosis in the control group. However, it is not clear today whether these diagnostic groups represent discrete categorical entities or rather degrees of a trans-diagnostic pattern of the same disorder due to the genetic liability for severe mental disorders^{13;212}. We have assigned parents to groups according to the hierarchy of ICD 10. However, we cannot rule out that several of the parents diagnosed as bipolar disorder with psychotic symptoms, later in life would fulfill the criteria for schizophrenia. This also applies to the control parents who theoretically could develop either of the case diagnoses. A longitudinal follow-up study would control for these developments and enhance the validity of the psychiatric diagnoses in the cohort²¹⁴. Furthermore, diagnoses should rather than by their broad diagnostic category be based more precise “by physiological, anatomical, histological, chromosomal, or molecular abnormalities”²¹⁴. Currently, this way of defining psychiatric diagnoses on a scientific evidence base is not possible for severe mental disorders. Even though psychiatric diagnoses are not well-defined and well-delimited categories, but share an underlying genetic liability, we have used traditional diagnostic categories to define our cohort.

The fact that the invited parents in our study were selected based on broad diagnostic groups lumping together different diagnoses of the schizophrenia and bipolar spectrum, which assured a large enough sample, precluded us from examining specific endophenotypes underlying certain genetic constellations. Moreover, the presence of genetic liability between schizophrenia and bipolar disorder, and to a smaller extent the genetic liability with major depression²¹², increases the risk of developing not only the disease of the parent, but other mental disorders³⁸. Based on these findings, viewed from a trans-diagnostic perspective, as opposed to a categorical perspective, future studies should include a comparison group of offspring of parents with (major) unipolar depression, due to a possible transition to bipolar disorder or schizophrenia later in life. Because the participating parents had a mean age between 38-41 years, their current set of symptoms could still evolve into another diagnosis. Owing to the genetic overlap between these three diseases makes the assessment of those children at risk more complete.

8.3 Motor Function

The meta-analysis of unaffected first-degree relatives of individuals with schizophrenia, in which motor deficits were reported within the first year of childhood and through development to the age of 21 years⁹⁹ documented that prior studies have examined heterogeneous samples and used widely different and often not standardized instruments. This work was a relevant background for our investigation in a larger, population-based sample using a standardized and fine-grained test of motor function, which showed that motor deficits were present at the age of 7 years in children with a familial risk of schizophrenia. Together, these findings provide

robust evidence for motor deficits during development on a group level among first-degree relatives of those with schizophrenia. We could not detect a significant difference between children with a familial risk of bipolar disorder and controls. However, we cannot reject that there is a difference considering the borderline significance in the same two subdomains of motor performance that were aberrant in children of parents with schizophrenia.

Neurological soft signs have repeatedly been reported in adults with schizophrenia^{52;68;70;73}, in pre-morbid groups^{52;76;77} and in adults with a first-degree relative risk of schizophrenia.^{215;216} Results from our meta-analysis did not support similar findings in children and adolescents of first-degree relatives with schizophrenia. The small number of studies available for inclusion in our meta-analysis (k=4, n= 548) was a limitation for our review. Additionally, two of the included studies^{97;98} used the neurological evaluation scale (NES scale), which is designed to evaluate adults with schizophrenia. Therefore, the NES scale may lack sensitivity when assessing children and adolescent without psychosis. However, contrasting reports (with large to small sample sizes) reflect that the global neurological soft signs score increases with age in individuals with schizophrenia (n=204²¹⁷, n=21²¹⁸) and in controls (n= 133²¹⁷, n=38⁶⁶), whereas other reports suggest that neurological soft signs decrease with age in healthy individuals⁵² (n=39²¹⁹, n=30²²⁰, n=27²¹⁸) and remain stable in patients with schizophrenia (n=24²²⁰). This is vital for understanding our results of the neurological soft sign domain⁹⁹. The observation that offspring of schizophrenia and controls did not differ when assessed at a younger age along with the fact that the presence of neurological soft signs may be positively associated with age, could explain why adult first-degree relatives display a higher rate of neurological soft signs than controls. Motor development as part of the neurodevelopmental hypothesis may show a delay or a lasting impairment that gets apparent in the older age group, where controls usually have lost these early signs of developmental delay. However, conclusions are difficult to draw due to conflicting reports.

Nonetheless, we divided motor outcomes reported in the studies in to six domains of motor function⁹⁹. One could argue that several of the studies used in the impaired coordination domain could have been applied in the domain of neurological soft signs instead and affected the result. For example, a 5-year follow-up study used a neurological examination with domains of coordination, sensory-perceptual signs, motor overflow, speech articulation, lateralization, and posture.¹⁹⁸ We chose to include the data from coordination in our domain of impaired coordination and motor overflow in the domain of abnormal movement instead of using the total score in order to avoid overlooking changes of impairment in specific domains of motor function that be concealed in the total score²¹⁷.

“Familial risk” entails a genetic vulnerability and an environmental exposure, and it is difficult to differentiate these components. Models suggest that the emergence of schizophrenia in an individual is due to the interplay of genetic and environmental factors, which together also may impair motor development and cognitive abilities. This stands in contrast to a subgroup of individuals that develop bipolar disorder and perform as well as the general population in these two domains.²²¹ The demographic description of the VIA 7 cohort illustrates the differences in the environments in which children with and without familial risk grows up. We entered variables representing distinct aspects of the child’s environmental influences in our statistical model to understand whether these environmental factors influenced the child’s motor performance. This exploratory investigation indicated that higher education of the index parent and a good personal and social functioning of the healthy biological co-parent had a positive effect on the motor performance of the child. Within the observational design of the study, however, we were unable to determine whether these findings indicate that characteristics of the biological parent may influence the motor performance of the child as truly environmental

factors, or if genes mediate these environmental factors, or if they are a result of a combination of environmental and genetic factors.

Given prior evidence suggesting that schizophrenia and bipolar disorder are considered neurodevelopmental disorders, which are heritable and influenced by environmental exposures, the current findings suggest that both the familial risk group and environmental characteristics of the biological parent influence motor abilities during childhood. However, we were unable to determine whether the effects on children's motor performance were of purely environmental nature, whether genes mediated these environmental factors, or whether they were the result of a combination of environmental and genetic factors.

In conclusion, children with a familial risk of schizophrenia on a group level displayed a lower level of motor function compared with controls, opposed to children with a familial risk of bipolar disorder, who did not perform different from controls. Prior evidence suggested that schizophrenia and bipolar disorder may be considered neurodevelopmental disorders,^{3;5;179;222} which are heritable and influenced by environmental exposures. The current findings indicated that motor deficits in childhood are influenced by both the familial risk group and environmental characteristics of the biological parent. Finally, motor deficits may represent an endophenotype for schizophrenia, characterized by deviations in developmental pathways and differences in the profile of motor ability.

8.4 Sustained attention and cognitive control

Our examinations indicated that children with a familial risk of schizophrenia displayed deficits in overall sustained attention on CPT-2. Moreover, children with a familial risk of schizophrenia displayed deficits in cognitive control abilities. In contrast, children with a familial risk of bipolar disorder and controls displayed similar skills in all the measures of sustained attention and cognitive control (with the exception of reduced accuracy during incongruent trials in the Flanker task).

Our data provide evidence of a clear distinction in sustained attention between children with a familial risk of schizophrenia from children with a familial risk of bipolar disorder. All measures on CPT-2 were significantly different between these two familial risk groups indicating two distinct developmental paths at the age of 7 years regarding sustained attention.

Our results are consistent with other reports of deficits in sustained attention among offspring of parents with schizophrenia.^{91;172} Furthermore, our findings are in line with studies assessing children with ADHD where intra-individual variability is regarded a prominent behavioral characteristics and the most replicated finding²²³. Previous findings regarding deficits of sustained attention in children with a familial risk of bipolar disorder are not as strong and report conflicting findings.^{174;176-178} Nevertheless, longitudinal cohort studies indicate that individuals who later developed mania⁸⁰ or bipolar disorder,²⁴ displayed either similar cognitive skills (IQ) as controls⁸⁰ or either excellent or extremely poor school performance²⁴. These results reflect that individuals with bipolar disorder may subgroup into different cognitive profiles prior to the development of bipolar disorder. These subgroups could be bipolar disorders I or bipolar disorder II, as well as subgroups of bipolar with and or without psychotic symptoms. Evidence suggests that differences in neurocognitive performance of individuals diagnosed with bipolar disorder I and II²²⁴ and reduced neurocognitive performance (i.e., inhibitory control, working memory and verbal memory) among individuals diagnosed with bipolar disorder I, compared with individuals with bipolar disorder II.²²⁴ To further map the

specificity of deficits in executive function and motor performance, we should have divided the bipolar disorder group by bipolar disorder subtype (I and II), the presence versus absence of psychosis, lithium responders or non-lithium responders²²⁵, and early onset versus later onset of bipolar disorder. Unfortunately, we did not have the necessary data to perform such an analysis, although such analyses are planned at later stages of the VIA project.

Error adaptation has been measured in individuals with schizophrenia and bipolar disorder, but few studies have assessed error adaptation in offspring¹⁵³. Our work provides novel knowledge regarding error adaptation behavior in children at familial risk for serious mental disorders. However, we found no difference in post-error slowing across groups. Moreover, all three groups showed a decrease in post-error improvement of accuracy (negative PIA), which is the opposite of what we expected. These results could reflect the possibility that post-error slowing does not lead to improved accuracy, because PES is not a result of an adaptive adjustment at the age 7 years, but rather an automatic orienting response.¹²⁸ The automatic orienting response may briefly inhibit the voluntary motor response, while the child fixates on the new event, which could be the feedback from the error response or the internal realization of the mistake in the non-feedback paradigm. Nevertheless, our behavioral data does not support the occurrence of adaptation of behavior because no improvement of accuracy was observed after an erroneous response.

The anterior cingulate cortex (ACC)¹³⁶ and the prefrontal cortex (PFC) are tightly interconnected and involved in cognitive control and error adaptation. The development of error adaptation depends on the maturation of the dorsal ACC, the PFC and the dopaminergic connections and metabolism in these brain areas.¹³⁶ The notion that cognitive control and error adaptation are relatively immature at the age of 7 years thus is coherent with the fact that ACC, PFC and the dopaminergic connections mature relatively late during development¹³⁶, reaching maturity after puberty and into early adulthood. Therefore, the lack of PIA and lack of difference in post-error slowing between groups, despite the presence of PES in our study, could just reflect the immature error adaptation system, which have not matured enough to distinguish a difference. Moreover, the maturation of the error adaptation system is reflected in the interaction of group-by-age of post-error reduction of interference. Specifically, in group of children with a familial risk of schizophrenia the performance of post-error reduction of interference improved with age, where in the group of familial risk of bipolar disorder age had no effect on post-error reduction.

8.5 The correlation of motor and cognitive development

Children with a familial risk of schizophrenia display significantly different motor function and sustained attention/cognitive control at the age of 7-years, whereas children with a familial risk of bipolar disorder did not differ from controls, despite the shared genetic liability for both disorder.^{226;227} However, to gain a better understanding of the differences and similarities across diagnostic groups of familial risk, a longitudinal perspective, exploring these variables at various stages of development, would add valuable information. Furthermore, our data show a strong correlation between deficits in motor abilities and sustained attention, which could indicate that the cognitive system is interconnected and related with the motoric system during development.^{57;183;194}

The tight, abundant anatomical connections between the motor and cognitive control system during development¹⁸³ and the continuous interplay between the two systems could explain

why children with a familial risk of schizophrenia have both motor⁹⁹ and cognitive deficits during development⁹¹, whereas children with a familial risk of bipolar have neither motor nor executive control deficits in childhood. One reason could be the fact that already one single deficit or delay development occurring in either the motor or the executive system would affect the other system owing to the abundant connections and interplay between the two systems. Along the same lines, prior findings suggest that neurological soft signs are associated with specific cognitive domains, such as executive attention, working memory and visual memory in individuals with schizophrenia and in controls.^{68;228}

It is important to consider whether researchers should control for motor function or not when assessing sustained attention, which is based on a measure of reaction time, if cognitive and motor development and performance are correlated. Likewise, researchers should consider whether controlling for cognition/IQ or not when assessing motor function. Nonetheless, one cannot discard that the same underlying (biological /genetic) factors may influence both measures. Thus, controlling for intellectual ability in a motor analysis and controlling for motor function in an analysis of sustained attention/cognitive control may 'over-adjust' for group differences²²⁹. This is consistent with the empirical literature on ADHD, discussing this type of 'over-adjusting' in statistical analyses²²⁹. It is difficult to gain an answer from our analysis had we controlled for IQ or sustained attention, because in addition to a neurological element, also a behavioral element of motor stimulation and training equally may affect the ability of motor function.²³⁰ Due to the collinearity of the two measures, as well as the possibility of a latent underlying factor influencing both measures, we decided neither to adjust for IQ in the explorative analysis with the outcome variables in the motor domains nor to adjust for motor function in analysis with sustained attention as main outcome variable. Furthermore, the question whether intellectual ability or motor function could act as a mediator would ask research questions that go beyond the hypotheses addressed by this thesis.

8.6 Endophenotypes

Deficits in motor performance in childhood precede the onset of schizophrenia.²³¹ Impaired motor function may predict schizophrenia spectrum disorder in adulthood.^{88;91} In the present thesis, children with a familial risk of schizophrenia displayed developmental motor impairments, as well as deficits in sustained attention and cognitive control on a group-level. These impairments in motor function and in sustained attention could represent endophenotypes (two separate, but still interrelated endophenotypes) for a genetic vulnerability for schizophrenia, even though motor impairment sometimes are being seen by the unaided eye, which is not in line with the traditional concept of endophenotypes.⁴³ Another criterion for an endophenotype is the postulation that a feature should be present in unaffected family members to a greater extent than in the general population⁴³. Our results support the assertion that motor and sustained attention deficits meet this criterion. Furthermore, an endophenotype should be heritable to some degree and as well animal as genetic studies provide evidence that this is the case for cerebellar abnormalities and motor impairments.^{232;233} Furthermore, individuals diagnosed with schizophrenia are widely reported to exhibit state-independent motor impairments^{63;234;235} and state-independent deficits in sustained attention.²³⁶ In line with our results, a meta-analysis concerning endophenotypes for schizophrenia, including children and adults as first-degree relatives, reported a large effect size for "neuromotor deviations" (Cohen's $d = 1.6$) and "sustained attention" (Cohen's $d = 1.5$)²³⁷

8.7 Limitations

These cross-sectional data, however, cannot predict whether children with motor impairments and/ or cognitive deficits will continue to deviate from the general population throughout development. It is possible that these deviations are transitory deviations that may normalize during development.⁴² Only longitudinal studies can address these issues.

We were able to enroll 55% of the invited families into the study, which is considered a moderate response rate. However, since families were identified through registries, the large sample size and the equal distribution of urban and rural from all parts of Denmark across groups, we still deem the cohort to be highly representative for the population.

A disadvantage of our study was the limitation that we to date were not able to further divide parents into subgroups based on the following: history of psychotic symptoms, disorder subtype, age of onset, and response to medicine. Subgrouping of patients of schizophrenia spectrum and bipolar disorder would allow investigating whether children of parents within such subgroups differed in motor performance, sustained attention, or cognitive control.

Children in the VIA 7 study completed an excessive number of tasks, and children did not complete these tasks at the same time of the day. The context-dependent nature of deficits, as reported in children with attention deficit disorder, reflects variation in motivation and energetic state, which can impact test results.²³⁸ Therefore, children who participated in the VIA 7 study may have been fatigued and may have experienced a varying amount of motivation during testing.

The use of imaging and electrophysiology beyond the examination of behavioral characteristics, would have contributed to a more profound mapping of the neural mechanism of cognitive control before puberty typical in those populations of familial risk. However, it was crucial that the children and their families had a good experience participating in VIA 7 and thus we chose not to apply any form of brain mapping at the age of 7 years, to avoid any form of challenging examinations. However, it is planned to examine with brain imaging and electrophysiology in the follow-up study at the age of 11 years.

9 Conclusion and future directions

9.1 Conclusion

The meta-analysis of studies reporting motor abilities in unaffected first-degree relatives of individuals with schizophrenia younger than 21 years provided evidence for impaired motor function among first-degree relatives of individuals with schizophrenia compared with controls. Several domains of motor function were assessed. Impairment of coordination was the most robust finding, with a moderate effect size, a narrow confidence interval and no detected publication bias or heterogeneity.

Further, the Danish High Risk and Resilience Study VIA 7, a prospective and representative cohort, has provided empirical evidence for the presence of impaired motor performance, deficits in sustained attention and subtle deviations in the cognitive control system in pre-pubertal children with a familial risk of schizophrenia compared with controls. Children with a familial risk of bipolar disorder displayed no significant differences in motor performance, nor deficits in sustained attention or cognitive control (except for less accuracy during incongruent trials) compared with controls. Moreover, children with a familial risk of schizophrenia differed significantly from children with a familial risk of bipolar disorder in all measures of sustained attention on the CPT-2.

Taken together, the findings in Papers I and II provide robust evidence for motor deficits during development on a group level among first-degree relatives of individuals with schizophrenia. Paper III demonstrates a distinction of development path of sustained attention between children with a familial risk of schizophrenia and children with a familial risk of bipolar disorder on a group level. Moreover, paper III indicates a relationship between motor abilities and attention present in all three groups.

By assessing offspring of individuals with either schizophrenia or bipolar disorder, this thesis contributes to the understanding of neurodevelopmental vulnerability in childhood. Furthermore, our results indicate that motor deficits and deficits in sustained attention may be regarded as possible interrelated endophenotypes for schizophrenia, indicating deviation from normal developmental paths of motor function and sustained attention.

9.2 Directions for future research

Future research should investigate motor abilities and cognitive abilities in children with familial risk of schizophrenia or bipolar disorder, based on more fine-grained diagnostic subgroups. These subgroups could be created based on age of onset, medicine responders/non-responders, psychotic/ non-psychotic, bipolar I or II/not otherwise specified. Despite the potential problem of reduced power with smaller group sizes, such an analysis would have the potential to map differences between subgroups enabling the identification of more specific endophenotypes.

It will be essential to continue following this cohort at regular intervals to investigate the course of development of motor and cognitive control abnormalities and assesses the development of vulnerabilities and resilience factors. Specifically, it would benefit to examine the cohort before and after the onset of puberty, during late adolescence, early adulthood, and mid-adulthood. Additionally, future studies should test any childhood anomalies in motor and cognitive

development as predictors of severe mental disorders in adulthood. In this way, we could identify vulnerability factors. Future research should also aim at identifying resilience factors by examining the developmental profiles of children who do not develop severe mental disorders as adults.

