Impairments of motor function among children with a familial risk of schizophrenia or bipolar disorder at 7 years old in Denmark: an observational cohort study

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Summary

Background Owing to the genetic overlap between schizophrenia and bipolar disorder, we aimed to assess domain-specific motor aberrations and disorder specificity among 7-year-old children with a familial risk of schizophrenia or bipolar disorder by comparing children in familial risk groups with each other and with children not in these risk groups.

Methods In the Danish High Risk and Resilience Study, we established a cohort of 7-year-old children with no, one, or two parents with schizophrenia or bipolar disorder in Denmark between Jan 1, 2013, and Jan 31, 2016. We matched children of parents diagnosed with schizophrenia to children of parents without schizophrenia on the basis of their home address, age, and sex. Even though we did not match children of parents with bipolar disorder directly to controls because of resource constraints, we only recruited children into the three groups who did not differ in terms of age, sex, and urbanicity. We investigated motor function in children using the Movement Assessment Battery for Children–Second Edition. Motor function raters were masked to participants' clinical risk status during assessments. We assessed the effects of familial risk group in a mixed-model analysis with repeated measures with an unstructured variance component matrix.

Findings We studied 514 children (198 [39%] children of parents with schizophrenia, 119 [23%] of parents with bipolar disorder, and 197 [38%] of parents without schizophrenia or bipolar disorder). Children of parents with schizophrenia showed impaired motor performance compared with those of parents without in the subdomains of manual dexterity (mean difference –1·42 [95% CI –2·08 to –0·77]; p<0·0001) and balance (–1·38 [–2·03 to –0·72]; p<0·0001), but not of aiming and catching (–0·39 [–0·97 to 0·19]; p=0·18). Children of parents with bipolar disorder did not show any significant difference in motor performance to children of parents without in the subdomains of manual dexterity (–0·69 [–1·44 to 0·07]; p=0·08), balance (–0·68 [–1·44 to 0·08]; p=0·08), and aiming and catching (–0·36 [–1·03 to 0·31]; p=0·29). Comparison of familial risk groups of mental disorders revealed no significant differences in the subdomains of manual dexterity (–0·74 [–1·49 to 0·02]; p=0·06), balance (–0·70 [–1·46 to 0·06]; p=0·07), or aiming and catching (–0·03 [–0·70 to 0·63]; p=0·92).

Interpretation Motor abnormalities in children with a familial risk of schizophrenia are specific at 7 years of age with respect to fine motor function and balance, but non-specific with respect to familial risk of bipolar disorder. Clinicians should be aware of motor symptoms and refer children with definite motor problems (below the fifth percentile) to a child physiotherapist.

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Introduction

Severe mental disorders in adults might originate from neurodevelopmental disturbances, with different deviations presenting in childhood.[1,2] Motor impairments are seen in individuals with schizophrenia either well before the disorder manifests[3–6] or at diagnosis.[7] Similarly, numerous studies of individuals with a familial risk of schizophrenia support the existence of motor deficits, particularly impaired coordination during development.[8] Most of the previous studies of individuals at high familial risk, however, included children of parents with schizophrenia across a broad age range and so puberty and developmental stages might have influenced the findings.[9–11]

Schizophrenia shares common characteristics and genetic liability (ie, shares some of the same genes) with bipolar disorder,[12] but the two disorders present with different behavioural characteristics and symptoms. One of these differences might be motor performance, which has not been examined in depth in individuals with bipolar disorder[13] or their first-degree relatives.[14] In a prospective study[6] derived from a birth cohort, individuals developing mania before the age of 26 years displayed better general motor performance during childhood than did healthy participants. One study[14] reported impairment of fine motor speed coordination in 28 offspring of parents with bipolar disorder. Slightly

Research in context

Evidence before this study

In a previously published meta-analysis, we searched 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 for articles published up to July 9, 2012. We did a similar search in the same databases exchanging "schizophrenia" with "bipolar disorder" OR "mood disorder"' for articles published up to Oct 2, 2012. We found various studies reporting motor function in first-degree relatives of individuals with schizophrenia, but only few assessed motor function among first-degree relatives of individuals with bipolar disorder. We did 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 of individuals with schizophrenia, with a moderate effect size (n=8619; Hedges' g 0·625 [95% CI 0·453–0·797]; p<0·0001). The search emphasised the differences in recruitment of participants and the little information about recruitment processes, which did not allow for a strict assessment of selection bias and representativeness of the samples. 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 assessing motor function in first-degree relatives of individuals with bipolar disorder (at that point of time) was not possible due to the scarce literature.

Added value of this study

Our study is, to our knowledge, one of the largest studies of individuals with a high familial risk, with a sample size of 514. We assessed the specificity of motor deviations in children of parents with schizophrenia to substantiate and extend previously reported findings. Moreover, inclusion of 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 prepubertal children using a gold standard motor measurement, which has shown cross-cultural validity. Our results show convincing evidence of impaired motor function among children of parents with schizophrenia, whereas children of parents with bipolar disorder did not perform significantly differently to children of parents without bipolar disorder.

Implications of all the available evidence

This study raises awareness among clinicians of the potential presence of motor deficits in prepubertal children with a familial risk of schizophrenia—an area in need of special clinical attention and examination, as well as further research. Clinicians should provide particular attention to children with a motor ability placed below the fifth percentile, indicating definite motor problems, for whom a referral to a child physiotherapist should be considered.

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more studies have been done of offspring of mothers with affective disorders, reporting either motor performance similar to offspring of mothers without affective disorders[15] or gross motor impairments.[11] Yet, offspring of parents with affective disorder included parents with unipolar or bipolar disorder I or II or even affective schizoaffective disorder. Differences in definitions of affective disorder might thus explain conflicting findings in the area of motor function.[16] Few studies have assessed motor skills among offspring of individuals exclusively with bipolar disorder[14] and none have compared motor abilities in children with a familial risk of schizophrenia with those with a familial risk of bipolar disorder using a comprehensive, validated motor tool to assess the different domains of motor function.

Studies of individuals with schizophrenia report prominent differences between the sexes with respect to incidence[17] and most domains of cognitive function,[18] with men showing worse outcomes in both. However, the incidence of manifest bipolar disorder is higher for women than for men,[17] and a greater loss of function occurs among women diagnosed with bipolar II than

among men diagnosed with biopolar II.[19] Motor deviations in offspring could represent a surrogate measure for genetic risk variants combined with environmental influences that differ among individuals with severe mental disorders. Interactions between genetic risk variants and environmental factors, mediated through brain structure and circuitry, could result in different phenotypic presentations of behaviour or neuropsychological profiles[20] between individuals with severe mental disorders.[21]

The purpose of this study was to substantiate 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, assess motor ability in children with a familial risk of bipolar disorder. We thus aimed to examine the specificity of motor aberrations with respect to motor domains and disorder specificity among 7-year-old children with a familial risk of schizophrenia or bipolar disorder to establish whether or not children with two different types of familial risk display distinct profiles of motor function when using a fine-grained objective motor test. In this large cohort of

prepubertal children in a narrow age range, we expected that children with a familial risk of schizophrenia would display more pronounced motor impairments than would those without a familial risk, whereas children with a familial risk of bipolar disorder would show less pronounced motor deficits than would those without a familial risk.

Methods

Study design and participants

We did the Danish High Risk and Resilience Study (VIA 7)[22] in Denmark between Jan 1, 2013, and Jan 31, 2016. We established a prospective cohort of 7-year-old Danish children with either no, one, or two parents diagnosed with a schizophrenia spectrum psychosis or bipolar disorder. We invited children 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, or F25 or ICD-8 codes 295, 297, 298.29, 298.39, 298.89, or 298.99) or bipolar disorder (defined as ICD-10 code F31 or ICD-8 codes 296.19 or 296.39) and also registered in the Danish Civil Registration System as a biological parent to a 7-year-old child. Originally, we aimed to include additional groups of children with two parents with schizophrenia or bipolar disorder. However, we could recruit only eight children with this high genetic loading and thus decided to include these children in the main familial risk group. Owing to the hierarchical principle of the ICD-10 classification for mental and behavioural disorders, we classified the one child with one parent with schizophrenia and the other with bipolar disorder to the group of familial risk of schizophrenia. We matched children of parents diagnosed with schizophrenia to children of parents with no schizophrenia on the basis of their home address (same municipality), age, and sex. We did not match children of parents with bipolar disorder because of resource constraints, but we only recruited children into the three groups who did not differ in terms of age, sex, and urbanicity.