Although the sample size is smaller than in previous GWAS studies, future studies should investigate gene material from the current cohort using a longitudinal design to assess the role of specific genes, gene mutations, as well as epigenetic changes throughout the life circle. The current cohort provides a unique opportunity to match genetic information with environmental data on the individual- and family-level allowing the identification of polygenetic risk scores needed to investigate the relative influence of genes and environmental factors. A follow-up study at age 11 is already planned at Mental Health Center Copenhagen and Risskov, as well as the Child and Adolescent Mental Health Centre in the Capital Region of Denmark. This follow-up will reassess the children from VIA 7 at 11 years with an extensive battery, including a repetition of the here presented tests, complemented by brain imaging and electrophysiology

9.3 Clinical Implications for children with a familial risk of severe mental disorder

Given the potential presence of motor deficits and deficits in sustained attention and executive function in children with a familial risk of schizophrenia, clinicians may consider screening children of parents with schizophrenia for these deficits. Clinicians could then identify children who may benefit from additional support. Our finding of significantly impaired attention capacity in offspring of individuals with schizophrenia compared with offspring of individuals with bipolar disorder and controls may not only reflect differences in executive function, but also differences in motivation and the energetic state of the children. The theoretical construct of attention is difficult to examine separately because many domains of functioning are involved. Despite the difficulty in differentiating aspects of attention, further research should evaluate the non-executive function of attention (motivation, reward processing, reward decision making) to disentangle the influence of executive and non-executive functions of attention.

Future research would benefit from testing the effect of interventions, for families in which one or both of the parents are diagnosed with schizophrenia or bipolar disorder, on the course of development of severe mental disorder. This line of research would investigate whether family-based interventions are able to enhance resilience factors or protect children from the development of severe mental disorders. These family interventions could be multidisciplinary i.e., providing support to parents and children. There are likely several areas in which to support families. One area worth testing involves motor stimulation and training from infancy to late childhood to support healthy motor development. Clinicians could advise parents on how to physically stimulate their infant to support motor skills. If necessary, physiotherapists could provide additional help. Another area worth investigation involves interventions aimed at improving attention skills. Either parent could receive psychoeducation on how to support their child, or the child could receive attention stimulation training. These suggestions should be tested in an intervention trial in order to determine the effect.

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Research Review: Do motor deficits during development represent an endophenotype for schizophrenia? A meta-analysis

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Background: Early detection of schizophrenia risk is a critical goal in the field. Endophenotypes in children to relatives of affected individuals may contribute to this early detection. One of the lowest cost and longest theorized domains is motor development in children. **Methods:** A meta-analysis was conducted comparing individuals ≤ 21 years old with affected first-degree relatives (FDR) with (1) individuals from unaffected families (controls), or (2) individuals with FDR having other psychiatric disorders. Studies were classified by motor outcome and separate meta-analyses were performed across six correlated domains, with available N varying by domain. **Results:** Inclusion criteria were met by $k = 23$ independent studies with a total $N = 18,582$, and N across domains varying from 167 to 8619. The youth from affected families had delays in gross and fine motor development in infancy ($k = 3$, $n = 167$, Hedges' $g = 0.644$, confidence intervals (CI) = [0.328, 0.960], $p < .001$), walking milestones ($k = 3$, $n = 608$, $g = 0.444$, CI = [0.108, 0.780], $p = .01$), coordination ($k = 8$, $n = 8619$, $g = 0.625$, CI = [0.453, 0.797], $p < .0001$), and had more abnormal movements such as involuntary movements ($k = 6$, $n = 8365$, $g = 0.291$, CI = [0.041, 0.542], $p = .02$) compared with controls. However, not all effects survived correction for publication bias. Effects for neurological soft signs were small and not reliably different from zero ($k = 4$, $n = 548$, $g = 0.238$, CI = [-0.106, 0.583], $p = .18$). When comparing the FDR group to youth from families with other psychiatric disorders, the FDR group was distinguished by poorer gross and fine motor skills ($k = 2$, $n = 275$, $g = 0.847$, CI = [0.393, 1.300], $p < .001$). **Conclusions:** Motor deficits during development likely represent an endophenotype for schizophrenia, although its specificity is limited in relation to other serious mental disorders. It holds promise as a low cost domain for early risk detection, although it will have to be combined with other indicators to achieve clinically usable prediction accuracy. Impaired coordination was the most robust result with a moderate effect size and lack of heterogeneity and publication bias. **Keywords:** Motor function; endophenotype; early detection; first-degree relatives; schizophrenia.

Introduction

Schizophrenia is considered a neurodevelopmental disorder (Catts et al., 2013; Feinberg, 1982; Lewis & Levitt, 2002; Murray & Lewis, 1987; Weinberger, 1987), and various motor impairments are observed in individuals with schizophrenia even in the medication-naïve state (Walther & Strik, 2012). Such impairments include abnormal involuntary movements (Pappa & Dazzan, 2009; Walther & Strik, 2012), neurological soft signs (NSS), catatonic symptoms, psychomotor slowing, and Parkinsonian signs (Walther & Strik, 2012). Studies investigating birth- and high-risk cohorts document motor impairments before the onset of schizophrenia (Cannon et al., 2002; Jones, Rodgers, Murray, & Marmot, 1994; Marcus, Hans, Lewow, Wilkinson & Burack, 1985; Marcus, Hans, Auerbach & Auerbach, 1993; McNeil,

Harty, Blennow, & Cantor-Graae, 1993; Niemi, Suvisaari, Haukka, & Lonnqvist, 2005; Rosso et al., 2000; Walker, Savoie & Davis, 1994). Impaired motor skills in childhood have been categorized as a biomarker for predicting development of schizophrenia in adulthood (Erlenmeyer-Kimling et al., 2000; Niemi et al., 2005). Several other developmental cognitive disturbances, such as attention- and executive control deficits and lower IQ, are present in first-degree relatives (FDR) of individuals with schizophrenia (Erlenmeyer-Kimling et al., 2000; Seidman et al., 2006).

Motor and cognitive dysfunctions often co-occur in individuals with neurodevelopmental disorders (Diamond, 2000), owing to abundant connections between motor and cognitive systems. Such connections, observed in the thalamo-cortico-thalamic circuits and the cerebellum, facilitate the tight interplay of motor and executive control systems during development (Castellanos et al., 1996; Diamond, 2000; Raichle et al., 1994).

Conflict of interest statement: No conflicts declared.

To our knowledge, this is the first meta-analysis assessing specific motor abilities in young (≤ 21 years), unaffected FDR of individuals with schizophrenia compared with control groups. A previous meta-analysis, restricted to individuals who later developed schizophrenia, revealed impaired motor dysfunction in that population (measured as a composite index) (Dickson, Laurens, Cullen, & Hodgins, 2012). However, no evaluation of specific motor impairments was reported. Furthermore, a review of developmental abnormalities during childhood measured in individuals at high risk of schizophrenia concluded that motor and neurological developmental problems appear to predict schizophrenia (Niemi, Suvisaari, Tuulio-Henriksson, & Lonnqvist, 2003). Our meta-analysis provides new cross-sectional information about which *specific* motor domains are impaired in children and adolescents with a familial risk of developing schizophrenia. This group is clinically identifiable and may have the potential for early intervention to forestall or mitigate the emergence of this disorder.

Here, we aim to investigate the occurrence of deviations in motor function during the development (≤ 21 of age) and the presence of specific motor deficits in unaffected FDR of individuals with schizophrenia (hereafter referred to as FDR) compared with controls. Using a systematic review and meta-analysis, we aimed to test whether children and adolescents with a genetic risk of developing schizophrenia and without manifest symptoms of psychosis display evidence for a motor impairment on a group level, which could represent an endophenotype. More specifically, we examined: Do FDR differ in their motor development or specific motor abilities compared with individuals without a genetic predisposition?

Methods

Study registration

This study adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The protocol for the study was registered at PROSPERO international prospective register of systemic reviews (registration number CRD42012002591), before starting the literature search.

Study selection

Searches were performed in PubMed, PsycINFO, EMBASE, and the Cochrane Library. Search terms used were: ('high risk' OR 'high-risk' OR 'clinical high risk' OR 'schizophrenia'[TIAB] OR 'psychos*[TIAB] OR 'psychotic'[TIAB] OR 'mental illness'[TIAB]) AND ('child*[TIAB] OR 'adolescen*[TIAB] OR 'infan*[TIAB] OR 'offspring') AND ('motor' OR 'motor abilities' OR 'NSS' OR 'motor milestones' OR 'functional outcome' OR 'movement abnormalities' OR 'developmental abnormalities' OR 'developmental disabilities' OR 'motor skills disorder' OR 'dyskines*' OR 'pandysmatur*'). Further, references were examined for relevance and included if appropriate. No limitations were imposed regarding language, publication date, or country of origin.

Studies were included if they: (a) investigate FDR (offspring or siblings) of individuals with schizophrenia; (b) assess motor abilities or neurodevelopment; (c) include a control group; and (d) include a sample ≤ 21 years of age to investigate motor development in children and adolescents. We chose this age cutoff as we aimed to assess individuals in development. The majority of brain maturation in gray matter is completed at this age, although there is some further white matter development (Lenroot & Giedd, 2006). The peak debut of schizophrenia onset is 22 years, (Thorup, Waltoft, Pedersen, Mortensen, & Nordentoft, 2007). Therefore, young FDR under this age constitute a veritable high-risk group. In this study, motor ability reflects motor system functions, including the motor cortex, pyramidal tract, motor neurons, and cerebellum. Despite evidence for saccadic eye movements as an endophenotype for schizophrenia (Calkins, Iacono, & Ones, 2008; Greenwood et al., 2011), we did not include this function in our study. This was because of its etiologic complexities, involving several domains other than the motor domain (Meyhofer et al., 2015), and because of our restriction to measures obtained in clinical settings. Exclusion criteria were: (a) manifest symptoms of schizophrenia in FDR; (b) ultrahigh-risk status in FDR; and (c) studies not providing data for the actual motor function of the child/adolescent.

Data extraction

Two researchers (BKB, CH) independently screened all records obtained in the literature search, focusing on the relevance of titles to inclusion and exclusion criteria. The records were then entered into a Reference Manager 12 database. The data selection from both researchers was merged into a single database and duplicates were removed. The two researchers independently screened the abstract and full article of all records. Reasons for exclusion were recorded in an Excel database for each researcher: (a) FDR were not at genetic risk of developing schizophrenia; (b) FDR had a psychotic episode or diagnosis of schizophrenia; (c) FDR were at ultra high-risk state; (d) no motor outcomes; (e) included population were older than 21 years; (f) duplicate record; and (g) other, i.e., no motor data available for analysis or review papers. Each included or excluded record was assessed by both researchers until a consensus was reached.

Two authors independently extracted data and agreement statistics were subsequently estimated. Ultimately, consensus was sought in case of disagreement, which was reached in all such cases. Data were extracted manually to a prepiloted data-collection sheet and then entered into a database. Where included studies did not report sufficient statistical information for inclusion in the meta-analysis, the authors of the studies were not contacted for additional data.

Outcome measures

A variety of different motor outcomes were reported in the included studies and studies were classified into six domains of motor function. Meta-analyses were performed for each domain and we report the results within the following categories:

- *Gross and fine motor development*: assessed in infants aged 0–3.5 years using the Psychomotor Development Index (PDI) from the Bayley Scale of Infant Development (Bayley, 1969). Test items for the PDI included motor skills, such as rolling, crawling, grasp, and use of utensils.
- *Delay in walking*: age at which the child reached the milestone of walking. Categories were walking with support at the age of 10 months (Mednick, Mura, Schulsinger, & Mednick, 1971), walking at 12 months (Niemi et al., 2005),

or walking without support at the age of 18 months versus later (Henriksson & McNeil, 2004).

- **Impaired coordination:** several measures of coordination were recorded, including finger opposition, diadochokinesis, rapidly opening and closing the hand (Marcus, Hans, Lewow, et al., 1985), placing matches into a box (Hans et al., 2009), patterned movements of arm and hand, tapping finger and foot, finger following, visual motor coordination (copying of simple geometric figures) (Marcus, Hans, Mednick, Schulsinger & Michelsen, 1985), finger-nose, finger pursuit, heel-knee, rapid alternation, and rapid finger movement. Furthermore, activities such as buttoning, writing (Rosso et al., 2000), or inability to draw (Henriksson & McNeil, 2004) were recorded. Fine motor skills (Bagedahl-Strindlund, Rosencrantz-Larsson, & Wilkner-Svanfeldt, 1989; McNeil et al., 1993) were assessed using the Eye-Hand Coordination subscale of the Griffiths Developmental Scale (Alin-Åkerman & Nordberg, 1980; Griffiths, 1970). Eye-hand coordination and finger dexterity were also assessed using the Lincoln-Oseretsky Motor Development Scale (Myles-Worsley et al., 2007; Sloan, 1955).
- **Abnormal movements:** defined as tremors, tics, spasms, or athetoid movements (Rosso et al., 2000). Mirror movements, associated movements, or involuntary movements were also included (Hans et al., 1999; Marcus, Hans, Lewow, et al., 1985). Furthermore, choreoathetoid movements, abnormal facial movements, repetitive and spastic movements, hyper-/hypotonicity, bradykinesia, abnormal hand posture, abnormal posture (Walker et al., 1994), or motor overflow (Marcus, Hans, Mednick, et al., 1985) were assessed. Finally, studies reporting a composite neuromotor measure, where movement abnormalities were the main contributor (Hans et al., 1999; McNeil et al., 1993; Walker et al., 1994).
- **Neurological soft signs:** assessed using the Neurological Evaluation Scale (NES) (Buchanan & Heinrichs, 1989) or during a general neurological examination (Niemi et al., 2005; Rieder & Nichols, 1979). One study divided the NES into repetitive-motor and cognitive-perceptual subscales (Keshavan et al., 2008). The data from the repetitive motor subscale only were used in this meta-analysis.
- **Fine and gross motor skills:** The Lincoln-Oseretsky Motor Development Scale (Sloan, 1955) was used to assess finger dexterity, eye-hand coordination, and gross activity of hands, arms, legs, and trunk in children 6–14 years old (Erlenmeyer-Kimling et al., 2000). One study (Hanson, Gottesman, & Heston, 1976) assessed gross motor skills, such as hopping, walking in a line, and catching a ball, as well as fine motor skills, such as using pegboards, stringing beads, and the Porteus Maze Test.

Individuals from the same sample could be included in several motor outcome domains. For example, if the study tested coordination and abnormal movements, the sample was included in both domains. Furthermore, if the study had an outcome measure comprising many different motor skills, we chose the most relevant motor outcome group to that specific outcome.

Statistical synthesis and analysis

The meta-analysis compares specific motor abilities in young FDR with controls. The relevant heterogeneous data were synthesized using random effects models. Individual effect sizes [Hedges' g with 95% CI] for each study and an overall effect size were calculated and presented as forest plots. We used Hedges' g because Cohen's d is biased for small study samples (Borenstein, Hedges, Higgins, & Rothstein, 2009). Furthermore, meta-regressions were performed in several motor outcome groups, including age as a moderator in outcome

measures with more than $n = 5$ studies. We assessed heterogeneity with I^2 statistics, using a cutoff for $I^2 > 75\%$ to indicate too high a level of heterogeneity to calculate meaningful overall effect sizes (Higgins, Thompson, Deeks, & Altman, 2003). We assessed the potential for publication bias by using funnel plot asymmetry and Egger's test of intercept in a random effects model (Egger, Davey, Schneider, & Minder, 1997). The funnel plot is a scatter plot of study size (standard error) on the vertical axis as a function of effect size on the horizontal axis. Studies are distributed symmetrically about the combined effect size, if a publication bias is not present. Asymmetry in a funnel plot indicates that studies with nonsignificant results may have remained unpublished. Egger's test of intercept quantifies the degree of asymmetry of the funnel plot by regressing a measure of the observed effect to the study's precision. The size and direction of the effect is captured by the slope of the regression line, whereas bias is captured by the intercept (β_0). The larger the intercepts deviation from zero the more pronounced the asymmetry. Reported p -values are two-sided, with alpha at 0.05 for the null-effect test and 0.10 for the regression-based asymmetry tests (Ioannidis & Trikalinos, 2007; Jennions & Moller, 2002). Finally, a 'Trim and Fill' analysis in the random effects model was conducted to quantify the effect of missing studies on the observed effect size and recalculate the meta-estimate based on hypothetical studies that would have generated a symmetrical funnel plot (Duval & Tweedie, 2000). Analyses were performed in Comprehensive Meta-Analysis (2.0) (Borenstein et al., 2009).

Results

Search results and study characteristics

A total of 13,305 records were identified from the literature search after duplicates were removed (Figure 1). According to the predetermined inclusion and exclusion criteria, records were screened first by title and 12,323 records were excluded. The high number of exclusions based on titles alone was due to articles concerning neonates, also referred to as 'high-risk'. Thereafter, 982 full text articles were assessed, resulting in the exclusion of 961 records. Two further articles were identified from reference lists of the identified articles (Mednick et al., 1971; Ragins et al., 1975).