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 assessment, but because of the absence of any intervention, ethical approval was not deemed necessary by the authority.

Procedures

We assessed motor abilities using the Movement Assessment Battery for Children–Second Edition (Movement ABC-2),[23] which is a standardised 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 ball 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 11 raters (doctors, psychologists, and a nurse) were trained, approved, and certified by a physiotherapist authorised in assessing Movement ABC-2. Each rater had to show satisfactory abilities of doing Movement ABC-2 assessments documented in videos of themselves assessing one or two different children doing Movement ABC-2 tasks (appendix). Raters were masked to participants' clinical risk status during assessments. Movement ABC-2 assessments were preferably done in the same room where outlines for the assessment (ie, throwing a ball and walking on a line) were designated. We did regular inter-rater reliability assessments during data collection using the ratings of ten videos of children doing the Movement ABC-2 tasks selected by the raters.

Statistical analysis

We present data according to the Movement ABC-2 manual by converting raw scores to standard scores using the normative data from the manual, which have proven cross-cultural validity.[24] These standard scores are used in a clinical context and are in line with other Movement ABC-2 studies. Furthermore, we assessed the proportion of children who scored in the fifth percentile or lower, which signifies clinically significant movement difficulties according to the Movement ABC-2 manual.[23]

We assessed the main effects of familial risk group in a mixed-model analysis with repeated measures with an unstructured variance component matrix. The model included the three subdomains of Movement ABC-2 and the three familial risk groups. We included children in all three familial risk groups in the model as random effects. We adjusted the model 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. We eliminated non-significant interaction terms via backward stepwise regression, with the constraint that the model at each step had to be hierarchically well formulated. We included all low-order terms—ie, sex, age, familial risk group, and motor subdomain—in the model, regardless of significance, because of their biological or experimental plausibility. Because of the small number of sibling pairs (n=16), we did not consider the effect of sibling or high genetic loading (eight children had two parents with schizophrenia or bipolar disorder) in the model. All analyses are thus based on the entire cohort, regardless of having one or two parents with either schizophrenia, bipolar disorder, or both.

We used logistic regression to analyse the binary outcome of having definite motor problems (children who scored in the fifth percentile or lower on the total

standard score) or not, adjusting for age (in months) and sex. Furthermore, we explored the following intermediate variables in the repeated mixed-model analysis: handedness, living with both biological parents, living with the biological index parent, living with a single parent for the child, and personal and social performance (PSP) score[25] of the biological index parent and healthy coparent, in addition to educational level for biological index parent and coparents. We considered p values of less than 0·05 significant. We used F-tests for hypothesis testing on type three fixed effects and *t* tests for reporting estimates. We did all analyses in SAS (version 9.4).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 522 children included in the entire VIA 7 cohort (202 [39%] children of parents with schizophrenia, 120 [23%] of parents with bipolar disorder, and 200 [38%] of parents without schizophrenia or bipolar disorder), 514 completed Movement ABC-2 (198 [39%] children of parents with schizophrenia, 119 [23%] of parents with bipolar disorder, and 197 [38%] of parents without schizophrenia or bipolar disorder; figure 1).

A higher proportion of children did not live with both biological parents and a higher proportion lived with a single parent in the familial risk groups than in the non-risk group, and a higher proportion of the biological parents were unemployed or on leave (sick leave, maternity leave, or retirement) in the familial risk groups than in the non-risk group (table 1). Index parents with schizophrenia and healthy coparents were considerably less educated than index parents with bipolar disorder and healthy coparents and parents without schizophrenia or bipolar disorder. No differences
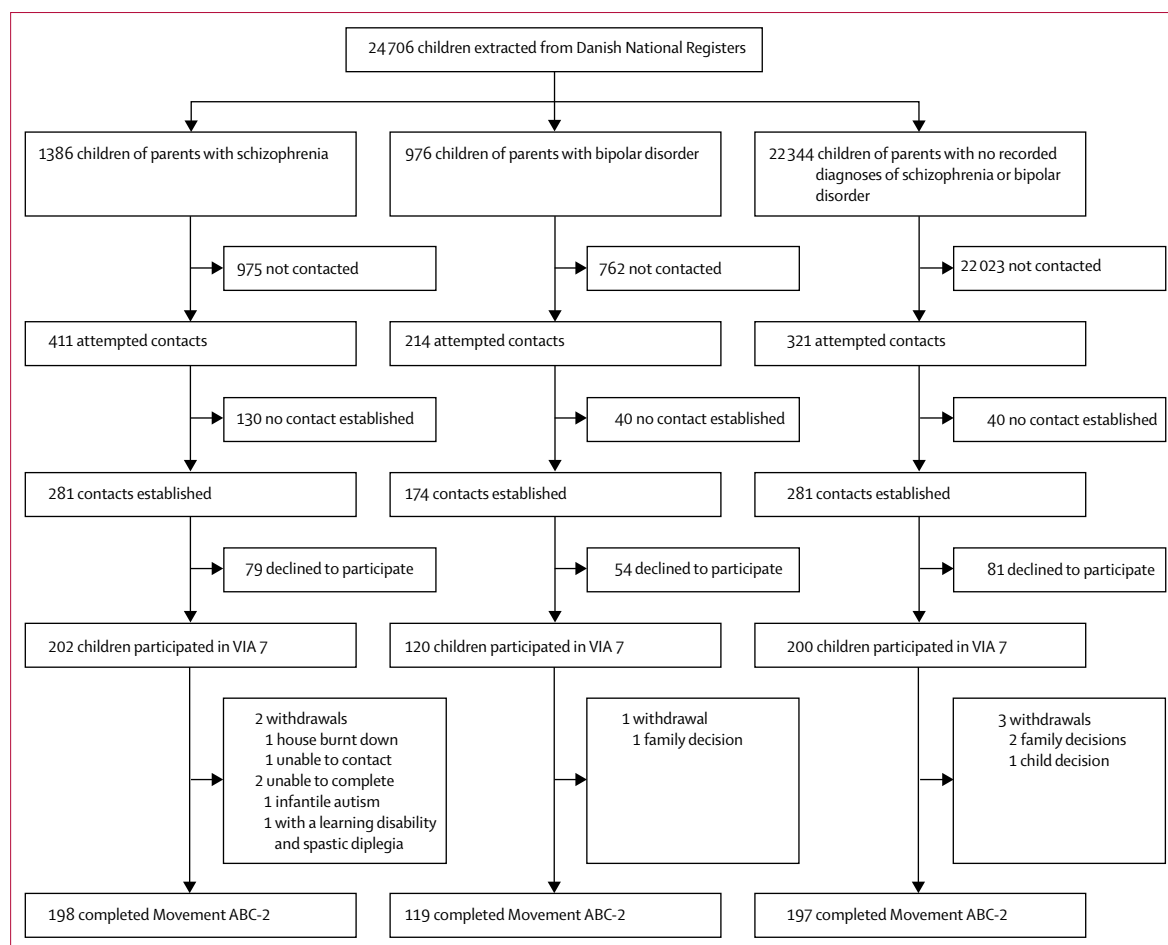

Figure 1: Study profile
Six families discontinued participation before they completed Movement ABC-2 because of serious circumstances in the family (appendix). Two children were not able to complete Movement ABC-2 and were not included in the analysis. ABC-2=Movement Assessment Battery for Children–Second Edition. VIA 7=Danish High Risk and Resilience Study.