Twenty-three studies were included in the systematic review (Bagedahl-Strindlund et al., 1989; Erlenmeyer-Kimling et al., 2000; Hans et al., 1999; 2009; Hanson et al., 1976; Henriksson & McNeil, 2004; Keshavan et al., 2008; Marcus, Auerbach, Wilkinson & Burack, 1981; Marcus, Hans, Lewow, et al., 1985; Marcus, Hans, Mednick, et al., 1985; McNeil, Fish & Schubert, 2011; McNeil et al., 1993; Mednick et al., 1971; Myles-Worsley et al., 2007; Niemi et al., 2005; Onal, Demir, & Ceylan, 2002; Ragins et al., 1975; Rieder & Nichols 1979; Rosso et al., 2000; Sameroff, Barocas, & Seifer, 1984; Sohlberg, 1985; Walker et al., 1994; Yoshida, Marks, Graggs, Smith, & Kumar, 1999), of which 20 were included in the meta-analysis (Table 1) (Bagedahl-Strindlund et al., 1989; Erlenmeyer-Kimling et al., 2000; Hans et al., 1999, 2009; Hanson et al., 1976; Henriksson & McNeil, 2004; Keshavan et al., 2008; Marcus et al., 1981; Marcus, Hans, Lewow, et al., 1985; Marcus,

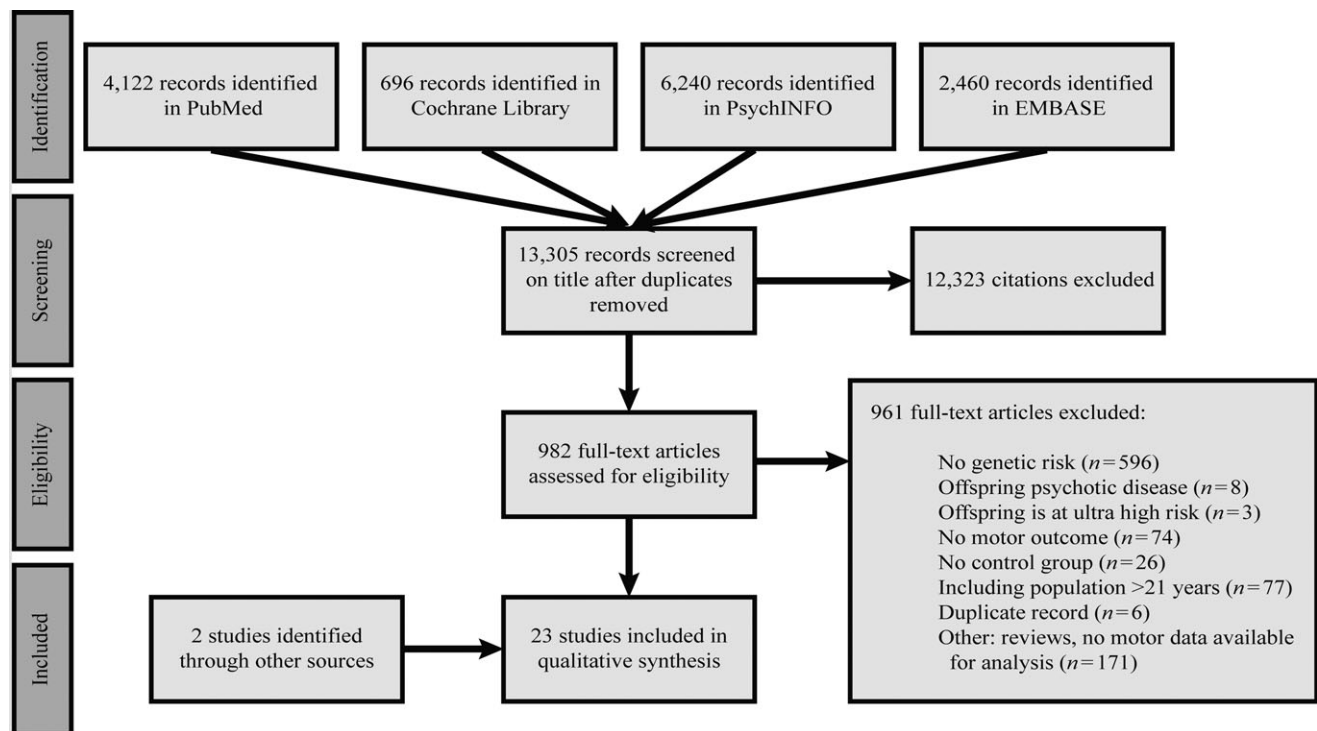


Figure 1 PRISMA flow chart. Note: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (www.prisma-statement.org)

Hans, Mednick et al., 1985; McNeil et al., 1993; Mednick et al., 1971; Myles-Worsley et al., 2007; Niemi et al., 2005; Onal et al., 2002; Rieder & Nichols, 1979; Rosso et al., 2000; Sameroff et al., 1984; Walker et al., 1994; Yoshida et al., 1999). Those not included in the meta-analysis either dealt with follow-up data (McNeil et al., 2011; Sohlberg, 1985) or lacked sufficient information to perform the calculations needed for the meta-analysis (Ragins et al., 1975). Additionally, one article was translated from Turkish (Onal et al., 2002).

Twenty-one studies examined offspring of individuals with schizophrenia, and the two remaining studies were cohort studies that evaluated individuals with schizophrenia and their unaffected siblings (Rosso et al., 2000), and a case-control study (Walker et al., 1994). Populations were assessed in Israel (Hans et al., 1999, 2009; Marcus et al., 1981; Marcus, Hans, Lewow, et al., 1985; Sohlberg, 1985), Europe (Bagedahl-Strindlund et al., 1989; Henriksson & McNeil, 2004; Marcus, Hans, Mednick et al., 1985; McNeil et al., 2011; McNeil et al., 1993; Mednick et al., 1971; Niemi et al., 2005; Onal et al., 2002; Yoshida et al., 1999), the United States (Erlenmeyer-Kimling et al., 2000; Hanson et al., 1976; Keshavan et al., 2008; Ragins et al., 1975; Rieder & Nichols 1979; Rosso et al., 2000; Sameroff et al., 1984; Walker et al., 1994), and the Republic of Palau (Myles-Worsley et al., 2007). All studies included a control group, and two studies also included a nonhealthy control group with psychiatric diagnoses other than schizophrenia assessing a composite motor measure (Erlenmeyer-Kimling et al., 2000; Hanson et al., 1976).

Meta-analyses

Meta-analysis of study results regarding gross and fine motor development suggested that children at high risk performed significantly worse than controls ($g = 0.644$, $p < .001$, $CI = [0.328, 0.960]$) (Figure 2). Moreover, meta-analysis of delayed walking outcomes revealed that infants at high risk for schizophrenia had delayed achievement of walking milestones compared with controls ($g = 0.444$, $p = .01$, $CI = [0.108, 0.780]$). A meta-analysis of impaired coordination demonstrated that FDR were impaired in their motor coordination compared with controls ($g = 0.625$, $p < .0001$, $CI = [0.453, 0.797]$), representing a moderate effect size. Metaregression with age (children vs. adolescents) did not indicate an age-dependent difference in coordination (regression coefficient = -0.0123 , $p = .94$, $CI = [-0.384, 0.360]$). FDR also had a slightly higher risk of abnormal movements compared with controls ($g = 0.291$, $p = .02$, $CI = [0.041, 0.542]$), as revealed by the meta-analysis. Furthermore, the presence of abnormal movements was independent of age (regression coefficient = 0.275 , $p = .25$, $CI = [-0.195, 0.744]$). One study (Rosso et al., 2000) provided data for two age groups (4 and 7 years old). For this study, we included the 7-year-old group to match the ages of children in the other studies in the abnormal movement meta-analysis. However, using the 4-year-old group instead did not influence our estimated effect size ($g = 0.315$, $p = .01$, $CI = [0.066, 0.564]$), $I^2 = 13.2\%$). Meta-analysis of studies investigating NSS revealed no differences between FDR and controls ($g = 0.238$, $p = .18$, $CI = [-0.106, 0.583]$).

Table 1 Characteristics of studies included in the systematic review and meta-analyses of first-degree relatives to individuals with schizophrenia and their motor outcomes

First author (reference)	Country/ town	Type of Study	Sample Size		Female (%)		Motor outcome all	Age (mean or range)	Outcome measure used in meta-analysis
			HR	Control	HR	Control			
Yoshida (1999)	UK	HR	19	24	53	36	Bayley Scale of Infant Development	2 and 7 months	Gross and fine motor development
Sameroff (1984)	Rochester	HR	29	57	NK	NK	Bayley Scales of Infant Development	2.5 years and 4 years	Gross and fine motor development
Marcus (1981)	Israel	HR	19	19	42	NK	Bayley scales of Infant Development	8 months	Gross and fine motor development
Mednick (1971)	Denmark	HR	207	104	NK	NK	Late walking with support and late in holding their heads	4 and 10 months	Delayed walking
Niemi (2005)	Finland	HR	111 & 88	53 & 97	NK	NK	Not able to walk at 1 year. Neurological soft signs.	1 year & childhood or adolescent	Delayed walking
Henriksson (2004)	Sweden	HR	33	100	36	54	Not walking without support, not sitting stable, and coordination/abnormal movements	8 months and 1.5 years.	Delayed walking
Hanson (1976)	US	HR	30	29	NK	NK	Poor motor skills (gross and fine motor, composite measure)	0–4 years	Coordination
Erlenmeyer-Kimling (2000)	US	HR	79	133	NK	NK	Lincoln–Oseretsky Motor Development Scale, (composite measure).	4 years	Motor skills compared with other mental diseases
Keshavan (2008)	US	HR	75	82	54.7	51	NSS [NES scale (repetitive motor)]	7–12 years	Motor skills compared with other mental diseases
Rieder (1979)	US	HR	59	59	41	41	Neurological signs	Mean age: 15.68 and 15.92	NSS
Onal (2002)	Turkey	HR	43	45	58.1	55.6	NSS (NES scale)	7 years	NSS
Hans (2009)	Israel	HR	20	16	NK	NK	Fine motor dyscoordination	8–18 years	NSS
Bagedahl-Strindlund (1989)	Sweden	HR	15	17	NK	NK	Griffiths locomotor test and eye-hand coordination test.	Mean age: 10.35 years	Coordination
Mytles-Worsley (2007)	Republic of Palau	HR	44	99	52.9	54.5	Lincoln–Oseretsky Motor Development Scale	5–7.3 years	Coordination
Marcus, Hans, Mednick (1985a)	Denmark	HR	59	59	52.5	52.5	Coordination, laterality, motor impersistence, motor overflow	14–19 years	Coordination
Rosso (2000)	US	Co	63	7941	49.2	49.7	Unusual movements and coordination	11–13 years	Abnormal movements
Marcus, Hans, Lewow (1985b)	Israel	HR	46	47	NK	NK	Balance, coordination, and motor overflow	4 & 7 years	Abnormal movements
McNeil (1993)	Sweden	HR	23 & 23	37 & 38	NK	NK	Griffiths Developmental Scale: eye-hand coordination test and Touwen and Precl's neurological examination.	7–14 years	Coordination
Walker (1994)	US	CC	28	21	42.9	66.7	Neuromotor abnormalities, motor skills and milestones combined	6 years	Abnormal movements
Hans (1999)	Israel	HR	24	16	54	31	Neurobehavioral functioning (coordination and abnormal movements)	0–15 years and 0–2 years	Abnormal movements
Sohlberg (1985)	Israel	HR	50	50	NK	NK	Bender–gestalt test	14–21 years	Abnormal movements
McNeil (2011)	Sweden	HR	38	91	34.2	52.7	Delayed motor mile stones as part of pandysmaturation	8.1–14.8 years	Sample already used in coordination (Marcus, Hans, Lewow, et al., 1985) Follow-up data
Ragins (1975)	US	HR	10	10	NK	NK	Bayley Scale of Infant DevelopmentLate walking	NK	Not enough data provided in the paper for performing meta-analysis

HR, high risk study; CC, case-control study; Co, cohort study; NSS, neurological soft signs; NES, neurological evaluating scale; NK, not known.

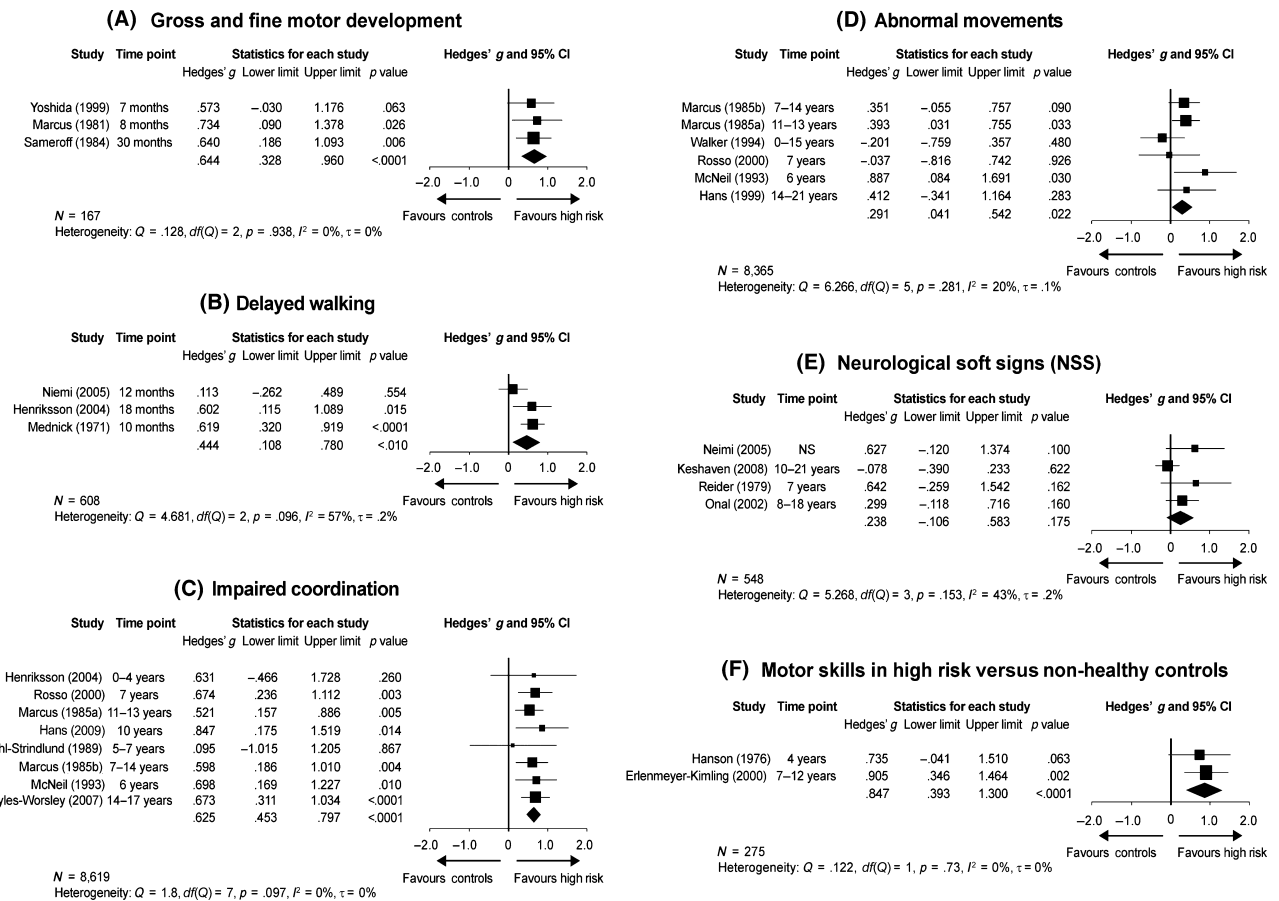


Figure 2 Forest plots with effect size and heterogeneity of the six motor outcome measures: (A) gross and fine motor development, (B) delayed walking, (C) impaired coordination, (D) abnormal movements, (E) neurological soft signs and (F) motor skills in high risk versus non-healthy controls

Assessment of gross and fine motor skills in FDR compared with offspring of parents diagnosed with a mental disorder other than schizophrenia demonstrated that the FDR had poorer motor skills ($g = 0.847$, $p < .001$, $CI = [0.393, 1.300]$), representing a large effect size albeit based on two studies only.

Assessment of publication bias by visually inspecting the funnel plots indicated three asymmetrical funnel plots (coordination, abnormal movement, and NSS) (Figure 3). Egger's regression methods testing for funnel plot asymmetry were conducted (Table 2). For NSS studies, the intercept β_0 , which provides a measure of asymmetry, was 2.703 with a significant two-tailed p -value = .09, implying possible publication bias. The remaining funnel plots were not significant for asymmetry. A Trim and Fill analysis for NSS (Table 2) suggested two missing studies to the left side of the mean effect, suggesting negative results remain unpublished. The imputed point estimate was 0.076 ($CI = [-0.264, 0.417]$), indicating no significant difference between FDR and controls.

A Trim and Fill analysis for the remaining studies (Table 2) showed one missing study for impaired coordination, but the recalculated effect size 0.610 ($CI = [0.443, 0.776]$) still revealed a significant

difference between FDR and controls. In contrast, the Trim and Fill analysis for abnormal movement suggested one missing study and an imputed effect size of 0.229 ($CI = [-0.038, 0.496]$), indicating no difference between FDR and controls when assessing for abnormal movement.

Discussion

Results of the present meta-analysis demonstrated significant impairments in several specific motor outcomes in unaffected FDR of individuals with schizophrenia compared with healthy controls and offspring of parents with other mental disorders. These include impaired coordination which had the most robust estimate owing to the moderate effect size and small 95% CI. Further impairments are seen in delayed gross and fine motor development in infancy, delayed achievement of walking, and the presence of more abnormal movements. However, we did not detect a significant difference in the presence of NSS. Furthermore, gross and fine motor skills in FDR compared with offspring of parents with other mental illnesses revealed a high effect size, but the wide 95% CI makes the estimate more uncertain. Overall, the results of the present meta-analysis

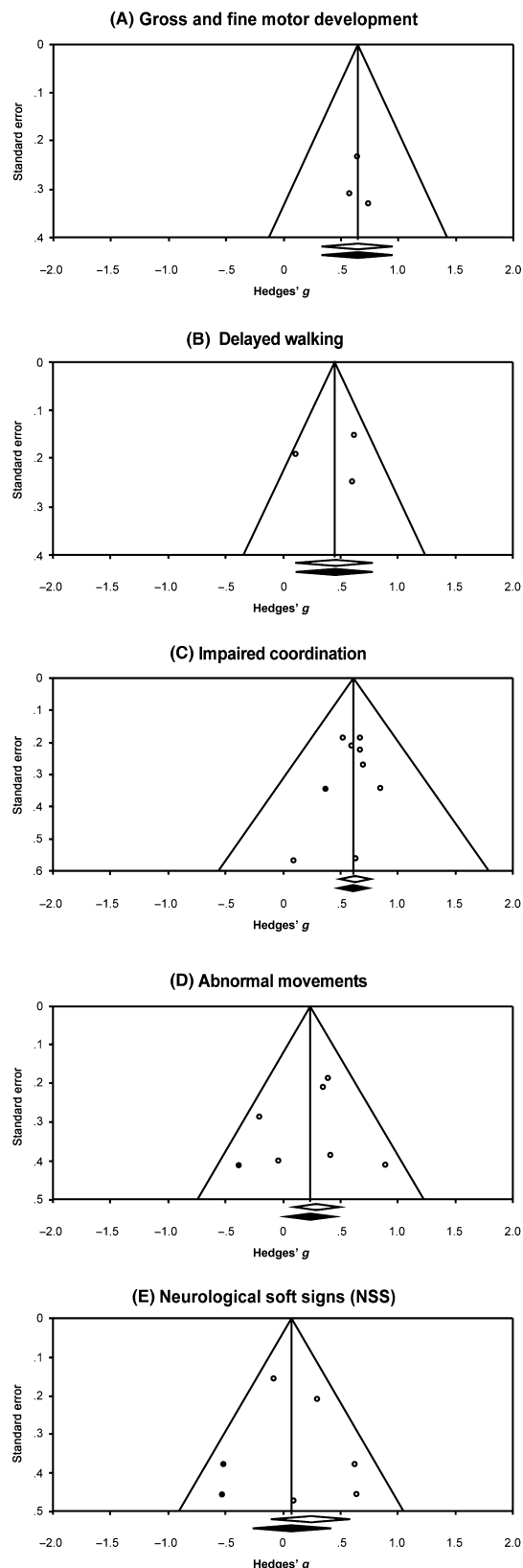


Figure 3 Publication bias. Funnel plots with a Trim and Fill analysis of (A) gross and fine motor development, (B) delayed walking, (C) impaired coordination, (D) abnormal movements and (E) neurological soft signs. The clear dots represent the actual studies, and the clear diamond represents the effect size and CI. The black dots represent the missing studies suggested by the Trim and Fill analysis, and the black diamond represents the recalculated estimated effect size and CI where the potential missing studies are incorporated

demonstrated poorer motor abilities in unaffected FDR compared with controls.