	Schizophrenia familial risk group	Bipolar disorder familial risk group	No familial risk group
Child			
Total number of children	198	119	197
Female	92 (46%)	56 (47%)	90 (46%)
Two biological parents with schizophrenia or bipolar disorder	7 (4%)	1 (1%)	..
CBCL score*	27·3 (21·0)	23·5 (19·7)	17·1 (14·8)
CGAS†	68·1 (15·5)	73·5 (14·9)	77·7 (13·5)
Child home environment			
Living with both biological parents	79 (40%)	62/117 (53%)	168 (85%)
Living out of home	11 (6%)	0/117	1 (1%)
Living with index parent	119 (60%)	81 (68%)	187 (95%)
Living with a single parent	74 (37%)	37/117 (32%)	21 (11%)
Biological index parent			
Total number of index parents	196	115	201
Female	107 (55%)	64 (56%)	112 (56%)
Age at inclusion (years)	38·0 (6·0)	41·0 (7·0)	40·7 (4·9)
PSP score‡	66·9 (15·7)	68·8 (14·0)	84·2 (10·0)
Unemployed or on leave	82/169 (49%)	46/103 (45%)	18/191 (9%)
Education			
Primary or lower secondary	49/168 (29%)	9/106 (8%)	7/189 (4%)
Upper secondary, vocational, or short-cycle tertiary	71/168 (42%)	44/106 (42%)	91/189 (48%)
Bachelor degree or equivalent or higher	48/168 (29%)	53/106 (50%)	91/189 (48%)
Biological coparent			
Total number of coparents	182	113	189
Female	82 (45%)	50 (44%)	83 (44%)
Age at inclusion (years)	38·8 (6·4)	41·0 (5·4)	40·7 (4·3)
PSP score‡	76·3 (14·3)	81·8 (13·1)	85·5 (8·5)
Unemployed or on leave	44/171 (26%)	14/106 (13%)	11/186 (6%)
Education			
Primary or lower secondary	30/174 (17%)	5/104 (5%)	9/185 (5%)
Upper secondary, vocational, or short-cycle tertiary	85/174 (49%)	43/104 (41%)	88/185 (48%)
Bachelor degree or equivalent or higher	59/174 (34%)	56/104 (54%)	88/185 (48%)

Data are n (%) or mean (SD). PSP=personal and social performance. CBCL=Child Behavior Check List. CGAS=Children's Global Assessment Scale. *A parent-rated measure of problem behaviour in children, with higher scores reflecting more problems. †A measure of general functioning in children rated by trained interviewers, ranging from 0 to 100, with higher scores reflecting better functioning. ‡A measure of personal and social functioning, ranging from 0 to 100, with higher scores reflecting better functioning.

Table 1: Characteristics of children and their parents

The test for fixed effects in a mixed model for overall motor performance revealed significantly poorer standard scores in the familial risk of schizophrenia group than in the non-risk group ($p<0.0001$), and a significant effect of age, indicating a poorer performance in younger children than in older children ($p=0.0005$). Moreover, we found an effect of the different subdomains of Movement ABC-2 on the dependent variable motor performance ($p=0.045$), as well as sex differences ($p<0.0001$). Specifically, the effect of sex and group differed across subdomains, with significant interactions of sex-by-subdomain ($p<0.0001$) and group-by-subdomain ($p=0.03$). No three-way or four-way interactions were significant, nor was the interaction of group-by-sex ($p=0.94$).

Children with a familial risk of schizophrenia showed significantly impaired motor performance compared with children without a familial risk in the subdomains of manual dexterity (mean difference -1.42 [95% CI -2.08 to -0.77]; $p<0.0001$) and balance (-1.38 [-2.03 to -0.72]; $p<0.0001$), but no difference in the subdomain of aiming and catching (-0.39 [-0.97 to 0.19]; $p=0.18$; table 2, figure 2). Children with a familial risk of bipolar disorder displayed no significant differences in motor performance to children with parents without in all three subdomains: manual dexterity (-0.69 [-1.44 to 0.07]; $p=0.08$), balance (-0.68 [-1.44 to 0.08]; $p=0.08$), and aiming and catching (-0.36 [-1.03 to 0.31]; $p=0.29$). Comparison of children with a familial risk of schizophrenia with children with a familial risk of bipolar disorder did not reveal significant differences in motor performance in the subdomains of manual dexterity (-0.74 [-1.49 to 0.02]; $p=0.06$), balance (-0.70 [-1.46 to 0.06]; $p=0.07$), or aiming and catching (-0.03 [-0.70 to 0.63]; $p=0.92$). Boys performed worse than girls in the subdomains of manual dexterity (-2.29 [-2.87 to -1.72]; $p<0.0001$) and balance (-2.21 [-2.78 to -1.63]; $p<0.0001$). By contrast, boys outperformed girls in the domain of aiming and catching (0.80 [0.29–1.31]; $p=0.002$), with a significant sex-by-subdomain interaction ($p<0.0001$). Means and SDs for the standard scores between familial risk groups are presented in table 3.