Delayed walking was the only domain with heterogeneity above 50%. However, no evidence of significant between-study heterogeneity was detected in any of the five meta-analyses. This suggests that the estimates of motor abilities are not dependent on the population investigated or reflected by where the study was performed, but was determined by whether the child/adolescent was a FDR or not.

As no large and significant between-study heterogeneity was identified, we applied tests to evaluate potential publication bias (Ioannidis & Trikalinos, 2007). In the domain of NSS, both Egger's test and the Trim and Fill analysis found significant potential of publication bias. Incorporating the possibility of publication bias for NSS further strengthened the result of the observed meta-analysis, showing no difference between FDR and controls when assessing for NSS.

Neurological soft signs and neurological abnormalities have been reported repeatedly in patients with schizophrenia (Boks, Russo, Kneegtering, & van den Bosch, 2000; Bombin, Arango, & Buchanan, 2005; Heinrichs & Buchanan, 1988; Ismail, Cantor-Graae, Cardenal, & McNeil, 1998; Keshavan et al., 2003; Peralta et al., 2011; Quitkin, Rifkin, & Klein, 1976; Rossi et al., 1990; Scheffer, 2004; Woods, Kinney, & Yurgelun-Todd, 1986), in pre-morbid groups (Leask, Done, & Crow, 2002; Walker & Lewine 1990; Cannon et al., 2002), and in adult FDR. However, results from our meta-analysis did not confirm these findings. Subtle neurological impairments, as measured with NSS, typically increase with age (Chen, Lam, Chen, & Nguyen, 1996; Rossi et al., 1990). In contrast to our findings, higher NES scores have elsewhere been detected in individuals with schizophrenia and their relatives, and deviations were positively correlated with age in both groups (Compton et al., 2007). The influence of age could explain why two meta-analyses (Chan, Xu, Heinrichs, Yu, & Gong, 2010; Neelam, Garg, & Marshall, 2011) assessing adult FDR of individuals with schizophrenia reported a significantly higher proportion of NSS in this group, whereas we did not observe any differences across groups in younger individuals. Moreover, the NES was designed to assess adults diagnosed with schizophrenia (Buchanan & Heinrichs, 1989) and may therefore lack sensitivity for the assessment of younger populations without psychosis, where motor and neurological development is ongoing. We suggest that the existing measures may not sufficiently accommodate the inherent characteristics of motor development in children and adolescents and could be considered as possible contributors to the negative findings. There is a need for studies that are either longitudinal or sufficiently broad in age range to enable the evaluation of the effects of age and development on the expression of NSS reported in schizophrenia.

However, the results from each motor domain are not independent of each other, due to both an

Table 2 Assessment of publication bias

	Egger's test of the intercept			Missing studies	Duval and Tweedie's trim and fill			
	β_0	95% CI	<i>p</i> -value (two sided)		Observed effect size	95% CI	Imputed Point estimate	95% CI
Gross and fine motor development	0.316	[-15.975, 16.609]	0.846	0	0.644	[0.328, 0.960]	Unchanged	Unchanged
Delay in walking	-1.246	[-82.430, 79.938]	0.877	0	0.444	[0.108, 0.780]	Unchanged	Unchanged
Impaired coordination	-0.234	[-1.589, 1.122]	0.688	1	0.625	[0.453, 0.80]	0.610	[0.443, 0.776]
Abnormal movements	-0.164	[-4.672, 4.343]	0.924	1	0.291	[0.041, 0.542]	0.229	[-0.038, 0.496]
Neurological soft signs	2.702	[-1.056, 6.462]	0.09	2	0.238	[-0.106, 0.583]	0.076	[-0.264, 0.417]

overlap among individuals in the different motor domains and an overlap among the motor subdomains. Consequently, though the domains represent different aspects of the motor system, they cannot be regarded as specific discrete entities. The domains are connected through circuits and networks within the motor system itself, and via interactions with other functional systems in the brain. Finally, we cannot dismiss the possibility that the deviations reported here in unaffected FDR could be transitory deviations (Gogtay, 2007) that may normalize during development. Only longitudinal studies can address this.

It is notable that none of the motor tests included in the present meta-analysis used more advanced physiological measures, such as actigraphs. This probably reflects the relatively recent attention to the use of these measures. However, future studies assessing motor function in FDR should strive to add digital measures of movement sequences and motor patterns to detect subtle differences in a comprehensive way.

Studies of motor abilities in FDR of individuals with schizophrenia compared with FDR of individuals with bipolar disorder or other neurodevelopmental disorders could further determine the specificity of these motor deviations in relation to schizophrenia. Alternatively, they may suggest a shared biological pathway of neurodevelopmental disorders. Adult psychiatric illnesses may originate from developmental disorders, with different symptom presentations in childhood (Rutter, Kim-Cohen, & Maughan, 2006). Given the status of the field and that children and young people included in this study are in development, caution should be taken when advising about interventions for this FDR group to avoid unnecessary false alarms. Early warning signs may disappear at later stages in FDR, due to minor deviations, resilience factors, or as part of normal development (Gogtay, 2007). Thus, ideally we want to identify specific and early warning markers, characterized by a clinically quantifiable risk factor index such as a composite risk score. This could comprise, for example, a genetic polygenic risk score

(or a family history), early symptoms, environmental components, and other measures of cognition or motor function, which specifically differentiate FDR from controls. Although still not definitive, a composite risk score is probably more accurate with a higher rate of positive and negative predictive values and thus yields a higher sensitivity and specificity than a single test.

Deficits of saccadic eye movements among others are established as valid endophenotypes for schizophrenia (Greenwood et al., 2011). In the present meta-analysis, young FDR showed evidence for group-level motor deficits during development, which could represent a potential endophenotype for a genetic vulnerability to develop schizophrenia.

Strengths and limitations

This is the first meta-analysis to assess specific motor outcomes in young unaffected FDR of individuals with schizophrenia compared with control groups. Our meta-analysis has several strengths including broad search criteria and independent selection of studies by two assessors to minimize the risk of assessor bias. Furthermore, we evaluated different age groups and specific motor functions in a systematic way, which has not been done previously.

Several limitations should be borne in mind. This is a meta-analysis of cross-sectional studies, thus we are unable to determine whether the same individuals show both early and late motor abnormalities – only longitudinal data can address this. In addition, inferences drawn relate to genetic and environmental consequences of having a parent diagnosed with schizophrenia and not necessarily the antecedents of schizophrenia in adulthood. Furthermore, two of the studies included were of siblings rather than offspring. Siblings and offspring differ genetically (siblings share dominance effects, while parents and offspring do not) and environmentally (offspring are typically reared by parents with schizophrenia, siblings are not). Moreover, we divided the included studies into domains of function to compare the same motor outcome measures in a single meta-

analysis. This resulted in fewer studies in each domain, but revealed that FDR and controls did not differ in terms of NSS. This finding may have been veiled in studies reporting profiles or composite measures of motor function. Finally, the variety of instruments and differences in sources of information used in the present studies in addition to the differences for recruiting the cohorts and the limited amount of information concerning the method of recruitment did not allow for a stringent evaluation of the degree of validity of the instruments or the selection bias. Future studies should therefore attempt to use validated instruments and describe the process of recruitment and the composition of their sample, inclusive its representativeness in more detail.

Conclusions

We report specific motor impairments in unaffected FDR of individuals with schizophrenia who are 21 years or younger when compared with controls demonstrating poorer motor abilities in FDR. The effect across studies assessing for impaired coordination may be considered the most robust with a moderate effect size, a narrow confidence interval, and no detected heterogeneity or publication bias. Thus, this domain is worthy of future research. Furthermore, the occurrence of delayed gross and fine motor development in infancy and delayed walking in FDR compared with controls is also supported. Additionally, we observed a significant difference in abnormal movements between the FDR and controls, however, due to a possible publication bias this finding should be interpreted cautiously. Further, no overall differences could be demon-

strated in the assessment of NSS when comparing these groups. The adult measure of NSS may lack sensitivity for age-dependent assessment of soft signs in developing children and adolescents. Individuals at familial risk of schizophrenia had poorer gross and fine motor skills than children of parents with other mental disorders. These motor deficits suggest that delayed motor development may represent a potential endophenotype for schizophrenia, and likely reflect the underlying neurodevelopmental vulnerability. However, the limited amount of accessible studies did not allow the exploration of the specificity of this finding in depth. The fact that motor deficits are present through early childhood and into adulthood reflects the complexity of neuro-motor development and is consistent with the hypothesis that schizophrenia represents a neurodevelopmental disorder.

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Key points

- A meta-analysis demonstrated poorer motor abilities in the unaffected first-degree relatives (≤ 21 years) of individuals with schizophrenia than in the youth from unaffected families, suggesting motor deficits during development may represent a potential endophenotype for schizophrenia.
- Impaired coordination, represented the most reliable finding with a medium effect size.
- In contrast, neurological soft signs did not yield reliable effects.
- Fine and gross motor skills were impaired in relatives of individuals with schizophrenia compared with relatives of individuals with other major psychiatric disorders.

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Motor Impairments among Children with a Familial Risk of Schizophrenia or Bipolar Disorder at 7 Years Old – The Danish High Risk and Resilience Study VIA 7

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Abstract

Background: We aimed to thoroughly characterize motor impairments in a large cohort of young children of parents with schizophrenia or bipolar disorder and compare their motor abilities with controls. Owing to the genetic overlap between these two disorders, the specificity of motor aberrations in children with a familial risk is of interest.

Methods: We have established a cohort of 7-year-old children, with no, one, or two parents with schizophrenia or bipolar disorder. We investigated motor function in 514 children using the Movement Assessment Battery for Children–Second Edition.

Outcomes: Children with a familial risk of schizophrenia demonstrated impaired motor performance compared with controls in the subdomains of manual dexterity (mean difference= -1.42, 95% CI: [-2.08– -0.77], $T_{(510)}=-4.27$, $P<0.0001$) and balance (mean difference= -1.38, 95% CI: [-2.03– -0.72], $T_{(508)}=-4.12$, $P<0.0001$), but not the subdomain of ball skills, including aiming and catching (mean difference= -0.39, 95% CI: [-0.97– -0.19], $T_{(510)}=-1.33$, $P=0.18$). Children with a familial risk of bipolar disorder displayed motor performance not significantly different from controls in all three subdomains manual dexterity (mean difference= -0.69, 95% CI: [-1.44– -0.07], $T_{(512)}=-1.79$, $P=0.075$), balance (mean difference= -0.68, 95% CI: [-1.44– -0.08], $T_{(510)}=-1.75$, $P=0.08$), and aiming and catching (mean difference= -0.36, 95% CI: [-1.03– -0.31], $T_{(511)}=-1.05$, $P=0.29$).

Interpretation: Motor deficits may represent an endophenotype for schizophrenia, suggesting deviation of developmental paths and different profiles of motor ability.

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Key words: Motor function, manual dexterity, ball skills, balance, coordination, first-degree relatives, offspring, schizophrenia, mood disorders, bipolar disorder

Introduction

Severe mental disorders in adults may originate from neurodevelopmental disturbances, with different deviations presenting in childhood.^{1,2} Evidence shows motor impairments in individuals with schizophrenia well before the disorder manifests³⁻⁶ or at diagnosis.⁷ Equally, numerous studies of individuals with familial risk of schizophrenia support the existence of motor deficits, particularly impaired coordination during development.⁸ Most of the previous high-risk studies, however, included children of parents with schizophrenia across a broader age range where puberty and developmental stages may have influenced the findings.⁹⁻¹¹ Even though schizophrenia shares common characteristics and genetic liability with bipolar disorder¹² the evidence of motor deficits is not as robust for individuals with bipolar disorder.^{13,14} In a prospective study derived from a birth cohort, individuals developing mania before the age of 26 displayed superior general motor performance during childhood compared with healthy participants.⁶ In offspring of mothers with affective disorders, studies reported either motor performance comparable with controls¹⁵ or gross motor impairments.¹¹ Yet, offspring of parents with ‘affective disorder’ included parents with unipolar and bipolar disorder I/II. Differences in definitions of ‘affective disorder’ may thus

explain conflicting results.¹⁶ Hence, few studies have assessed motor skills among offspring of individuals exclusively with bipolar disorder and no studies have compared motor abilities in children with a familial risk of schizophrenia and a familial risk of bipolar disorder using a comprehensive, validated motor tool to assess the different domains of motor function.

Recent evidence suggests sex differences during development may have implications for predictors of mental disorder in young adulthood.¹⁷ Indeed, studies report prominent differences between the sexes with respect to incidence¹⁸ and cognitive function,¹⁹ with men showing worse outcomes on both parameters. However, the incidence of bipolar disorder is higher for women than men,¹⁸ and there is a greater loss of function among women diagnosed with bipolar II.²⁰

Interactions between genetic risk variants and environmental factors, mediated through brain structure and circuitry, may result in different phenotypic presentations of behavior or different neuropsychological profiles²¹ among individuals with severe mental disorders.²²

The overarching purpose of this study was to confirm and extend previously reported findings by examining the specificity of motor deviations in children of parents with schizophrenia using a comprehensive motor test, and, in a novel approach, to

Research in context

Evidence before this study

After acceptance of the protocol at the international prospective register of systematic reviews PROSPERO (registration number CRD42012002591) we searched in PubMed, PsychINFO, EMBASE and the Cochrane Library with the following search terms “(‘high risk’ OR schizophrenia[TIAB] OR psychoses[TIAB] OR mental illness) AND (child*[TIAB] OR adolescen*[TIAB] OR offspring OR infan*[TIAB]) AND (motor OR ‘motor abilities’ OR ‘neurological soft signs’ OR ‘movement abnormalities’ OR ‘motor skill disorder’ OR pandysmatur* OR dyskines*) with no language restrictions in July 2012. We performed a similar search in the same databases exchanging schizophrenia with ‘bipolar disorder’ OR ‘mood disorder’ a few months later.

We found various studies reporting motor function in first-degree relatives of schizophrenia but only few studies assessed motor function among first-degree relatives of bipolar disorder. We performed a meta-analysis of studies assessing motor abilities during development in young (≤ 21 years) unaffected first-degree relatives of individuals with schizophrenia. The most robust finding across studies was impaired coordination in unaffected first-degree relatives to individuals with schizophrenia with a moderate effect size ($k=8$, $n=8619$, Hedges’ $g=0.625$, $CI=[0.453-0.797]$, $P<0.0001$).

The search emphasized the differences in recruiting participants and the limited information regarding recruitment processes, which did not allow for a strict evaluation of selection bias and the representativeness of the sample. Beyond these necessities, the search highlighted the need for future research of motor performance among first-degree relatives

of individuals with bipolar disorder. A meta-analysis of studies evaluating motor function in first-degree relatives of individuals with bipolar disorder (at that point of time) was not possible due to the limited literature.

Added value of this study

Our study is one of the largest familial high risk studies, with a sample size of $n=514$. We assessed the specificity of motor deviations in children of parents with schizophrenia to confirm and extend previously reported findings. Moreover, including children with a familial risk of bipolar disorder is a novel aspect of examinations of first grade relatives. The similar age across participants allows for a comparison of developmental stage. This study provides new prospective, cross-sectional, representative information about motor function in two identifiable groups of pre-pubertal children using a golden standard motor measurement that has shown cross cultural validity. Our results demonstrate convincing evidence of impaired motor function among offspring of individuals with schizophrenia, whereas offspring of individuals with bipolar disorder did not perform significantly different from controls.

Implications of all the available evidence

This study contributes to raise awareness among clinicians concerning the potential presence of motor deficits in pre-pubertal children with a familial risk of schizophrenia— an area in need of special attention and examination. Clinicians should provide special attention to children with a motor ability placed below the 5th percentile, indicating definite motor problems, where a referral to a child physiotherapist should be considered.

evaluate motor ability in children with familial risk of bipolar disorder. We thus aimed to examine differences and similarities between 7-year-old children with a familial risk of schizophrenia or bipolar disorders and children without this vulnerability to determine whether children with familial risk display distinct profiles of their motor function, when using a fine-grained objective motor test. In this large cohort consisting of pre-pubertal children in a narrow age-range, we expected that children with a familial risk of schizophrenia would display more pronounced motor impairments compared with controls, whereas children with a familial risk of bipolar disorder would show less pronounced motor deficits compared with controls.

Methods

Participants’ parents gave written informed consent. The Danish Data Protection Agency approved the study protocol. The Danish National Committee on Health Research Ethics received the protocol for approval and we obtained a general evaluation, but due to the absence of any intervention, ethical approval was not deemed further necessary by the authority.²³

Study design and participants

The Danish High Risk and Resilience Study VIA 7 was conducted in Denmark between December 2012 and March 2016.²³ This prospective cohort consists of 522 7-year-old Danish children with either no, one or two parents diagnosed with a schizophrenia spectrum psychosis or bipolar disorder. Children were invited to participate if at least one of the parents was registered in The Danish Psychiatric Central Research Register with either a schizophrenia spectrum psychosis (ICD 10 codes: F20, F22, and F25, or ICD 8 codes: 295, 297, 298.29, 298.39, 298.89, and 298.99) or a bipolar disorder (defined as ICD 10 code: F31 or ICD 8 codes: 296.19 and 296.39), and if this

individual also was registered in the Danish Civil Registration System as a biological parent to a 7-year-old child (Figure 1).

Children with a parent diagnosed with schizophrenia were matched to a control participant based on their home address (same municipality), age, and sex. Offspring of parents with bipolar disorder were not matched, but were overall similar in terms of age, sex, and urbanicity.

Procedures

We assessed motor abilities using the Movement Assessment Battery for Children—Second Edition (Movement ABC-2),²⁴ which is a standardized test comprising three components: manual dexterity, aiming and catching, and balance. Manual dexterity measures abilities requiring fine motor skills using tasks such as placing pegs, threading lace, and drawing a trail. The aiming and catching subdomain measures balls skills, with assessment of catching with two hands and throwing beanbags onto a mat. Finally, the balance subdomain, which measures static and dynamic balance, entails one-board balance, walking heel-to-toe forwards, and hopping on mats. All raters were trained, approved, and certified by a physiotherapist authorized in assessing Movement ABC-2 and were blinded to participants’ clinical risk statuses when conducting assessments.

Data collection and inter-rater reliability

Movement ABC-2 assessments were preferably conducted in the same room where outlines for the assessment (i.e., throwing a ball, walking on a line) were designated. A few children were assessed at home at the wish of parents that examinations take place in familiar surroundings. Most assessments were recorded on video ($n=469$). We conducted regular inter-rater reliability assessments during data collection using the ratings of ten videos of children performing the Movement ABC-2. Intra-class

correlation for single measures varied between ICC=0.71–1.0 except for the item walking heel-to-toe forwards (ICC=0.52). One single rater (BKB), blinded to risk status, consistently scored the item ‘drawing trail 2’. Intra-rater reliability for ten sets of ‘drawing trail 2’ between the rater and the instructing physiotherapist was ICC=0.98, and the within-rater reliability across four weeks was ICC=0.97.

Statistical analyses

The Movement ABC-2 scale consists of three domains (manual dexterity, aiming and catching, and balance) and a total score.²⁴ We present data according to the Movement ABC-2 manual by converting raw-score data to standard scores using the normative data from the manual, which have proven cross-cultural validity.²⁵ This provides standard scores used in a clinical context and in line with other Movement ABC-2 studies. Furthermore, we assessed the proportion of children who scored $\leq 5^{\text{th}}$ percentile, which signifies clinically significant movement difficulties according to the Movement ABC-2 manual.²⁴

We tested our main hypothesis by assessing the main effects of familial risk group in a mixed-model analysis with repeated measures with an unstructured variance component matrix. The model included within-subjects factors ‘subdomains of Movement ABC-2’ with 3 levels (manual dexterity, aiming and catching, and balance) and ‘groups’ with 3 levels (familial risk of schizophrenia, familial risk of bipolar and controls). Both the individually matched children with a familial risk of schizophrenia and the non-matched children with a familial risk of bipolar disorder and controls were included in the model as random effects. The model was adjusted for age and sex, as well as all two-way, three-way and four-way interactions of familial risk group, sex, age, and motor subdomains. Statistically nonsignificant interaction terms were eliminated via backward stepwise regression, with the constraint that the model at each step had to be hierarchically well formulated. All lower-order terms that is sex, age, group and subdomain were included in the model, regardless of statistical significance and due to their biological or experimental plausibility. Because of the relatively few sibling pairs (16) the effect of sibling or higher genetic loading (8 children had two ill parents) was not considered in the statistical model (Table 1). We considered P -values $< .05$ as statistically significant. F-test was used for hypothesis testing on type three fixed effects and T-test was used reporting estimates. All statistical analyses were conducted in SAS (version 9.4).

We used a logistic regression to analyze the binary outcome of having definite motor problems (children who scored $\leq 5^{\text{th}}$ percentile on the total standard score) or not, adjusting for age (in decimal years) and sex. Furthermore, we explored the following intermediate variables in the repeated mixed model analysis: handedness, ‘living with both biological parents’, ‘living with index parent’, and ‘living with single parent’ for the child, and ‘personal and social performance score (PSP)’²⁶ of the biological index parent and the biological healthy co-parent, in addition to ‘education level’ for index and biological co-parents.

Role of the Funding source

The sources of funding had no involvement in the study design, data collection, data analysis, interpretation, writing the manuscript or decision to submit the manuscript for publication. The corresponding author had full access to all the data in the

study and had final responsibility for the decision to submit for publication. All authors have approved the final version of the manuscript.

Results

A higher percentage of the biological parents were divorced and unemployed/on leave (sick leave, maternity, or retirement) in the familial risk groups than in the control group, and a larger proportion of children in the familial risk groups lived with a single parent. Index parents with schizophrenia and the healthy co-parent were both considerably less educated than index parents and healthy co-parents with bipolar disorder and control parents (Table 1). Of 522 included children in the entire cohort, 514 children completed the Movement ABC-2.

The test for fixed effects in a mixed model for overall motor performance revealed significantly poorer standard scores in the familial risk groups ($F_{(2,509)}=9.31$, $P<0.0001$), in younger children ($F_{(1,509)}=12.31$, $P=0.0005$), in the subdomains of the Movement ABC-2 ($F_{(2,508)}=3.13$, $P=0.045$) as well as sex differences ($F_{(1,509)}=32.42$, $P<0.0001$). The effect of group and of sex differed across subdomains, with significant interactions of ‘group-by-subdomain’ ($F_{(4,609)}=2.74$, $P=0.0278$) and ‘sex-by-subdomain’ ($F_{(2,508)}=62.84$, $P<0.0001$), indicating that the effect of group and of sex was not the same for each subdomain. No three- or four-way interactions were significant nor the interaction of ‘group-by-sex’.

Children with a familial risk of schizophrenia demonstrated significantly impaired motor performance compared with controls in the subdomain of manual dexterity (mean difference= -1.42, 95% CI: [-2.08– -0.77], $T_{(510)}=-4.27$, $P<0.0001$) and balance (mean difference= -1.38, 95% CI: [-2.03– -0.72], $T_{(508)}=-4.12$, $P<0.0001$), but no difference compared with controls in the subdomain of aiming and catching (mean difference= -0.391, 95% CI: [-0.97– 0.19], $T_{(510)}=-1.33$, $P=0.18$) (Table 3).

Children with a familial risk of bipolar disorder displayed no significant differences in motor performance compared with controls in all three subdomains: manual dexterity (mean difference= -0.69, 95% CI: [-1.44– 0.07], $T_{(512)}=-1.79$, $P=0.075$), balance (mean difference= -0.68, 95% CI: [-1.44– -0.08], $T_{(510)}=-1.75$, $P=0.08$) $T_{(510)}$, and aiming and catching (mean difference= -0.36, 95% CI: [-1.026– 0.31], $T_{(511)}=-1.05$, $P=0.29$.) (Figure 2A and Table 3).

Boys performed poorer than girls in the domains of manual dexterity (mean difference= -2.29, 95% CI: [-2.87– -1.72], $T_{(510)}=-7.83$, $P<0.0001$) and balance (mean difference= -2.21, 95% CI: [-2.78– -1.63], $T_{(507)}=-7.52$, $P<0.0001$). In contrast, boys outperformed girls in the domain of aiming and catching (mean difference= 0.80, 95% CI: [0.29– 1.31], $T_{(509)}=3.10$, $P=0.002$) with a significant ‘sex-by-subdomain’ interaction (Figure 2B and Table 3). Means and standard deviations for the standard scores between familial risk groups are presented in Table 2.

Boys had 2.57 (95% CI: [1.64– 4.0]) times higher odds of definite motor problems than girls and older children had 3.97 (95% CI: [1.57– 9.96]) times higher odds of definite motor problems than younger children. The odds of having definite motor problems were 2.02 (95% CI: [1.23– 3.32]) times higher for children with familial risk of schizophrenia compared with children without familial risk of schizophrenia. In contrast the odds of having definite motor problems did not differ between

children with a familial risk of bipolar disorder and controls 1.57 (95% CI: [0.88–2.79]).

In the repeated measure mixed model, the influence of handedness on motor ability was not significant ($F_{(1,508)}=1.86$, $P=0.173$), nor were the effect of ‘child living with both biological parents’ ($F_{(1,506)}=0.05$, $P=0.83$), of ‘child living with the index parent’ ($F_{(1,509)}=0.09$, $P=0.77$), or of ‘child living with a single parent’ ($F_{(1,507)}=1.0$, $P=0.32$). We found no effect of the function of the biological index parent (measured with PSP) ($F_{(1,434)}=2.07$, $P=0.15$) on the child’s motor ability. Interestingly, a better PSP score of the healthy biological co-parent had a significant positive effect on the child’s motor performance ($F_{(1,415)}=14.4$, $P=0.0002$), on account of the effect of group disappearing ($F_{(2,417)}=2.21$, $P=0.11$). A higher education of the index parent had a significant positive effect on motor performance ($F_{(1,471)}=7.79$, $P=0.0055$), whereas the education of the healthy co-parent did not reveal any significant effect on motor performance ($F_{(1,471)}=0.82$, $P=0.37$).

Discussion

This prospective cross sectional cohort study demonstrates evidence of impaired motor function among 7-year-old children with a familial risk of schizophrenia, whereas children of parents with bipolar disorder displayed motor performance that did not significantly differ from controls. Moreover, girls outperformed boys in the domains of manual dexterity and balance, whereas the opposite was true for aiming and catching. Children with a familial risk of schizophrenia were twice as likely to demonstrate definite motor problems ($\leq 5^{\text{th}}$ percentile) compared with controls. Again, boys displayed higher odds ratios of having definite motor problems than girls. These findings reflect motor impairments on a group level in children of individuals with schizophrenia and sex differences of motor abilities in childhood. Although we could not detect a significant difference between children with a familial risk of bipolar disorder and controls, we cannot reject that there is a difference owing to the borderline significance in the same two subdomains of motor performance that were aberrant in children of parents with schizophrenia. Finally, we did not detect any handedness differences between groups.

Our results that motor deficits are present at the age of 7 years in children with a familial risk of schizophrenia are supported by the meta-analysis of unaffected first-degree relatives of individuals with schizophrenia, where motor deficits are displayed within the first year of childhood and through development to the age of 21 years.⁸ These findings together provide robust evidence for motor deficits during development on a group level among first-degree relatives of those with schizophrenia.

Sex differences in motor performance probably represent a combination of biological differences mirroring the brain’s dimorphism and of external influences, such as training of fine motor skills in girls and ball competences in boys.²⁷ Furthermore, a study reported similar sex differences among healthy 3- to 5-year-old Australian children comparable with the 7-year-old children in the present study using Movement ABC assessment.²⁸ Interestingly, boys with a familial risk of schizophrenia were twice as likely in the present study to demonstrate definite motor problems than girls. If motor impairments hold true as a predictor for schizophrenia (beyond an endophenotype), as indicated by a follow-up study¹¹ then this

finding may relate to the fact that men have a higher incidence of schizophrenia than women, thus reflecting a higher developmental vulnerability in men.

The Danish High Risk and Resilience study is unique as a familial high risk study in the sense that all children were invited to participate in the study when they were 7 years old. Despite this homogeneous age range, we confirmed that motor performance improves with increasing age. Although the group-by-age interaction was not significant in the formal statistical testing, we argue for the presence of developmental differences across groups, because the Movement ABC-2 measures the maturation of motor development, and as such group differences signify at least a developmental delay.

Being at “familial risk” entails a genetic and environmental exposure, and it is difficult to differentiate these components. Models suggest that the emergence of schizophrenia in an individual is due to the interplay of genetic and environmental factors, their interactions and correlations, which together impair motor development and cognitive abilities. This stands in contrast to a subgroup of individuals that develop bipolar disorder and perform as well as the general population.²⁹ The description of the VIA 7 cohort illustrates the differences in environment under which these children are brought up. In an explorative manner, we tested these variables representing distinct aspects of the child’s environmental influences in our statistical model to understand whether these environmental factors influenced the child’s motor performance. However, only higher education of the index parent and a good personal and social functioning of the healthy biological co-parent had a positive effect on the motor performance of the child. Within the observational design of the study, it is not possible to know whether these findings indicate that characteristics of the biological parent may influence the motor performance of the child as truly environmental factors, or if genes mediate these environmental factors, or a combination of both.

These cross-sectional data cannot predict whether children with a motor impairment will continue to deviate in their motor performance during development. Moreover, we cannot dismiss the possibility that these deviations are transitory deviations that may normalize later during development.² Only longitudinal studies can address these two issues. These results may reflect that motor deficits could be regarded as an endophenotype for schizophrenia because state-independent motor impairments are present in individuals with schizophrenia, and motor deficits are present in first degree-relatives. This is despite motor impairment sometimes being seen by the unaided eye as traditionally conceptualized.³⁰

The parents are divided into separate groups depending on diagnostic criteria for a schizophrenia spectrum disorder or bipolar disorder or neither. However, in the past 10 years evolving debate has occurred as to which diagnoses representing valid discrete entities or rather dimension representing different trans-diagnostic pattern, due to a considerable amount of genetic overlap of serious mental disorders¹². Moreover, this study cannot make any interference about the diagnostic long-term outcome.

Motor impairment and intellectual ability have shown correlations.³¹ However, one cannot discard that the same underlying (biological/genetic) factors may influence both measures. Thus, controlling for IQ or intellectual ability may over-adjust group differences. The question whether intellectual

ability could act as a mediator would answer another research question than the hypothesis addressed in this study and would require more comprehensive analysis.

Strengths of this prospective cohort study include its large sample size, the narrow age group, and the representativeness of this population-based sample. Moreover, raters were blind to familial risk groups, strengthening the validity of motor behavior ratings. Inter-rater reliability was satisfactory, except for the item walking heel-to-toe forward. Even though, this resulted in reduced precision for this item, the balance domain included three tasks and so this is unlikely to have influenced the results. Finally, systematic assessor bias was minimized owing to the 12 raters with regular ratings of reliability.

Despite the strength of the study, notable limitations include a modest response rate, inherent limitations derived from the instrument used and the group membership based on broad diagnostic categories. Each is discussed in turn. 1. The Movement ABC-2 manual converts raw scores to standard scores for each year with no separate norms for boys and girls. The estimates of the motor test would be more precise, if standard scores were applied in three-month intervals instead of years, and preferably divided by sex. 2. We were able to enroll 55% of the invited families into the study (figure 1), which is considered a moderate response rate. However, due to the fact that families were identified through registries, the large sample size and the equal distribution of urban and rural from all parts of Denmark across groups, we still deem the cohort to be highly representative for the population. 3. A considerable limitation to the study was the unavailability of dividing parents in to subgroups such as (psychotic/non-psychotic periods for bipolar disorder, bipolar disorder I/ II/NOS, early onset/late onset bipolar disorder and schizophrenia, medicine responders/non-responders) precluding us from assessing whether children to parents of these diagnostic subgroups differed in motor performance. In future studies and analyses it would be relevant to further explore motor ability between subgroups within the schizophrenia spectrum and across different types of bipolar disorder to examine whether specific endophenotypes in the domains of motor function underlie certain subgroups of the disorders.

Conclusion

The Danish High Risk and Resilience Study VIA 7, a prospective and representative cohort, has provided evidence for impaired motor performance among 7-year-old children with a familial risk of schizophrenia compared with controls. Children with a familial risk of bipolar disorder displayed no significant differences in motor performance compared with controls. By assessing offspring of individuals with these two severe mental disorders, this study contributes to the understanding of neurodevelopmental vulnerability in childhood. Our results might indicate that motor deficits are a possible endophenotype for schizophrenia, indicating deviation of developmental paths of motor function.

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Contributors

AT, JRJ, OM, MN, KP developed the study design, provided methodological advice and supervised the conduct of the study. BKB, AT, JRJ, DE, KSS, CJC, NH, DG, AG collected data. BKB, GP, KP conducted the statistical plans and analysis. GP and BKB conducted the figures and tables. BKB and KP wrote the first draft. All authors contributed to data interpretation, commenting and editing the report and approved the final version of this manuscript. All authors are accountable for the work.

Declaration of interest

We have no competing interests to declare.

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Table 1. Characteristics of children who completed movement ABC-2 and their parents participating in the Danish High Risk and Resilience Study VIA 7. Index parents refer to the biological parents with schizophrenia or bipolar disorder or, in the control group, the matched biological parent without any of these disorders.

	Schizophrenia familial-risk group	Bipolar disorder familial-risk group	Control group
Index Parent			
Total number of index parents	196	115	201
Female, N (%)	107 (54.6%)	64 (55.6%)	112 (55.7%)
Age at inclusion, mean (SD)	38.0 (6.0)	41.0 (7.0)	40.7 (4.9)
PSP, mean (SD)*	66.9 (15.7)	68.8 (14.0)	84.2 (10.0)
Unemployed or on leave	82 (48.5%)	46 (44.7%)	18 (9.4%)
Education			
Primary/ lower secondary education	49 (29.2%)	9 (8.5%)	7 (3.7%)
Upper secondary, vocational, short-cycle tertiary	71 (42.3 %)	44 (41.5%)	91 (48.1%)
Bachelor degree, equivalent or higher	48 (28.6%)	53 (50.0%)	91 (48.1%)
Biological co-parent			
Total number of co-parents	182	113	189
Female, N (%)	82 (45.0%)	50 (44.2%)	83 (43.9%)
Age at inclusion, mean (SD)	38.8 (6.4)	41.0 (5.4)	40.7 (4.3)
PSP, mean (SD)*	76.3 (14.3)	81.8 (13.1)	85.5 (8.5)
Unemployed or on leave	44 (25.7%)	14 (13.2%)	11 (5.9%)
Education, N (%)			
Primary/ lower secondary education	30 (17.2%)	5 (4.8%)	9 (4.9%)
Upper secondary, vocational, short-cycle tertiary	85 (48.9%)	43 (41.3%)	88 (47.6%)
Bachelor degree, equivalent or higher	59 (33.9%)	56 (53.8%)	88 (47.6%)
Child			
Total number of children	198	119	197
Age at inclusion, mean (SD)	7.8 (0.2)	7.9 (0.2)	7.8 (0.2)
Female, N (%)	92 (46.5%)	56 (46.7%)	90 (45.7%)
Two biological parents with SZ or/and BD, N (%)	7 (3.5%)	1 (0.8%)	-
CBCL score, mean (SD) **	27.3 (21.0)	23.5 (19.7)	17.1 (14.8)
CGAS, mean (SD) ***	68.1 (15.5)	73.5 (14.9)	77.7 (13.5)
Home environment			
Living with both biological parents, N (%)	79 (39.9%)	62 (53.0%)	168 (85.3%)
Living out of home, N (%)	11 (5.6%)	0 (0.0%)	1 (0.5%)
Living with index parent, N (%)	119 (60.1%)	81 (68.1%)	187 (94.9%)
Living with a single parent, N (%)	74 (37.4%)	37 (31.6%)	21 (10.7%)

* Personal and social performance scale (PSP) is a measure of personal and social functioning and ranges from 0 to 100 with higher scores reflecting better functioning.