Boys had 2·57-times higher odds (95% CI 1·64–4·0; $p<0.0001$) of definite motor problems than did girls, and older children had 1·12-times higher odds (1·04–1·21; $p=0.004$) than did younger children. The odds of having definite motor problems were 2·02-times higher (1·23–3·32; $p=0.006$) for children with a familial risk of schizophrenia than for children without a familial risk of schizophrenia. By contrast, the odds of having definite motor problems did not differ between children with a familial risk of bipolar disorder and children without a familial risk of bipolar disorder (odds ratio 1·57 [95% CI 0·88–2·79]; $p=0.13$).

In the repeated mixed model, the influence of handedness on motor ability was not significant ($p=0.17$), nor were the effects of children living with both biological parents ($p=0.83$), with the index parent ($p=0.77$), or with a

in age ($p=0.08$), sex ($p=0.97$), or urbanicity were shown across groups and differences in the dependent variable across groups were not underestimated as a result of adjustment for age and sex (appendix). Furthermore, no floor or ceiling effects (defined as a 15% threshold of participants achieving the highest or lowest score) could be shown (five [1%] of 514 children had a standard score of the lowest value and two [<1%] of 514 children scored maximum standard scores). 17 (3%) children were assessed at home at the wish of parents that examinations take place in familiar surroundings. Most assessments were recorded on video (469 [91%] of 514).

single parent (p=0·32). We found no effect of the function of the biological index parent (measured with PSP score) on children's motor abilities (p=0·15). A high PSP score of the healthy biological coparent had a significant positive effect on children's motor performance (p=0·0002), on account of the effect of group disappearing (p=0·11). A high education level of the biological index parent had a significant positive effect on children's motor performance (p=0·006), whereas the education of the healthy biological coparent did not reveal any significant effect on children's motor performance (p=0·37).

Average measures intraclass correlation (ICC) was 0·997 for the manual dexterity subdomain, 0·997 for the aiming and catching subdomain, and 0·967 for the balance subdomain (appendix). One single rater (BKB) consistently scored the item drawing trail 2. Inter-rater reliability for ten sets of drawing trail 2 assessments between the rater and instructing physiotherapist was an ICC of 0·98 and within-rater reliability across 4 weeks was an ICC of 0·97.

Discussion

Findings from this prospective cross-sectional cohort study show 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 to that of children without a familial risk. Children of parents with schizophrenia compared with children of parents with bipolar disorder did not display significant differences. These findings reflect motor impairments on a group level in children of parents with schizophrenia. Age and sex did not differ between groups and we substantiated that differences in the dependent variable across groups were not underestimated as a result of adjustment for sex and age. Although we could not detect a significant difference between children with a familial risk of bipolar disorder and children without a familial risk or between the two familial risk groups of schizophrenia and bipolar disorder, we cannot reject that a difference exists owing to the borderline significance in the same two subdomains of motor performance that were aberrant in children of parents with schizophrenia (manual dexterity and balance). Children with a familial risk of schizophrenia were about twice as likely to show definite motor problems (in fifth percentile or lower) than were children without a familial risk. Moreover, girls outperformed boys in the subdomains of manual dexterity and balance, whereas the opposite was true for aiming and catching, and boys displayed higher odds ratios of having definite motor problems than did girls. 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 a meta-analysis[8] of unaffected first-degree relatives of individuals with schizophrenia, who displayed motor deficits within the first year of childhood

	Mean difference (95% CI)	SE	p value
Schizophrenia familial risk group versus non-risk group			
Manual dexterity	–1·42 (–2·08 to –0·77)	0·33	<0·0001
Aiming and catching	–0·39 (–0·97 to 0·19)	0·29	0·18
Balance	–1·38 (–2·03 to –0·72)	0·33	<0·0001
Bipolar disorder familial risk group versus non-risk group			
Manual dexterity	–0·69 (–1·44 to 0·07)	0·39	0·08
Aiming and catching	–0·36 (–1·03 to 0·31)	0·34	0·29
Balance	–0·68 (–1·44 to 0·08)	0·38	0·08
Schizophrenia versus bipolar disorder familial risk group			
Manual dexterity	–0·74 (–1·49 to 0·02)	0·38	0·06
Aiming and catching	–0·03 (–0·7 to 0·63)	0·33	0·92
Balance	–0·70 (–1·46 to 0·06)	0·39	0·07
Boys versus girls*			
Manual dexterity	–2·29 (–2·87 to –1·72)	0·29	<0·0001
Aiming and catching	0·80 (0·29 to 1·31)	0·26	0·002
Balance	–2·21 (–2·78 to –1·63)	0·29	<0·0001

*Girls are the reference level.