** Child Behavior Check List (CBCL) is a parent-rated measure of problem behavior in children. Larger scores reflect more problems.

*** Children's Global Assessment Scale (CGAS) is a measure of general functioning in children rated by trained interviewers. The scale ranges from 0 to 100 with higher scores reflecting better functioning.

Table 2. Means and standard deviations for the standard scores in Movement ABC-2 between familial risk groups.

	Schizophrenia familial-risk group (N=198)	Bipolar disorder familial-risk group (N=119)	Control group (N=197)
Boys	107 (54%)	63 (53 %)	107 (54.3%)
Mean age, year (SD)*	7.91 (0.25)	7.94 (0.23)	7.88 (0.23)
Manual dexterity	7.98 (3.44)	8.69 (3.56)	9.44 (3.57)
Ball skills	8.42 (2.92)	8.4 (3.06)	8.87 (2.99)
Balance	7.63 (3.22)	8.31 (3.44)	9.04 (3.75)
Total motor score	7.32 (3.14)	7.95 (3.26)	8.73 (3.45)
Definite motor problems ($\leq 5^{\text{th}}$ percentile)	28.93 % (57/197)	24.58 % (29/118)	16.75% (33/197)
Right handedness	89.4% (177/198)	88.2% (105/119)	88.32% (174/197)

*SD=standard deviation

Table 3. Mean difference of standard scores of Movement ABC-2 between familial risk of schizophrenia or familial risk of bipolar disorder and controls adjusted for sex, age, subdomains and the interaction group-by-subdomain and sex-by-subdomain.

	T-test (degree of freedom) T(F)	Standard error (SE)	Mean difference (95% CI)	P-value
Schizophrenia familial risk-group versus control				
Manual dexterity	-4.27 (510)	0.33	-1.42 [-2.08– -0.77]	<0.0001
Ball skills: Aiming and catching	-1.33 (510)	0.29	-0.39 [-0.97–0.19]	0.18
Balance	-4.12 (508)	0.33	-1.38 [-2.03– -0.72]	<.0001
Bipolar disorder familial risk-group versus control				
Manual dexterity	-1.79 (512)	0.39	-0.69 [-1.44–0.07]	0.075
Ball skills: Aiming and catching	-1.05 (511)	0.34	-0.36 [-1.03–0.31]	0.29
Balance	-1.75 (510)	0.38	-0.68 [-1.44– -0.08]	0.08
Sex differences: Boys versus girls*				
Manual dexterity	-7.83 (510)	0.29	-2.29 [-2.87– -1.72]	<0.0001
Ball skills: Aiming and catching	3.10 (509)	0.26	0.80 [0.29–1.31]	0.0021
Balance	-7.52 (507)	0.29	-2.21 [-2.78– -1.63]	<0.0001

*Girls are the reference level

Figure 1. Study profile.

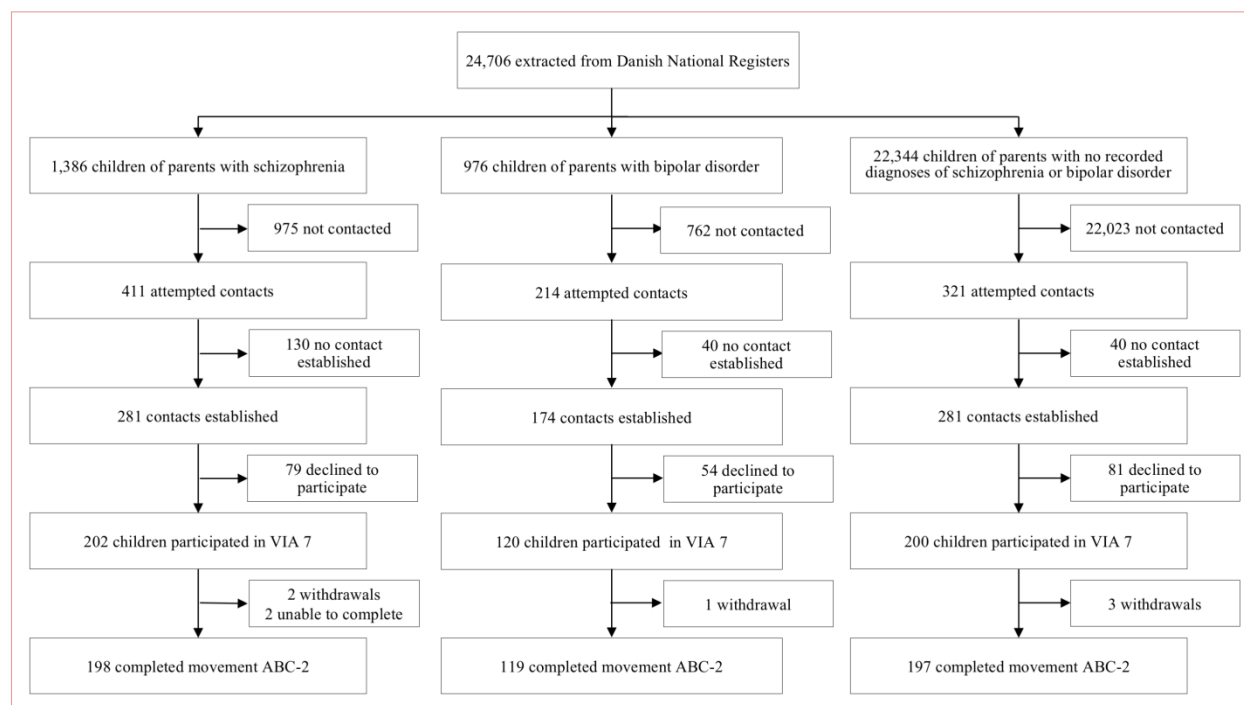
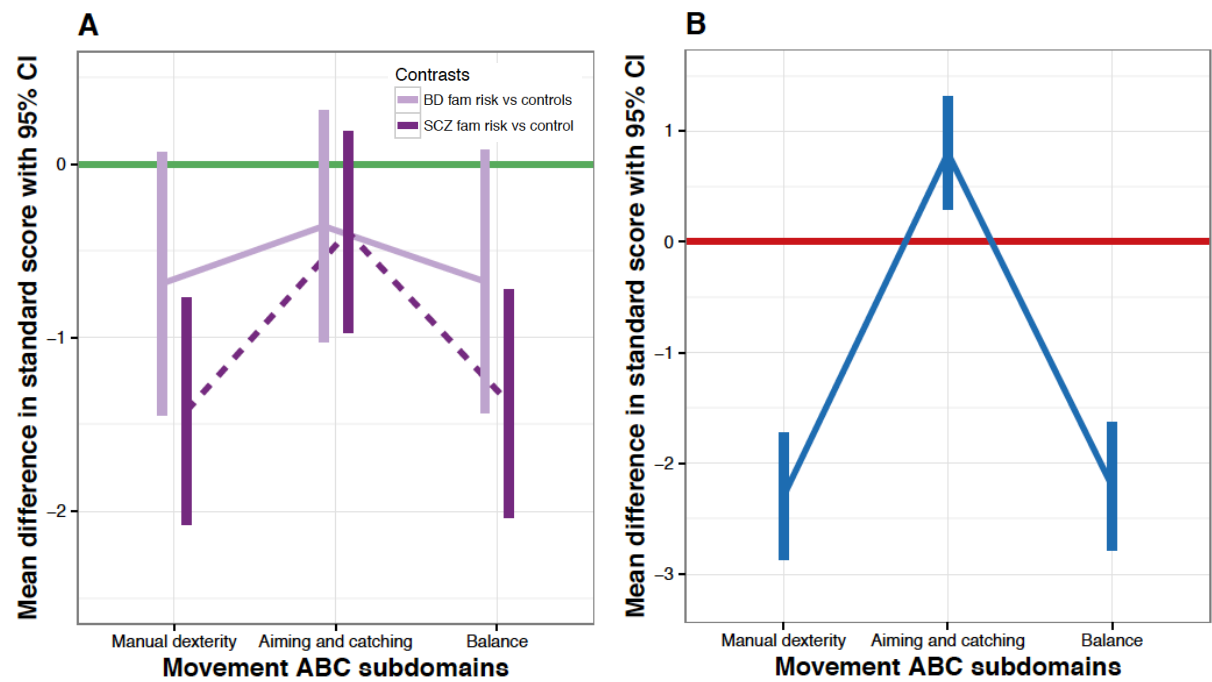


Figure 2. A. Mean difference from each subdomain in Movement ABC-2 between children with a familial risk of schizophrenia (dark purple dashed line) or familial risk of bipolar disorder (light purple solid line) compared with controls (green horizontal line). B. Mean difference between sexes in each subdomain of Movement ABC-2. Boys compared with girls (the reference level refers to the girls, illustrated with the red horizontal line).



Sustained Attention and Cognitive Control among 7-Year-Old Children with a Familial Risk of Schizophrenia or Bipolar Disorder

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Abstract:

Importance Individuals with severe mental disorders display early vulnerabilities, as do their offspring. Investigating the specific neurodevelopmental traits of these vulnerabilities in the offspring is important when aiming at preventing the emergence of mental disorders, because early deviations may present targets for preventive interventions.

Objective To determine whether 7-years-old children with a familial risk of schizophrenia or bipolar disorder display specific deficits in the domains of sustained attention and cognitive control abilities compared with controls.

Design, setting and participants The Danish High Risk and Resilience Study-VIA7 (December, 2012 to March, 2016) is a cross sectional cohort study. VIA 7 examined 522 children at the age of 7 years with no, one or two parents with schizophrenia or bipolar disorder, identified through the Danish Registers. Offspring of parents with schizophrenia were matched with control children with respect to sex, age and municipality. Assessment took place in the research department and in the homes of the families. Raters were blinded to the familial risk status of the parents.

Main outcomes and measures Measures of sustained attention using the Conner's Continuous Performance Test-2 and measures of cognitive control, assessed in an Erikson Flanker task.

Results Groups differed in terms of overall sustained attention in terms of vigilance ($F_{(2,336)}=3.30, p=0.038$) and overall RT consistency across the entire test ($F_{(2,362)}=5.81, p=0.0033$), as well as between block RT consistency ($F_{(2,349)}=5.35, P=0.0051$). Cognitive control abilities measured in a Flanker paradigm differed across groups in terms of accuracy ($F_{(2,494)}=3.06, P=0.048$), reaction time ($F_{(2,447)}=3.17, P=0.043$), and coefficient of variation ($F_{(2,340)}=8.15, P=0.0003$).

Conclusion and relevance Pre-pubertal children with a familial risk of schizophrenia displayed deficits in sustained attention compared with controls and with familial risk of bipolar disorder, as well as subtle deviations in cognitive control compared with controls. Children with a familial risk of bipolar disorder generally did not differ from controls in sustained attention and cognitive control except for a lower accuracy in a task assessing cognitive control. Beyond confirming deficits of sustained attention and cognitive control as an endophenotype for schizophrenia, our findings indicate distinct neurodevelopmental paths for children of parents with schizophrenia and bipolar disorder.

Introduction

Schizophrenia and bipolar disorder are severe mental disorders with a shared genetic liability and etiology^{1,2}. Individuals diagnosed with schizophrenia and bipolar disorder exhibit cognitive impairments^{3,4}, although cognitive deficits in individuals with schizophrenia tend to be more severe than in individuals with bipolar disorders^{5,6}. Interactions of the environment with genetic variants, mediated via brain circuits, may cause different phenotypic presentations of severe mental disorders⁷. Despite the existence of a genetic overlap for schizophrenia and bipolar disorder^{1,2}, adults with psychiatric disorders of neurodevelopmental origin, may present with similar or with different vulnerabilities during their developmental trajectories.⁸

Children who develop schizophrenia in adulthood display subtle cognitive impairments in sustained attention, cognitive control and working memory.^{9,10} A longitudinal cohort study documented increased risk of schizophrenia among children

with poor academic performance.^{11,12} The same study reported associations between poor and excellent academic performance and increased risk of bipolar disorder.¹³ Cognitive impairment was absent in a birth cohort of children who developed mania in adulthood.¹⁴ Given the strong genetic impact of both diseases, it is relevant to assess cognitive abilities among individuals with a familial risk of severe mental disorders. Cognitive impairment has been documented in first-degree relatives of individuals with schizophrenia^{15,16}, whereas the evidence for cognitive deficits among children with a familial risk of bipolar disorder is inconsistent. Even though the prevalence of attentional deficits in children who developed bipolar disorders as adults is low,^{17,18} a review reported between 0% - 67% occurrence of attention deficits hyperactivity disorder (ADHD) among children of parents with bipolar disorder.¹⁹ Along the same lines, a recent review concluded that a diagnosis of ADHD in childhood did not predict the presence of bipolar disorder in adulthood, despite

the presence of various deficits in attention during childhood among those who developed bipolar in adulthood.²⁰

Cognitive control is crucial for functioning in daily life due to its impact on school and job performance, as well as social functioning and physical and mental health.²¹ One aspect of cognitive control is the ability to suppress interference during cognitive processing and maintain adequate performance when faced with significant distraction.²² Post-error slowing (PES), a process of adjusting behavior after an erroneous response,²³ is considered a behaviorally measurable part of this process. Imaging studies have verified the abundant connections and interactions between the cognitive system and motor during development,²⁴⁻²⁶ which may explain why motor and cognitive deficits often co-occur in individuals with neurodevelopmental disorders.²⁶

Assessment of sustained attention, cognitive control, and error adaptation in unaffected children with a familial risk of schizophrenia or bipolar disorder enables identification of possible endophenotypes, as well as cognitive vulnerabilities, which will make early interventions possible. Training deficits of error processing to enhance cognitive adaptation and flexibility to changing environments may represent one option of intervention,²⁷ because successful self-regulation is considered an important factor of resilience²⁸.

The overarching purpose of this study thus is to confirm and extend previously findings by assessing sustained attention with a validated measure of attention in a large sample with a narrow age range of children with a familial risk of schizophrenia or bipolar disorder. This is the first study that assessed the cognitive control abilities of pre-pubertal children with a familial risk of severe mental disorders. We hypothesized that children with a familial risk of schizophrenia or bipolar disorder will i) display deficits in sustained attention with longer reaction times as a function of time (vigilance), lower overall reaction time (RT) consistency and lower between block RT consistency during a task requiring attention and ii) display deficits in cognitive control with less accuracy, higher RT, and greater coefficient of variation during a task requiring cognitive control compared with controls.

Methods

The Danish Data Protection Agency approved the study protocol. We received permission to draw data from registers from the Danish Ministry of Health. The Danish National Committee on Health Research Ethics received the protocol for consent and we attained a general evaluation, but due to the lack of any intervention, ethical approval was not regarded further necessary by the authority. Participating parents gave written informed consent.

Study design and participants

The Danish High Risk and Resilience Study -VIA7 was established in Denmark between December, 2012 and March, 2016²⁹. This prospective cohort consists of 522 Danish children aged 7 years with either no, one, or two parents diagnosed with a schizophrenia spectrum psychosis or bipolar disorder. We identified this cohort using a combination of registries. The Danish Psychiatric Central Research Register (DPCR)³⁰ provided diagnostic information based on in- and out-patient contact with psychiatry. The DPCR began to register in-patient contacts

with the psychiatric services on April 1st, 1969 and out-patient contacts on January 1st, 1995. We extracted data from April 1st, 1969 to the end of 2011. Schizophrenia spectrum psychosis was defined as schizophrenia, delusional disorder, or schizoaffective disorder (ICD 10-codes: F20, F22 and F25 or ICD 8-codes: 295, 297, 298.29, 298.39, 298.99). Bipolar disorder was defined as ICD 10-code F31 or ICD 8-codes 296.19 or 296.39. The Danish Civil Registration System (DCRS) was used to identify children born in Denmark who turned seven years old between September 1st, 2011 to August 31st, 2016. We also used the DCRS to link child data with parent data. Children were not excluded based on additional psychiatric diagnoses of the parents. For each child with a familial risk of schizophrenia, ten eligible control children matched on age, sex and home address (municipality) were identified and selected. Second, we used the sex of the ill parent to appoint an index parent in the control family. For families with two ill parents, we used both parents to appoint an index parent in the control family. Children of parents with bipolar disorder were not matched to control children, but overall they were similar in terms of age, sex, and urbanicity.

Procedure

In the present study we assessed sustained attention using the Conners' Continuous Performance test II (CPT-2)³¹ and cognitive control using the Erik Flanker paradigm.³² All raters were blinded to group affiliation throughout the examination and analyses.

Conners' Continuous Performing Test II

The child was instructed to click the mouse button as quickly and precisely as possible every time a letter (target) from the alphabet appeared on the computer screen. When the letter "X" (non-target) appeared on the screen (in 10% of the trials) the child was instructed not to press the mouse button. A short practice block preceded the actual CPT-II test. The CPT-II consists of 360 trials divided into 6 blocks, each comprising three sub-blocks of 20 trials with different inter-stimulus interval conditions of 1, 2, or 4 seconds. Each letter (target and non-target) remained on the computer screen for 250 milliseconds followed by a random order of inter-stimulus interval condition, resulting in a total test time of around 14 minutes.

Eriksen Flanker Task

We assessed cognitive control and error adaptation using a modified visuospatial task involving an interference effect, the Eriksen Flanker Task paradigm³² implemented in E-prime 2 software tool (Psychology Software Tools, 2012). A short training session preceded the actual flanker task. The child was instructed to fixate a dot presented in the center of a computer screen for 800ms. Trials started with 6 horizontal flanker arrows appearing below fixation. After 100 ms a central target arrow appeared pointing either in the same direction as the flanker arrows in congruent trials (<<< < <<<, >>> > >>>) or in the opposite direction in incongruent trials (<<< > <<<, >>> < >>>). The child was instructed to respond as quickly and precisely as possible with either a left or a right mouse button click following the direction of a central target arrow. The target- and flanker-arrows remained on the screen until a

response was registered. Trials were terminated by the response and followed by an 800-ms interval before the next trial started.

The flanker task consisted of 400 trials divided into two blocks of 200 trials. The overall probability of congruent and incongruent trials, and left and right responses was held at 0.5. The occurrence of each trial type was pseudorandomized separately for each child. An exclamation mark represented performance feedback and appeared when responses were erroneous or slower than an adaptive individual threshold value (i.e., the continuously updated mean response time plus 1.5 standard deviations).

Data processing

Conners' Continuous Performance Test-II

We removed three cases from the analysis due to invalid CPT-II (two cases had 100% omission and 0% commissions and one case had > 94 % omissions). We used raw scores in the analysis because the CPT-II manual does not provide Danish norms.

Eriksen Flanker Task

Response times above 10,000 milliseconds were considered omission errors and not included in the analyses for reaction time. For congruent trials, a total of 69 trials were removed and for incongruent trials, a total of 144 trials were removed. A response before 200 ms was considered a premature response, as we assumed that the premature response was based on the direction of the flankers only, rather than from the target arrow (anticipatory errors). For congruent trials, 285 trials were excluded. For incongruent trials, 284 trials were excluded. After the exclusion of omission errors and anticipatory errors from the data set, the remaining trials that had reaction times three standard deviations greater than the mean were excluded for congruent and incongruent trials. Participants who responded to fewer than 200 trials (out of 400 trials) were excluded from the data-calculations (n=6) because their estimate was considered too different in terms of variability compared with the remaining participants. In the familial risk group of bipolar disorder 0 participants were removed, in the familial risk group of schizophrenia 4 participants were removed, and in the control group 2 participants were removed. Finally, one individual was removed from the dataset due to performance reflecting that this person had not understood the task (4% accuracy in congruent trials).

Outcome measures for CPT-II

We analyzed sustained attention with three computer based measures: vigilance (hit RT block change), overall RT consistency across the entire test (Hit RT standard error) and between block consistency: ("variabilitySE") (Table 2 for definitions).

Outcome measures for Flanker task

We used measures of reaction time (RT), accuracy (ACC) and the coefficient of variation (CV) for congruent and incongruent trials. Accuracy was defined as the number of correct trials divided by the total number of trials, excluding omission trials, premature trials and trials exceeding three standard deviations from the mean. CV was defined as the standard deviation divided by the mean for individuals for congruent and

incongruent trials respectively. We included the following measures of error adaptation: post-error slowing (PES), post-error improvement of accuracy (PIA) (accuracy during post-error trials greater than the accuracy during post-correct trials) and post-error reduction of interference (PERI). PERI describes the notion that the irrelevant information is filtered out more easily after an error due to an increase in alertness, hence interference control (the ability to focus on the target while ignoring competing irrelevant information)³³ during post-correct trials is greater than interference during post-error trials (Table 2). PIA and PERI are expected to be positive if they reflect cognitive adaptation and adjusted behavior. PES was only assessed from consecutive sequences of trials (PES complex) consisting of the error trial (E) and the two previous correct trials before the error trials (E-1) and (E-2) followed by a correct post-error trial (E+1) to avoid contamination by global fluctuations in performance during the experiment, such as global changes in motivation or response caution.³⁴ A minimum of 5 consecutive sequences of trials per participant was required to calculate a meaningful PES (3 participants were excluded). PES for each subject was used in the overall mean of PES of all the participants from each group of cases or controls.

Statistical Analyses

A priori hypothesis:

The CPT-II outcome measures (vigilance, overall RT consistency and between block consistency) across groups were analyzed in a univariate Analysis of Covariance (ANCOVA) in a mixed model analysis, in which both individually-matched cases, non-matched cases (bipolar disorder cases) and controls were included in the model as random effects. Covariates included age and sex. In addition to these independent variables, we considered all two and three-way interactions of group, sex, and age.

Moreover, we tested the Flanker task outcome measures by assessing the effect of familial group in a mixed-model analysis with repeated measures with an unstructured variance component matrix. The model included a within subject condition with two levels: congruent and incongruent trials. The model also included a between subject factor with three levels: familial risk groups (familial risk of schizophrenia, familial risk of bipolar disorder and controls). Individually matched cases, the non-matched cases (bipolar disorder cases) and controls were included in the model as random effects. The model was adjusted for age, sex, and, condition (congruent or incongruent trials). In addition to these independent variables, we considered all three-way, and all two-way interactions of group, sex, age, and condition. Statistically nonsignificant interaction terms were eliminated via backward stepwise regression, with the constraint that the model at each step had to be hierarchically well formulated. If a three way-interaction was significant all two-ways interactions remained in the model regardless of their statistical significance due to the hierarchy. All lower-order terms such as sex, age, condition, and group were included in the model regardless of statistical significance due to their biological plausibility.

Given the low number of sibling pairs (n = 16), the effect of shared genetic material or of a higher genetic loading (eight children had two ill parents) (Table 1) were not considered in the statistical models of the CPT-2 or the Flanker task. We used

an *F*-test for hypothesis testing on Type 3 fixed effects and a *t*-test to report mean differences. We considered *p*-values < .05 as significant. All statistical analyses were conducted in SAS software (version 9.4).

Explorative analyses

We used a univariate Analysis of Covariance (ANCOVA) in a mixed model to explore the effect of familial risk group for the presence of adaption to errors (PES, PIA and PERI), in which both individually matched cases, non-matched cases (bipolar disorder cases) and controls were included in the model as random effects. Covariates included age and sex. We considered all two and three-way interactions of group, sex, and age.

In a Pearson correlation speed-accuracy-trade-offs were assessed by comparing the relationship of mean reaction time and accuracy for congruent and incongruent trials on a group level.

Finally, we assessed the association between sustained attention, motor ability (measured in the same sample with the Movement Assessment Battery for Children – second edition, total standard score (Burton et al. manuscript under review)) using a multiple linear regression, in which sustained attention (between block RT consistency, CPT-2) served as the dependent variable.

Results

Our cohort consisted of 522 children (Figure 1 & Table 1). A total of 500 children completed the Flanker task, 493 children completed CPT. As reported in Table 1, a considerably higher proportion of index parents with schizophrenia and biological co-parents were both less educated than index parents and biological co-parents with bipolar disorder and control parents (Table 1). A greater proportion of biological parents was divorced and unemployed or on leave (sick leave, maternity leave, or early retirement) in families with severe mental disorders than control families. A higher proportion of children with a familial risk of severe mental disorder lived with a single parent than control children.

Sustained attention (CPT-2)

We could confirm our first hypothesis that groups differed in terms of overall sustained attention in terms of vigilance and overall RT consistency across the entire test, as well as between block RT consistency during the CPT-2 task (Table 2 for definition of variables). Vigilance differed across groups ($F_{(2,336)}=3.30$, $p=0.038$), with no effect of age ($F_{(1,455)}=1.22$, $p=0.27$), sex ($F_{(1,280)}=1.72$, $p=0.19$) or any significant two or three-ways interactions. Post-hoc tests indicated that children with a familial risk of schizophrenia displayed reduced vigilance compared with children with a familial risk of bipolar disorder (mean difference=0.01, 95% CI: [0.002–0.019], $t_{(484)}=2.36$, $p=0.0018$), but only differed at trend significance from controls (mean difference=0.007, 95% CI: [-0.0002–0.014], $t_{(209)}=1.91$, $P=0.058$). Children with a familial risk of bipolar disorder did not differ from controls (mean difference=-0.003, 95% CI: [-0.012–0.0054], $t_{(484)}=-0.74$, $P=0.46$) (Table 3).

Overall RT consistency differed across groups ($F_{(2,362)}=5.81$, $p=0.0033$), sex ($F_{(1,307)}=10.35$, $p=0.0014$), but not with age ($F_{(1,458)}=0.95$, $p=0.33$) and none of the two or three-ways

interactions reached significance. Post-hoc tests indicated that children with a familial risk of schizophrenia displayed decreased overall RT consistency compared with controls (mean difference=2.23, 95% CI: [0.42–4.03], $t_{(242)}=2.43$, $p=0.016$) and compared with children with a familial risk of bipolar disorder (mean difference=3.4, 95% CI: [1.3–5.49], $t_{(485)}=3.20$, $p=0.0015$). Moreover, boys exhibited a decreased overall RT consistency than girls (mean difference=2.65, 95% CI: [1.03–4.27], $t_{(307)}=3.22$, $p=0.0014$) (Table 3).

Between block RT consistency differed with respect to group ($F_{(2,349)}=5.35$, $P=0.0051$), sex ($F_{(1,288)}=12.12$, $P=0.0006$), but not with age ($F_{(1,452)}=0.36$, $P=0.55$) and none of the two or three-ways interactions were significant. Post-hoc tests indicated that children with a familial risk of schizophrenia displayed lower RT consistency between blocks compared with controls (mean difference=5.37, 95% CI: [0.54–10.19], $t_{(223)}=2.19$, $P=0.029$) and compared with children with a familial risk of bipolar disorder (mean difference=8.85, 95% CI: [3.3–14.4], $t_{(488)}=3.13$, $P=0.0018$). Moreover, boys exhibited a lower RT consistency between blocks than girls (mean difference=7.58, 95% CI: [3.29–11.86], $t_{(288)}=3.48$, $P=0.0006$) (Table 3)

Flanker task

Cognitive Control (Flanker task)

Our second hypothesis was confirmed, because groups differed in terms of cognitive control abilities measured in a Flanker paradigm. The test for fixed effects in a repeated mixed model for the effect of accuracy revealed significance across familial risk groups ($F_{(2,494)}=3.06$, $p=0.048$), condition ($F_{(1,492)}=4.23$, $p=0.04$) and age ($F_{(1,498)}=4.09$, $p=0.044$), no significant effect of sex ($F_{(1,498)}=2.70$, $p=0.10$). The interaction group-by-age-by-condition (congruency) ($F_{(2,492)}=3.93$, $p=0.020$), the interaction sex-by-age-by-condition (congruency) ($F_{(1,492)}=3.91$, $p=0.049$) and the interaction group-by-condition (congruency) ($F_{(2,492)}=4.02$, $p=0.019$) reached significance. The remaining two-way interactions were not significant. Post-hoc tests indicated that girls with a familial risk of schizophrenia displayed significantly lower accuracy during incongruent trials (mean difference= -0.16, 95% CI: [-0.29– -0.015], $t_{(490)}=-2.19$, $p=0.029$) compared with girls in the control group. Moreover, children with a familial risk of bipolar disorder displayed lower accuracy during incongruent trials compared with controls (Table 4).

Reaction time differed across groups ($F_{(2,447)}=3.17$, $p=0.043$), across conditions ($F_{(1,493)}=4.22$, $p=0.04$) and with age ($F_{(1,547)}=4.61$, $p=0.032$), but not with respect to sex ($F_{(1,468)}=0.85$, $p=0.35$). Moreover, the interaction of group-by-sex-by-condition reached significance ($F_{(2,493)}=3.45$, $p=0.033$). No other interactions reached significance. Post hoc tests indicated that children with a familial risk of schizophrenia displayed slower mean reaction time compared with controls, and that reaction times were faster in the congruent condition and among older children in all groups (Table 4).

We tested for speed accuracy trade-off between reaction time and accuracy for congruent and incongruent trials, but a correlation between reaction time and accuracy was absent in the entire sample (Pearson correlation= -0.025, $p=0.56$ for congruent trials), (Pearson correlation= 0.034, $p=0.45$ for incongruent trials). For children with a risk of schizophrenia (Pearson correlation= 0.08, $p=0.27$ for congruent trials),

(Pearson correlation= 0.087, $p=0.23$ for incongruent trials) or for controls (Pearson correlation= 0.54, $p=0.53$ for congruent trials) (Pearson correlation= 0.008, $p=0.91$ for incongruent trials). For children with a familial risk of bipolar disorder the speed accuracy tradeoff was trend significant (Pearson correlation= -0.18, $p=0.051$ for congruent trials), but no correlation for incongruent trials (Pearson correlation= 0.026, $p=0.78$).

RT variability (measured with the coefficient of variation) differed across groups ($F_{(2,340)}=8.15$, $p=0.0003$), across conditions ($F_{(1,499)}=322.53$, $p<0.0001$), across sexes ($F_{(1,288)}=7.4$, $p=0.007$) and with age ($F_{(1,470)}=4.62$, $p=0.032$). Post-hoc tests indicated that children with a familial risk of schizophrenia displayed higher RT variability compared with controls (mean difference=0.05, 95% CI: [0.03–0.076], $t_{(209)}=3.84$, $p=0.0002$) and compared with children with a familial risk of bipolar disorder (mean difference=0.04, 95% CI: [0.01–0.074], $t_{(491)}=2.71$, $p=0.007$). RT variability was higher in the incongruent condition, young children and boys exhibited a significant higher coefficient of variation than girls (Table 4).

Explorative Analyses

Error adaptation

Our findings document that all three groups exhibited PES (a positive mean) (Table 2). The test for fixed effects in a ANCOVA mixed model for overall effect of PES did not reveal a significant effect of familial risk groups ($F_{(2,492)}=0.30$, $p=0.74$), age ($F_{(1,492)}=0.29$, $p=0.29$), but a significant effect of sex ($F_{(1,492)}=5.17$, $p=0.02$). The post-hoc test indicated that boys exhibited less post-error slowing compared with girls (mean difference=-56.4, 95% CI: [-105.2– -7.64], $t_{(492)}=-2.27$, $p=0.02$).

None of the three groups on average displayed PIA (Table 2). Groups did not differ with respect to the PIA among familial risk groups ($F_{(2,349)}=0.10$, $p=0.90$), nor with age ($F_{(1,467)}=0.24$, $p=0.62$) or sex ($F_{(1,293)}=0.59$, $p=0.44$) (Table 4).

On average the control group displayed the highest PERI (mean 28.9, SD 225.7), whereas children with a familial risk of schizophrenia displayed PERI (mean 6.15, SD 331.8) and the children with a familial risk of bipolar disorder displayed no PERI (mean -30.42, SD 291). The effect of PERI revealed a significant effect of group ($F_{(2,491)}=4.19$, $p=0.016$), no effect of age ($F_{(1,491)}=3.19$, $p=0.075$), or sex ($F_{(1,491)}=3.15$, $p=0.076$), but a significant interaction of age-by-group ($F_{(2,491)}=4.27$, $p=0.015$). Post-hoc analyses revealed that children with a familial risk of schizophrenia differed from controls, indicating that children with a familial risk of schizophrenia displayed less post-error reduction of interference compared with controls (mean difference=306.6, 95% CI: [70.87–542.3], $t_{(491)}=2.56$, $p=0.01$). The interaction age-by-group indicated that the effect of age was not the same for each group.

The relationship between sustained attention and motor performance

We tested the relationship between one measure of sustained attention (between block RT consistency) and motor skills performance (total score from Movement ABC-2) in a multiple linear regression, where “between block RT consistency” served as the dependent variable. Motor skill performance had a significant negative predicting effect ($F_{(1,468)}=16.38$, $p<0.0001$) on sustained attention indicating that

poorer motor performance/scores correlated with a decrease in consistency. The effect of group remained significant ($F_{(2,346)}=3.71$, $p=0.026$) as well as the effect of sex ($F_{(1,303)}=5.81$, $p=0.017$), but not age ($F_{(1,438)}=0.15$, $p=0.69$). No two or three-ways interactions were significant.

Discussion

This prospective cross-sectional cohort study documents evidence of children with a familial risk of schizophrenia displayed deficits in overall sustained attention on CPT-2, with trend-significant differences in vigilance, a lower overall RT consistency and a lower between block RT consistency compared with controls. Moreover, children with a familial risk of schizophrenia displayed deficits in cognitive control abilities compared with controls: slower reaction time, greater coefficient variation for boys, and lower accuracy during incongruent trials for girls. In contrast, children with a familial risk of bipolar disorder and controls displayed similar skills in all the measures of sustained attention and cognitive control (with the exception of lower accuracy during incongruent trials in the Flanker task).

Our data provides evidence of a clear distinction regarding their ability to sustain attention between children with a familial risk of schizophrenia and children with a familial risk of bipolar disorder. All measures of the CPT-2 differed between these two familial risk groups, indicating two distinct developmental paths for sustained attention at the age of 7 years.

Our results are consistent with other reports of deficits in sustained attention among offspring of parents with schizophrenia.^{9,35} Previous findings regarding deficits of sustained attention among children with a familial risk of bipolar disorder reported conflicting findings.^{18,19,36,37} Nevertheless, longitudinal cohort studies indicated that individuals who later developed mania¹⁴ or bipolar disorder,¹³ displayed either similar cognitive skills (IQ) as controls¹⁴ or either excellent or extremely poor school performance¹³. The latter suggests that individuals with bipolar disorder may belong to different subgroups based on specific cognitive profiles prior to the development of bipolar disorder^{38,39}.

Error adaptation has been measured in individuals with schizophrenia and bipolar disorder, but few studies have assessed error adaptation in offspring⁴⁰. Thus, this study provides novel knowledge regarding cognitive control and error adaptation behavior in children. We found, that children on average displayed PES, but no difference in post-error slowing between groups. Moreover, and in contrast to the expectations, all three groups showed a decrease in post-error improvement of accuracy (negative PIA). These results may reflect that post-error slowing does not lead to improved accuracy, because PES is not a result of an adaptive adjustment at the age 7 years, but rather an automatic orienting response⁴¹. Consensus is not established for the underlying mechanism of PES⁴¹⁻⁴³. Some consider post-error slowing to be a result from an increased motor threshold implemented by a general motor inhibition to avoid future mistakes,⁴⁴ whereas others consider post-error slowing a reflection of an unspecified orientation response and not the result of cognitive control.⁴¹ The automatic orienting response may briefly inhibit the voluntary motor response, while the child fixates on the

new event, which could be the feedback from the error response or the internal realization of the mistake in the non-feedback paradigm. Nevertheless, our behavioral data does not support the occurrence of adaptation of behavior since no improvement of accuracy was observed after an erroneous response.

The anterior cingulate cortex (ACC)⁴⁵ and the prefrontal cortex (PFC) are tightly interconnected and their function and maturation crucial for the ability of cognitive control and error adaptation. The development of error adaptation thus depends of the maturation of dorsal ACC, the PFC, as well as the dopaminergic connections and metabolism in these brain areas.⁴⁵ The notion that cognitive control and error adaptation are relatively immature at the age of 7 years thus is coherent with the fact that the ACC, PFC, and the dopaminergic connections mature relatively late during development⁴⁵, reaching maturity after puberty and into early adulthood. Therefore, the lack of PIA and lack of difference in PES between groups, despite the presence of an average PES in our study, may reflect this immature error adaptation system. Moreover, the maturation of the error adaptation system seems reflected in the group-by-age interaction of post-error reduction of interference. Specifically, in the group of children with a familial risk of schizophrenia the performance of post-error reduction of interference improved with age, whereas in the group of familial risk of bipolar disorder age had no effect on post-error reduction.