Table 2: **Mean difference in standard scores of the Movement Assessment Battery for Children–Second Edition**
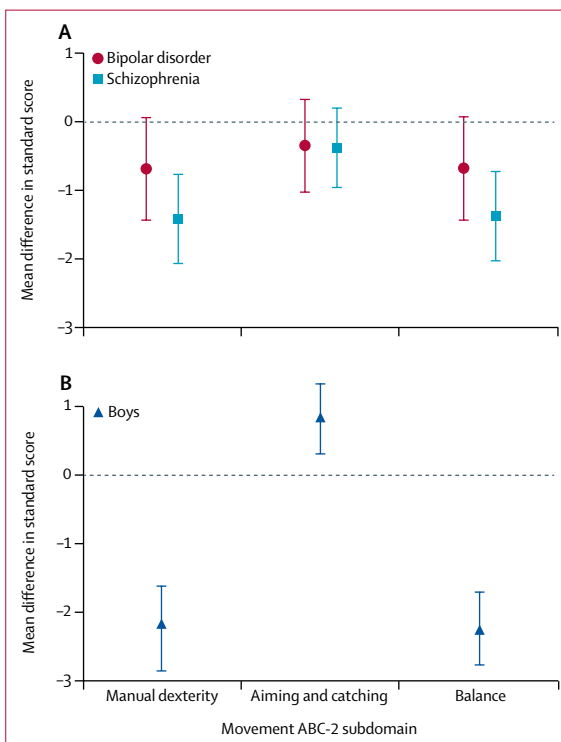

Figure 2: **Mean difference in ABC-2 standard scores**
(A) Difference between children with a familial risk of schizophrenia and children without and between children with a familial risk of bipolar disorder and children without. Error bars indicate 95% CIs. The reference level refers to children without familial risk (dashed line). (B) Difference between boys and girls. The reference level refers to girls (dashed line). Error bars indicate 95% CIs. ABC-2=Movement Assessment Battery for Children–Second Edition.

	Schizophrenia familial risk group (n=198)	Bipolar disorder familial risk group (n=119)	No familial risk group (n=197)
Boys	106 (54%)	63 (53%)	107 (54%)
Mean age (years)	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)
Aiming and catching	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 (in fifth percentile or lower)	57/197 (29%)	29/118 (25%)	33/197 (17%)
Right-handedness	177/198 (89%)	105/119 (88%)	174/197 (88%)

Data are n (%), mean (SD), or n/N (%).

Table 3: Standard scores in the Movement Assessment Battery for Children–Second Edition for each familial risk group

and through development up to the age of 21 years. 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 documented in all three subdomains and groups, but not between groups (ie, no significant sex-by-group interaction) probably represent a combination of biological differences mirroring the brain's dimorphism and external influences, such as training of fine motor skills in girls and ball competencies in boys.[26] A study[27] reported similar sex differences among healthy 3–5-year-old Australian children to those of the 7-year-old children in this study using Movement ABC assessment. Boys were about two and half times as likely in this study to show definite motor problems than were girls and children with a familial risk of schizophrenia were about twice as likely to present with definite motor problems than were those without a familial risk. If motor impairments hold true as a predictor of schizophrenia (beyond an endophenotype), as indicated by a follow-up study,[11] then this finding could relate to the fact that men have a higher incidence of schizophrenia than do women,[17] thus reflecting a higher developmental susceptibility in men than in women.

VIA 7 is unique as a study of children at high familial risk in the sense that all children were invited to participate in the study when they were 7 years old. Despite this homogeneous age range, which did not differ across groups, we substantiated that motor performance improves with increasing age. The significance of age reflects its crucial importance for development of motor abilities. Particularly in early childhood, small periods of ageing, such as a month, can result in clinically measurable changes of motor skills.[28] The instrument that we used to score motor development, Movement ABC-2, indicates substantially different scoring of motor skills dependent on the age of the individual, measured in years. Development, however, does not occur one step at a time or specifically in relation to that individual's chronological age as measured in

years. So even though we recruited 7-year-olds, we were still able to show a significant effect of age.