Our study demonstrated that children with a familial risk of schizophrenia have deficits in sustained attention and cognitive control abilities compared with children without a familial risk of schizophrenia. These deficits in sustained attention and cognitive control abilities reflect pre-pubertal vulnerabilities in children with a familial risk of schizophrenia. Our results also highlight that children with a familial risk of bipolar disorder do not display these vulnerabilities at the age of 7-years despite of the shared genetic liability for schizophrenia and bipolar disorder.^{1,2} These differences in phenotypes may be the result of the interaction between the environment and genetics.⁷ More in depth understanding these differences during development, however, requires further exploration in a longitudinal perspective and extending the behavioral examinations with brain mapping. Viewed from a developmental perspective, the close and abundant connections between the motor and cognitive systems during development²⁶ could explain why children with a familial risk of schizophrenia have both cognitive⁹ and motor deficits⁴⁶ during development, whereas children with a familial risk of bipolar disorder have neither motor (Burton et al. manuscript submitted) nor prominent deficits of cognitive control.

Previous studies have suggested sustained attention to represent an endophenotype for schizophrenia.^{35,47} Our study extends previous findings by including a large group of children with a familial risk of bipolar disorder, who displayed excellent sustained attention. This finding supports that deficits in sustained attention could be regarded as an endophenotype for schizophrenia for three reasons. First, we have demonstrated that there is a clear distinction in sustained attention between children with a familial risk of schizophrenia and children with a familial risk of bipolar disorder. Second, our data indicate that offspring of individuals with schizophrenia, to a greater extent

than in the general population, have deficits in sustained attention. Third, there are state-independent deficits in sustained attention in individual with schizophrenia³.

Our study has major strengths including the novelty of assessing cognitive control abilities in a large pre-pubertal sample with a narrow age range with a familial risk of severe mental disorders. Furthermore, the raters were blinded to the children's familial risk status, which minimizes the risk of assessor bias. Although, our study has several limitations that need to be addressed, these limitations indicate directions for future research. As our study is cross-sectional, we were unable to predict whether children with cognitive deficits would continue to deviate from the general population throughout development. It is possible that these deviations are transitory deviations that may normalize during development.⁴⁸ Only longitudinal studies can address these issues. We were able to include 55% of the invited families into the VIA 7 study, which is a moderate response rate. Nonetheless, as families were identified through registries and the sample size is large and representative of rural and urban areas across Denmark, the cohort is likely representative of the population. An important limitation of our study was that we were unable to divide parents with bipolar disorder into subgroups based on the following: history of psychotic symptoms, disorder subtype, age of onset, and response to medicine. These subgroups would have allowed us to investigate whether children of parents with these disease subgroups differed in sustained attention or cognitive control. A final limitation of our study is that cognitive control abilities were assessed using behavioral tasks. Future studies would benefit from assessing these abilities using brain imaging and electrophysiology to gain a more profound understanding of the neural mechanism of cognitive control before puberty.

Conclusion

Pre-pubertal children with a familial risk of schizophrenia show deficits of sustained attention and subtle deviations in their cognitive control abilities compared with controls. However, children with a familial risk of bipolar disorder do not exhibit any deficits in sustained attention nor in their cognitive control abilities, except for less accuracy during incongruent trials compared with controls. In fact our results show that pre-pubertal children with a familial risk of schizophrenia differ significantly from children with a familial risk of bipolar disorder in all measures of sustained attention of CPT-2. These results reflect distinct neurodevelopmental paths for these two severe mental disorders before puberty. By assessing offspring of individuals with either schizophrenia or bipolar disorder, this study contributes to the understanding of neurodevelopmental vulnerability in childhood. Furthermore, our results indicate that deficits in sustained attention could be regarded as possible endophenotypes for schizophrenia. Finally, our results demonstrated that consistency across sub-blocks correlated with motor abilities, which could reflect the tight interplay of the motor and cognitive control systems during development²⁶. Potential clinical implication could be the early identification of attention deficits among children of parents with schizophrenia, ideally before school start, because it may have a negative impact on their academic performance. Once identified, however, attention problems may be addressed

already early in school through special adaptation in settings of teaching. This is highly relevant, because the combination with a decreased cognitive control easily may lead to secondary behavioral and emotional consequences.

Declaration of interest

The authors declare that there are no conflicts of interest in relation to the subject of this study. This work was supported by the Mental Health Services of the Capital Region of Denmark and the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH). Both sources of funding had no involvement in this paper.

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Table 1. Characteristics of children and parents in the Danish High Risk and Resilience Study -VIA 7. Index parents refer to the biological parents with schizophrenia spectrum disorder or bipolar disorder or, in the control group, the matched biological parent without any of these disorders.

	Schizophrenia high-risk group	Bipolar disorder high-risk group	Control group
Index Parent			
Total number of index parents	200	116	204
Female, N (%)	110 (55.0%)	64 (55.2%)	114 (55.9%)
Age at inclusion, mean (SD)	38.1 (6.1)	41.0 (7.0)	40.7 (4.8)
PSP, mean (SD)*	66.9 (15.8)	68.5 (13.9)	84.2 (10.1)
Unemployed or on leave	84 (48.8%)	46 (44.7%)	18 (9.3%)
Education			
Primary/ lower secondary education	50 (29.2%)	9 (8.5%)	8 (4.2%)
Upper secondary, vocational, short-cycle tertiary	73 (42.7 %)	44 (41.5%)	91 (47.6%)
Bachelor degree, equivalent or higher	48 (28.1%)	53 (50.0%)	92 (48.2%)
Biological co-parent			
Total number of co-parents	186	114	192
Female, N (%)	83 (44.6%)	51 (44.7%)	84 (43.8%)
Age at inclusion, mean (SD)	38.8 (6.4)	41.0 (5.4)	40.7 (4.2)
PSP, mean (SD)*	76.1 (14.2)	81.8 (13.3)	85.5 (8.5)
Unemployed or on leave	46 (26.4%)	14 (13.2%)	12 (6.4%)
Education, N (%)			
Primary/ lower secondary education	31 (17.5%)	5 (4.8%)	9 (4.8%)
Upper secondary, vocational, short-cycle tertiary	87 (49.2%)	43 (41.3%)	89 (47.8%)
Bachelor degree, equivalent or higher	59 (33.1%)	56 (53.8%)	88 (47.3%)
Child			
Total number of children	202	120	200
Age at inclusion, mean (SD)	7.8 (0.2)	7.9 (0.2)	7.8 (0.2)
Female, N (%)	93 (46.0%)	56 (46.7%)	93 (46.5%)
Two biological parents with SZ or/and BD, N (%)	7 (3.5%)	1 (0.8%)	-
CBCL score, mean (SD) **	27.2 (21.0)	23.3 (19.7)	17.0 (14.8)
CGAS, mean (SD) ***	68.2 (15.5)	73.5 (14.9)	77.7 (13.5)
Home environment			
Living with both biological parents, N (%)	81 (40.3%)	62 (53.0%)	169 (84.9%)
Living out of home, N (%)	11 (5.5%)	0 (0.0%)	1 (0.5%)
Living with index parent, N (%)	121 (59.9%)	81 (67.5%)	188 (94.0%)
Living with a single parent, N (%)	75 (37.3%)	37 (31.6%)	21 (10.6%)

* Personal and social performance scale (PSP) is a measure of personal and social functioning and ranges from 0 to 100 with higher scores reflecting better functioning.

** Child Behavior Check List (CBCL) is a parent-rated measure of problem behavior in children. Larger scores reflect more problems.

*** Children's Global Assessment Scale (CGAS) is a measure of general functioning in children rated by trained interviewers. The scale ranges from 0 to 100 with higher scores reflecting better functioning.

Table 2. Definitions of CPT-2 and Flanker task variables, means and standard deviations.

Task/Concept	Variable	Definition	Children with a familial risk of schizophrenia N=190	Children with a familial risk of bipolar disorder N=116	Controls N=187
CPT-II					
Vigilance	Hit RT block change	The slope of change in hit RT across the different blocks (a positive slope indicates a slowing of RT as a function of time on the task)	0.03 (0.04)	0.02 (0.04)	0.03 (0.04)
Overall RT consistency	Hit RT SE	Consistency of response time as measured by the standard error for responses to target	19.1 (9.56)	15.84 (7.53)	17.0 (9.55)
Between block RT consistency (consistency in response speed across the sub-blocks)	Variability SE	Measure of response time consistency calculated as the standard deviation of the standard error values for each sub-block	41.13 (25.37)	32.41(22.11)	36.19(24.19)
Reaction time (RT)	Raw Hit RT	Average speed (RT) of correct responses across the entire test	519.99 (95.87)	494.70 (78.96)	502.8(92.08)
Accuracy	Omission	Number of none response to target letters (non-X)	36.72 (29.83)	27.72(20.03)	31.68(29.16)
	Commissions	Number of responses to the non-target (X)	24.81(6.24)	26.24(4.99)	24.96(5.62)
Flanker Task					
Mean RT	Mean RT for congruent trials	Mean RT of correct responses across the flanker task for all congruent trials	910.21 (230.31)	839.0 (173.94)	850.87 (203.5)
	Mean RT for incongruent trials	Mean RT of correct responses across the flanker task for all incongruent trials	1253.9 (428.96)	1124.7(348.59)	1138.72 (368.98)
Accuracy	Accuracy for congruent trials	Number of correct responses for congruent trials	0.90 (0.08)	0.91 (0.08)	0.91 (0.08)
	Accuracy for incongruent trials	Number of correct responses for incongruent trials	0.77 (0.20)	0.80 (0.15)	0.81 (0.14)
	Coefficient of variability (CV) for congruent trials	Standard deviation of RT with-in subjects divided by mean RT with-in subject for congruent trials	0.45 (0.14)	0.41 (0.14)	0.41 (0.14)
	Coefficient of variability (CV) for incongruent trials	Standard deviation of RT with-in subjects divided by mean RT with-in subject for congruent trials	0.53 (0.15)	0.49 (0.16)	0.48 (0.15)
	Post-error slowing (PES)	Post-error slowing was calculated as the difference in RT between post-error trial (E+1) and the associated pre-error trial (E-1) for each individual.	182.11 (318.64)	188.60 (241.2)	163.11 (251.78)
Error adaptation	Post error improvement in accuracy (PIA)	Accuracy in post-error trials minus accuracy in post-correct trials	-0.07 (0.09)	-0.08 (0.09)	-0.07 (0.09)
	Post-error reduction of interference (PERI)	Interference (incongruent mean RT- congruent mean RT) of post-correct trials minus interference of post-error trials	6.15 (331.8)	-30.42 (291.02)	28.92 (255.7)

Table 3. Mean difference of raw scores in CPT-2 between familial risk of schizophrenia or familial risk of bipolar disorder and controls adjusted for sex and age. No two or three way interactions were significant.

	T-test (degree of freedom) T(F)	Standard error (SE)	Mean difference (95% CL)	P-value
Schizophrenia familial risk-group versus control				
Vigilance	1.91 (209)	0.0037	0.007 [-0.0002; 0.014]	0.058
Overall RT consistency	2.43 (242)	0.92	2.23 [0.42; 4.04]	0.016*
Between block RT consistency	2.19 (223)	2.45	5.37 [0.54; 10.19]	0.029*
Reaction time	1.8 (243)	9.57	17.26 [-1.582;36.10]	0.072
Omissions	1.86 (269)	3.56	6.63 [-0.39; 13.66]	0.064
Commissions	-0.47 (488)	0.61	-0.28 [-1.49; 0.91]	0.636
Bipolar disorder familial risk-group versus control				
Vigilance	-0.74 (484)	0.004	-0.0032 [-0.01; 0.005]	0.46
Overall RT consistency	-1.09 (485)	1.07	-1.17 [-3.27; 0.93]	0.27
Between block RT consistency	-1.22 (488)	2.84	-3.47 [-9.06; 2.11]	0.22
Reaction time	-0.44 (486)	11.42	-5.08 [-27.53; 17.37]	0.65
Omissions	-1.37 (488)	4.16	-5.69 [-13.88; 2.48]	0.17
Commissions	1.93 (488)	0.70	1.35 [-0.027; 2.74]	0.054
Schizophrenia familial risk-group versus Bipolar Disorder				
Vigilance	2.36 (484)	0.004	0.01 [0.002; 0.019]	0.019*
Overall RT consistency	3.20 (485)	1.06	3.4 [1.3; 5.49]	0.0015*
Between block RT consistency	3.13 (488)	2.82	8.845 [3.3; 14.40]	0.0018*
Reaction time	1.97 (486)	11.34	22.34 [0.062; 44.62]	0.049*
Omissions	2.98 (488)	4.13	12.33 [4.21; 20.46]	0.003*
Commissions	-2.35 (488)	0.697	-1.64 [-3.01; -0.27]	0.019*

Table 4. Mean difference of mean reaction time (RT) between familial risk of schizophrenia or familial risk of bipolar disorder and controls adjusted for sex, age, condition (congruency) and the interaction group-by-sex-by-congruency and all 2 ways interactions. Mean difference of accuracy between familial risk of schizophrenia or familial risk of bipolar disorder and controls adjusted for sex, age, condition (congruency) and the interaction age-by-group-by-condition and age-by-sex-condition and all two ways interaction.

	T-test (degree of freedom) T(F)	Standard errors (SE)	Mean difference (95% CL)	P-value
Schizophrenia familial risk-group versus control				
Boys				
RT_mean Congruent	2.33 (372)	78.9	184 [28.8; 339.18]	0.02 *
RT_mean Incongruent	3.23 (555)	90.74	293 [115.2; 471.7]	0.0013*
Accuracy Congruent	-0.59 (490)	0.0336	-0.0197 [-0.09; 0.05]	0.55
Accuracy Incongruent	-1.71 (490)	0.0711	-0.122 [-0.261; 0.018]	0.087
Coefficient Variance	3.56 (106)	0.0184	0.065 [0.029; 0.102]	0.0006*
Girls				
RT_mean Congruent	2.31 (366)	78.39	181.42 [27.3; 335.5]	0.02*
RT_mean Incongruent	1.94 (568)	92.2	178.6 [-2.59; 359.9]	0.053*
Accuracy Congruent	-0.58 (490)	0.033	-0.019 [-0.08; 0.046]	0.563
Accuracy Incongruent	-2.19 (490)	0.07	-0.155 [-0.29; -0.015]	0.029*
Coefficient Variance	1.76 (101)	0.018	0.033 [-0.004; 0.069]	0.08
Bipolar disorder familial risk-group versus control				
Boys				
RT_mean Congruent	-0.95 (504)	100.16	-95.41 [-292; 101.3]	0.341
RT_mean Incongruent	-0.27 (716)	112.81	-30.45[-251.9; 191]	0.787
Accuracy Congruent	-1.02 (490)	0.0413	-0.042 [-0.123; 0.039]	0.309
Accuracy Incongruent	-2.78 (490)	0.087	-0.243 [-0.415; -0.07]	0.006*
Coefficient Variance	0.15(262)	0.022	0.0034 [-0.041; 0.048]	0.88
Girls				
RT_mean Congruent	-0.72 (504)	107.34	-77.69 [-288.5; 133.1]	0.469
RT_mean Incongruent	-1.24 (719)	121.12	-150.65 [-388.4; 87.1]	0.214
Accuracy Congruent	-1.15 (490)	0.044	-0.051 [-0.138; 0.036]	0.249
Accuracy Incongruent	-3.14 (490)	0.093	-0.292 [-0.478; -0.11]	0.0018*
Coefficient Variance	0.49 (226)	0.022	0.011 [-0.033; 0.055]	0.62

*level of significance p<0.05

Table 5. Error adaptation. Mean difference of either post-error slowing, post-error improvement of accuracy and post-error reduction of interference between familial risk of schizophrenia or familial risk of bipolar disorder and controls adjusted for sex, age. No three ways or two ways interactions were significant, except for Post-error reduction of interference where the interaction age-by-group was significant. Post-error reduction of interference is adjusted for a significant interaction of age-by-group at the age of 7 beyond sex and age.

	T-test (degree of freedom) T(F)	Standard Error (SE)	Mean difference (95% CL)	P-value
Schizophrenia familial risk-group versus control				
Post-error slowing	0.62 (492)	28.36	17.7 [-38.03; 73.43]	0.53
Post-error improvement of accuracy (PIA)	0.16 (221)	0.0087	0.0014 [-0.016; 0.019]	0.87
Post-error reduction of interference (PERI)	2.56 (491)	119.97	306.6 [70.9; 542.3]	0.01*
Bipolar disorder familial risk-group versus control				
Post-error slowing	0.68 (492)	32.73	22.37 [-41.93; 86.69]	0.49
Post-error improvement of accuracy (PIA)	-0.21(492)	0.01	-0.003 [-0.024; 0.017]	0.75
Post-error reduction of interference (PERI)	1.63 (491)	149.52	243 [-49.9; 537.5]	0.10

*level of significance p<0.05



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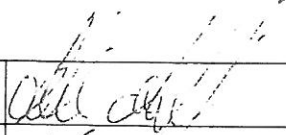
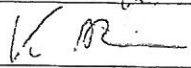
Title of PhD thesis:
Motor function, Attention and Cognitive Control in Children with a Familial Risk of Schizophrenia or Bipolar Disorder

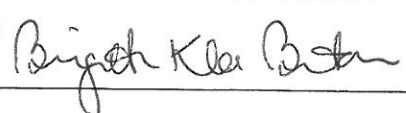
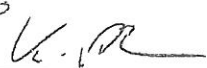
This declaration concerns the following article:
Research Review: Do deficits during development represent an endophenotype for schizophrenia? A meta-analysis

The PhD student's contribution to the article: (please use the scale (A,B,C) below as benchmark*)	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	C
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Motor function, Attention and Cognitive Control in Children with a Familial Risk of Schizophrenia or Bipolar Disorder

This declaration concerns the following article:
Motor Impairments among Children With a Familial risk of Schizophrenia or Bipolar Disorder at 7 Years Old - The Danish High Risk and resilience Study VIA 7

The PhD student's contribution to the article: (please use the scale (A,B,C) below as benchmark*)	(A,B,C)
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Motor function, Attention and Cognitive Control in Children with a Familial Risk of Schizophrenia or Bipolar Disorder

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