Being at familial risk entails both genetic and environmental exposures, and differentiation of these two components is difficult. Models suggest that emergence of schizophrenia in an individual is caused by the interactions of genetic risk variants and environmental factors, which together possibly impair motor development and cognitive abilities. Examples of environmental factors are maternal infections[29] or absence of maternal vitamin D,[30] which interfere with prenatal development. Furthermore, preterm birth and obstetric complications are environmental factors that are associated with increased risk of development of schizophrenia.[31] This finding is by contrast with the absence of association between risk of bipolar disorder and obstetric complications[32] and that a subgroup of individuals who develop bipolar disorder perform similarly to the general population regarding cognitive abilities.[33]

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 or not these environmental factors influenced the children's motor performance. However, only higher education of the biological index parent and a good personal and social functioning of the healthy biological coparent had a positive effect on the motor performance of the children. Higher education is related to higher IQ, which in turn is related to motor performance.[34] Within the observational design of this study, whether these findings indicate that characteristics of the biological parent might influence the motor performance of the child as truly environmental factors or that genes mediate these environmental factors, or a combination of both, is not possible to know.

These cross-sectional data cannot predict whether or not 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 and might normalise later during development.[2] Only longitudinal studies can address these two issues. These results might reflect the fact that motor deficits can 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 presence is despite motor impairment sometimes being seen by the unaided eye as traditionally conceptualised.[35]

The parents were divided into separate groups depending on diagnostic criteria for a schizophrenia spectrum disorder or bipolar disorder or neither. However, in the past 10 years, a debate has evolved as to whether diagnoses represent valid discrete entities or a dimension representing different transdiagnostic

patterns[36] because of a considerable amount of genetic overlap between serious mental disorders.[12] Furthermore, the validity of psychiatric diagnostic criteria is also affected by the fact that similar clinical symptoms can express different biological abnormalities. Moreover, this study cannot make any inference about the diagnostic long-term outcome.

Motor impairment and intellectual ability have shown associations[34] and the possibility cannot be discarded that the same influences (biological, genetic, and environmental) and their interaction might affect both measures. Thus, controlling for IQ or intellectual ability might overadjust group differences. The question of whether or not intellectual ability could act as a mediator would answer a different research question to the one addressed in this study and would require a 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 masked to familial risk groups, strengthening the validity of motor behaviour ratings. Inter-rater reliability was satisfactory. Finally, systematic assessor bias was minimised owing to the 11 raters with regular ratings of reliability.

Despite the strengths 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. Although Movement ABC-2 is recognised as the gold standard for measuring motor function, its validity has mostly been reported as convergent validity in comparison with other instruments. 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 3 month intervals instead of years and preferably divided by sex. We were able to enrol 55% of the invited families into the study, which is considered a moderate response rate. However, because of the fact that families were identified through registries, the large sample size, and the equal distribution of urban and rural locations from all parts of Denmark across groups, we still deem the cohort to be highly representative of the population. When correcting for nuisance variables in the exploratory analyses, such as parental education and marital status, which differ across groups, we cannot be certain that we do not overadjust for inherent group differences in the outcome variable. A considerable limitation to the study was the unavailability of division of parents into subgroups, such as psychotic or non-psychotic periods of bipolar disorder, bipolar disorder I or II or not otherwise specified, early-onset or late-onset bipolar disorder and schizophrenia, and medicine responders or non-responders, precluding us from assessing whether or not children of parents in these diagnostic subgroups

differed in motor performance. In future studies and analyses, further exploration of differences in motor ability between subgroups within the schizophrenia spectrum and across different types of bipolar disorder to examine whether or not specific endophenotypes in the domains of motor function underlie certain subgroups of the disorders would be relevant.

By assessing children of parents with schizophrenia and bipolar disorder, this study contributes to the understanding of neurodevelopmental susceptibility in childhood. Our results might indicate that motor deficits are a possible endophenotype for schizophrenia, indicating deviation of developmental characteristics of motor function. Future longitudinal follow-up studies should clarify the precision of our findings.

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